EMORY
UNIVERSITY
SCHOOL OF
MEDICINE

Department of Radiology
Division of Nuclear Medicine
and Molecular Imaging

September 1, 2011

Rafel Dwaine Rieves, M.D., Director
Division of Medical Imaging Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Attention: FDA Central Document Room (CDR)
5901-B Ammendale Rd
Beltsville, MD 20705-1266

Dear Dr. Rieves:

Enclosed is a new IND submission for the PET radiotracer [18F]FMISO in support of the following protocol which will be submitted to the Emory IRB: Tumor Hypoxia Imaging in Support of Radiofrequency Ablation (RFA) Success Prediction (RASP) Study for Metastatic Colorectal Liver Lesions. The proposed protocol has not yet been approved by the Emory IRB. Prior to initiating this trial, IRB approval will be obtained and if the IRB requires any amendments to protocol or informed consent, we will submit the amended protocol to this IND prior to initiation of clinical studies.

The radiotracer will be produced by Cardinal Health and a DMF, as well as supporting LOA are attached in the full IND submission which also includes an IB, Form 1571, Form 1572, Emory consent form, investigator CVs, LOA in reference to NCI IND # 70,005, as well as all other required documents printed in triplicate with electronic version on CD.

I look forward to hearing from you shortly. We will assume we may proceed with this protocol unless we have contact from your office.

Most sincerely,

David Schuster, MD
Director, Division of Nuclear Medicine and Molecular Imaging
Emory University Hospital, Room E152
1364 Clifton Road
Atlanta, GA 30322
Phone: 404-712-4859; Fax: 404-712-4860, dschust@emory.edu

Investigational New Drug Application

Regulatory Sponsor: David M Schuster, MD
Director, Division of Nuclear Medicine and Molecular Imaging
Department of Radiology and Imaging Sciences
Emory University Hospital, Room E152
1364 Clifton Road
Atlanta, GA 30322
404-712-4859
Fax: 404-712-4860
dschust@emory.edu

Study Product: [18F]FLUOROMISONIDAZOLE, 1H-1-(3-[18F]-FLUORO-2-HYDROXY-PROPYL)-2-NITRO-IMIDAZOLE, [18F]FMISO

Date: 9-1-11

***NOTE: Number of copies**: The Sponsor shall submit an **original and two copies** of all submissions to the IND file, including the original submission and all amendment and reports.*

1. FDA FORM 1571

12. **CONTENTS OF APPLICATION**

This application contains the following items: *(Check all that apply)*

- ☑ 1. Form FDA 1571 *[21 CFR 312.23(a)(1)]*
- ☑ 2. Table of Contents *[21 CFR 312.23(a)(2)]*
- ☑ 3. Introductory statement *[21 CFR 312.23(a)(3)]*
- ☑ 4. General Investigational plan *[21 CFR 312.23(a)(3)]*
- ☑ 5. Investigator's brochure *[21 CFR 312.23(a)(5)]*
- ☑ 6. Protocol(s) *[21 CFR 312.23(a)(6)]*
  - ☑ a. Study protocol(s) *[21 CFR 312.23(a)(6)]*
  - ☑ b. Investigator data *[21 CFR 312.23(a)(6)(iii)(b)]* or completed Form(s) FDA 1572
  - ☑ c. Facilities data *[21 CFR 312.23(a)(6)(iii)(b)]* or completed Form(s) FDA 1572
  - ☑ d. Institutional Review Board data *[21 CFR 312.23(a)(6)(iii)(b)]* or completed Form(s) FDA 1572
- ☑ 7. Chemistry, manufacturing, and control data *[21 CFR 312.23(a)(7)]*
  - ☑ Environmental assessment or claim for exclusion *[21 CFR 312.23(a)(7)(iv)(e)]*
- ☑ 8. Pharmacology and toxicology data *[21 CFR 312.23(a)(8)]*
- ☑ 9. Previous human experience *[21 CFR 312.23(a)(9)]*
- ☑ 10. Additional information *[21 CFR 312.23(a)(10)]*

13. IS ANY PART OF THE CLINICAL STUDY TO BE CONDUCTED BY A CONTRACT RESEARCH ORGANIZATION? ☐ YES ☑ NO

IF YES, WILL ANY SPONSOR OBLIGATIONS BE TRANSFERRED TO THE CONTRACT RESEARCH ORGANIZATION? ☐ YES ☑ NO

IF YES, ATTACH A STATEMENT CONTAINING THE NAME AND ADDRESS OF THE CONTRACT RESEARCH ORGANIZATION, IDENTIFICATION OF THE CLINICAL STUDY, AND A LISTING OF THE OBLIGATIONS TRANSFERRED.

14. NAME AND TITLE OF THE PERSON RESPONSIBLE FOR MONITORING THE CONDUCT AND PROGRESS OF THE CLINICAL INVESTIGATIONS

David M Schuster, M.D.

Director, Division of Nuclear Medicine and Molecular Imaging

15. NAME(S) AND TITLE(S) OF THE PERSON(S) RESPONSIBLE FOR REVIEW AND EVALUATION OF INFORMATION RELEVANT TO THE SAFETY OF THE DRUG

David M Schuster, M.D.
Director, Division of Nuclear Medicine and Molecular Imaging
and Manufacturer: Cardinal Health

I agree not to begin clinical investigations until 30 days after FDA's receipt of the IND unless I receive earlier notification by FDA that the studies may begin. I also agree not to begin or continue clinical investigations covered by the IND if those studies are placed on clinical hold. I agree that an Institutional Review Board (IRB) that complies with the requirements set fourth in 21 CFR Part 56 will be responsible for initial and continuing review and approval of each of the studies in the proposed clinical investigation. I agree to conduct the investigation in accordance with all other applicable regulatory requirements.

16. NAME OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE	17. SIGNATURE OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE	
David M Schuster, M.D.		
18. ADDRESS *(Number, Street, City, State and Zip Code)*	19. TELEPHONE NUMBER *(Include Area Code)*	20. DATE
Emory University Hospital, Department of Radiology Rm E152, 1364 Clifton Rd. NE, Atlanta, GA 30322	404-712-4859	09/01/2011

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Food and Drug Administration
Center for Drug Evaluation and Research (HFD-143)
Central Document Room
5901-B Ammendale Road
Beltsville, MD 207052-1266

Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (HFM-99)
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Rockville, MD 20852-1448

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

INVESTIGATIONAL NEW DRUG APPLICATION (IND)
(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) PART 312)

Form Approved: OMB No. 0910-0014.
Expiration Date: May 31, 2009
See OMB Statement on Reverse.

NOTE: No drug may be shipped or clinical investigation begun until an IND for that investigation is in effect (21 CFR 312.40).

1. NAME OF SPONSOR
David M. Schuster, M.D.

2. DATE OF SUBMISSION
09/01/2011

3. ADDRESS *(Number, Street, City, State and Zip Code)*
Emory University Hospital, Department of Radiology
Rm E152, 1364 Clifton Rd. NE, Atlanta, GA 30322

4. TELEPHONE NUMBER *(Include Area Code)*
404-712-4859

5. NAME(S) OF DRUG *(Include all available names: Trade, Generic, Chemical, Code)*
[^{18}F]FLUOROMISONIDAZOLE, 1H-1-(3-[^{18}F]-FLUORO-2-HYDROXY-PROPYL)-2-NITRO-IMIDAZOLE, [^{18}F]FMISO

6. IND NUMBER *(If previously assigned)*

7. INDICATION(S) *(Covered by this submission)*
IN VIVO DIAGNOSTIC FOR IMAGING HYPOXIA IN TUMORS

8. PHASE(S) OF CLINICAL INVESTIGATION TO BE CONDUCTED:
☐ PHASE 1 ☑ PHASE 2 ☐ PHASE 3 ☐ OTHER _____ *(Specify)*

9. LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS (21 CFR Part 312), NEW DRUG OR ANTIBIOTIC APPLICATIONS *(21 CFR Part 314)*, DRUG MASTER FILES *(21 CFR Part 314.420)*, AND PRODUCT LICENSE APPLICATIONS (21 CFR Part 601) REFERRED TO IN THIS APPLICATION.
DMF 23002,
IND#76,042 [^{18}F]FMISO

10. ***IND submission should be consecutively numbered. The initial IND should be numbered "Serial number: 0000." The next submission (e.g., amendment, report, or correspondence) should be numbered "Serial Number: 0001." Subsequent submissions should be numbered consecutively in the order in which they are submitted.***

SERIAL NUMBER
0 ___ ___ ___ ___

11. THIS SUBMISSION CONTAINS THE FOLLOWING: *(Check all that apply)*
☑ INITIAL INVESTIGATIONAL NEW DRUG APPLICATION (IND)
☐ RESPONSE TO CLINICAL HOLD

PROTOCOL AMENDMENT(S):
☐ NEW PROTOCOL
☐ CHANGE IN PROTOCOL
☐ NEW INVESTIGATOR

INFORMATION AMENDMENT(S):
☐ CHEMISTRY/MICROBIOLOGY
☐ PHARMACOLOGY/TOXICOLOGY
☐ CLINICAL

IND SAFETY REPORT(S):
☐ INITIAL WRITTEN REPORT
☐ FOLLOW-UP TO A WRITTEN REPORT

☐ RESPONSE TO FDA REQUEST FOR INFORMATION
☐ ANNUAL REPORT
☐ GENERAL CORRESPONDENCE
☐ REQUEST FOR REINSTATEMENT OF IND THAT IS WITHDRAWN, INACTIVATED, TERMINATED OR DISCONTINUED
☐ OTHER _____ *(Specify)*

CHECK ONLY IF APPLICABLE

JUSTIFICATION STATEMENT MUST BE SUBMITTED WITH APPLICATION FOR ANY CHECKED BELOW. REFER TO THE CITED CFR SECTION FOR FURTHER INFORMATION.

☐ **TREATMENT IND 21 CFR 312.35(b)** ☐ **TREATMENT PROTOCOL 21 CFR 312.35(a)** ☐ **CHARGE REQUEST/NOTIFICATION 21 CFR312.7(d)**

FOR FDA USE ONLY

CDR/DBIND/DGD RECEIPT STAMP	DDR RECEIPT STAMP	DIVISION ASSIGNMENT:
		IND NUMBER ASSIGNED:

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2. Table of Contents

3. Introductory Statement

[^{18}F]-fluoromisonidazole ([^{18}F]FMISO) is a radiolabeled imaging agent that has been used for investigating tumor hypoxia with positron emission tomography (PET). [^{18}F] decays by positron emission. FMISO binds covalently to cellular molecules at rates that are inversely proportional to intracellular oxygen concentration. In hypoxic cells, FMISO is trapped, which is the basis for the use of this tracer to measure hypoxia. Because tissue oxygenation may serve as a marker of perfusion, response to radiotherapy and chemotherapy, tumor grade, and prognosis, development of a PET imaging agent for tumor hypoxia is a potentially valuable avenue of investigation.

Positron emission tomography (PET) is a quantitative tomographic imaging technique, which produces cross-sectional images that are composites of volume elements (voxels). In PET images, the signal intensity in each voxel is dependent upon the concentration of the radionuclide within the target tissue (e.g., organ, tumor) volume. To obtain PET imaging data, the patient is placed in a circumferential detector array.

Patients undergo two separate components in a typical PET imaging procedure. One component is a transmission scan via a germanium rod source or, in the case of PET-CT, by CT imaging of the body region(s) of interest. The second component of the study is the emission scan which can be a dynamic imaging acquisition over a specific area of interest, or multiple acquisitions over the whole body. The typical PET study takes about 20 minutes to 2 hours to perform depending upon the nature of the acquisitions and the areas of the body that are imaged.

The [^{18}F]FMISO radiotracer (≤ 10 mCi) is administered by intravenous injection. Imaging can commence immediately upon injection for a fully quantitative study over one area of the body. More often only a static image is acquired for a 20-minute interval beginning between 100 and 150 minutes post injection.

4. General Investigational Plan

[^{18}F]FMISO is an azomycin-based hypoxic cell sensitizer that has a nearly ideal partition coefficient and, when reduced by hypoxia, binds covalently to cellular molecules at rates that are inversely proportional to intracellular oxygen concentration, rather than by any downstream biochemical interactions. We plan to study cellular level hypoxia in the brain as well as in the body, specifically in liver utilizing [^{18}F]FMISO PET-CT. An initial specific protocol is included in Section 6 of this IND application. As protocols are developed and submitted to the Emory IRB, these protocols will be submitted to the FDA as an amendment to this IND.

5. Investigator's Brochure

Included as attachment 1

6. Protocols

6a. Study protocol. Tumor Hypoxia Imaging in Support of Radiofrequency Ablation (RFA) Success Prediction (RASP) Study for Metastatic Colorectal Liver Lesions

Location of Study: Subject evaluation and PET imaging will be performed at Emory University Hospital in Atlanta, GA.
Estimated Duration: 5 Years
Maximum Number of Subjects: 50. No controls.
Clinical Uses: Metastatic Colorectal Liver Cancer.
Characteristics of Subjects: All ages over 18. Male and Female. All Performance Levels.

Description of the project
The goal of this research is to investigate the biomarker of tumor hypoxia utilizing the PET radiotracer of F-18 fluoromisonidazole (FMISO) in oncologic patients. The study will include patients with metastatic colorectal liver cancer with correlative investigations in tumor markers of hypoxia.

F-18 FMISO PET is known to correlate with hypoxia in tumors of the head and neck. The role of F-18 FMISO PET in imaging hypoxia in primary and metastatic liver disease has not been established. Our hypothesis is that F-18 FMISO PET will correlate with tumor hypoxia in patients with metastatic colorectal liver lesions as a biomarker to predict ultimate complete response to RFA.

Study aims are:
1. To investigate F-18 FMISO PET imaging for metastatic colorectal liver cancer and correlate to conventional F-18 FDG PET-CT.
2. To investigate F-18 FMISO PET imaging for metastatic colorectal liver cancer and correlate uptake parameters to ultimate response to radiofrequency ablation as measured with conventional imaging and clinical parameters.

Impact of research, including significance and probability of success
Hypoxia is known to contribute to resistance to chemotherapy and radiation. The relationship of hypoxia to resistance to radiofrequency ablation techniques has not been studied. In preclinical models, antiangiogenic molecularly targeted therapies and image-guided targeted therapy can inhibit tumor growth and normalize tumor vascularity, leading to decreased hypoxia. Currently there is no proven in-vivo imaging biomarker for tumor hypoxia. Advanced conventional imaging method such as DCE-MR is an indirect marker of tumor perfusion and/or capillary permeability but not proven for tumor hypoxia. Imaging hypoxia in liver tumors will allow for development of a biomarker for anti-angiogenic therapy and will facilitate planing external and selective intra-arterial radiotherapy and/or modify current RFA techniques to target areas of resistance due to hypoxia.
Successful accomplishment of the stated goals will also lay the grounds for future:
a. Application of F-18 MISO as biomarker in other primary and metastatic liver cancers
b. Application of F-18 MISO as biomarker in non-liver solid organ cancers
c. Application of F-18 MISO as adjuvant to planing loco-regional therapy to account for areas of potential resistance due to hypoxia.

Experimental Approach and Methods:

Patient Selection

Recruitment: All patients will be recruited form the Interventional Radiology Clinic of Dr. Kevin Kim at Emory University Hospitals.

Inclusion Criteria

- Patient with histologically confirmed metastatic colorectal carcinoma to liver eligible for RFA therapy.
- Two weeks or greater since biopsy
- Ability to lie still for up to 30 minutes for PET scanning
- Age >18
- Willingness to provide written informed consent
- Negative serum or urine pregnancy test within 24 hours

Exclusion Criteria

- Not meeting above criteria

Procedures for Screening and Enrollment

Written informed consent will be obtained before subject participation in the study. No procedures will be performed before written informed consent is obtained. Participants will be assigned an identification number for screening purposes; data collected during the screening process will be recorded using that number.

A screening visit will take place not more than 6 weeks before imaging. The following procedures will be performed at visit 1:

- Obtain written informed consent
- Inclusion/exclusion criteria review
- Vital signs measurements
- Medication history review
- Pregnancy based on serum or urine pregnancy test obtained within 24 hours prior to injection of F-18 FMISO.

F-18 FMISO injection and imaging session activities

The following procedures will be performed during F-18 FMISO injection and imaging visits:

- Baseline vital signs (record TPR & BP) before the start of F-18 FMISO infusion
- F-18 FMISO, (0.1 mCi/kg) (maximum 370 MBq, 10 mCi) injected intravenously with PET/CT imaging as detailed below
- Adverse event inquiry
- Baseline vital signs (record TPR & BP) immediately following imaging study

Follow-up Telephone contact

A telephone contact one day post the last imaging session will be made to assess for any adverse events.

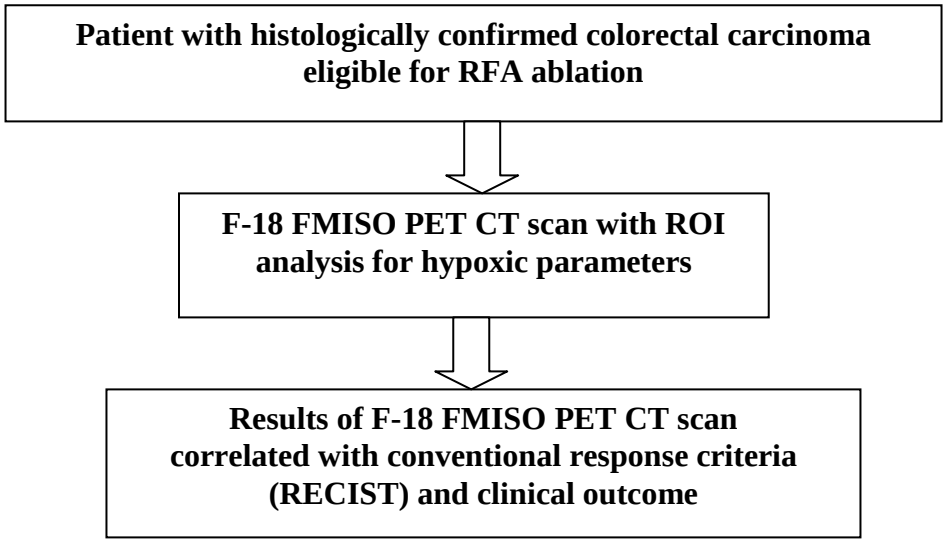
Study Activities and Visits

Visit 1- Consenting, enrollment, and baseline assessments, imaging session- bolus infusion and serial whole body imaging
Visit 2- Phone contact 1 day after injection

Safety Assessments

Safety will be evaluated by the following:
Adverse events
Vital signs performed at pre-injection baseline and immediately after the imaging study.
Phone contact 1 day after injection

Schema:



Imaging Procedures

F-18 FMISO PET Production: The radiotracer will be produce under contract with Cardinal Health, a commercial radiopharmacy. DMF and LOA attached in application.

FMISO-PET/CT:18F-fluoromisonidazole at a dose of 3.7 MBq/kg (0.1 mCi/kg) (maximum 370 MBq, 10 mCi) will be injected IV. The patient will be imaged on a state of the art PET-CT scanner (GE MV690, GE MV600, GE DST, Siemens Biograph 40). A low-dose CT scan without contrast for the PET/CT will be performed for attenuation correction and anatomic correlation. Emission acquisition typically encompassing 1-2 table positions to image the entire liver will begin 110 ± 10 minutes after FMISO injection. Participants will be imaged in the supine position.

Scans will be corrected for randoms, scatter using the models implemented by the supplied GE PET software, and attenuation as estimated by the CT image. Data will be reconstructed using the manufacturer provided order subset estimation maximization (OSEM) algorithm with no applied decay correction. Image analysis will be performed with software developed by the authors running on a GE AW or MimVista workstation.

Data Analysis

A 3-dimensional region of interest (ROI) will be defined on the FMISO-PET/CT scan as correlated with the already acquired standard of care contrast CT and/or FDG PET the candidate RFA lesions in each liver lobe. SUVmax, total lesion activity, and uptake volume will be determined for each index lesion. SUVmean will also be determined from a representative uninvolved region of each lobe of the liver as well as aorta. The ratios of SUVmax/liver SUVmean, SUVmax/blood pool SUVmean, hypoxic volume/total anatomic volume, and hypoxic volume/metabolic FDG volume will also be calculated. These parameters will be recorded and used to determine changes between baseline and follow-up in terms of various hypoxic parameters for index lesions, but also to correlate with RECIST response criteria, and ultimately patient outcome.

Description of Case Report Form:
Case report form will include standard patient demographics including name, age, sex, medical record number, history, pathologic proof, and results of other imaging including but not limited to CT, MR and FDG PET. All RFA candidate lesions in each lobe will be identified on the CRF. These will have recorded: SUVmax, total lesion activity, and uptake volume. Total anatomic volume of each lobe will be recorded. Metabolic FDG volume from each index lesion (from separate FDG PET study) will also be recorded on this form. Background structures will also have SUVmax and SUVmean recorded including uninvolved region of each lobe of the liver as well as aorta.

Radiation Methodology

The use of F-18 as a radioactive tracer is ideal for imaging with nuclear medicine cameras for PET imaging. F-18 is a safe, routinely used agent for cancer (2-FDG) scanning; it has a relatively short half-life (110 minutes) and is associated with low levels of radiation exposure to the subject. Several F-18 radiopharmaceutical are in clinical use for diagnostic nuclear medicine studies in the US and Europe. Whole-body F-18 imaging is a safe procedure. Patients must remain still during the scan, but most state-of-the-art imaging systems are designed to reduce head motion and patient discomfort.

Potential Risks and Benefits

Risks: Toxic pharmacologic effects of F-18 FMISO PET CT scan are not anticipated given that it has been widely studied with no reported adverse events. The radiopharmaceutical will produced by Cardinal Health, a commercial radiopharmacy. Rigorous testing will ensure radiochemical purity, quality, identity, sterility, and lack of pyrogenicity prior to administration.

Consent: Informed consent will be obtained from all subjects. A copy of the consent has been attached to this application. The consent will be obtained by one of the study staff after the research protocol and the risk of participating in the study have been fully explained. This consent will be obtained prior to enrolling any of the subjects in the study. A copy of the consent form will be provided to all subjects.

Potential Benefits: There are no benefits that a healthy subject could have from entering this study

Statistical Analysis

Standard statistical analysis will be performed including but not limited to T testing, ANOVA and other tests of statistical variance by one of two Radiology Department statisticians.

Adverse Event Reporting

Any patient death that may be due to the study procedure (i.e. severe radiotracer reaction), unanticipated problem, or protocol deviation/non-compliance would be promptly reported to the Emory IRB office. Additionally any patient death not associated with the study procedure or serious anticipated event (i.e. radiotracer allergy) will be reported to the Emory IRB and FDA upon continuing review. This radiotracer will be studied under IND with FDA guidance. No serious adverse events have been reported per the attached IB.

Data and Safety Monitoring Plan (DSMP):

Patients will be monitored by the technologists and study nurse before and after the studies for any adverse events/reactions. They will be given contact phone numbers to call if they experience any problems (i.e. problems with the IV site, any allergic reaction symptoms). They will be followed routinely by their referring physician with clinical exams, and the PI will work with the co-investigators and referring physicians to ensure that the patients continue to follow up as scheduled.

Any serious adverse events (see above) will be communicated by the PI to the Emory IRB using standard adverse event reporting forms. A data safety monitoring board is not necessary.

6b. Investigator Data

Included as attachment 2. FDA Form 1572.

6c. Facilities Data

Included as Attachment 2. FDA Form 1572.

6d. Institutional Review Board Data

Included as Attachment 2. FDA Form 1572.

7. Chemistry, manufacturing, and control data

The radiotracer will be obtained from Cardinal Health under LOA attached (Attachment 3).

8. Pharmacology and Toxicity data.

This section is incorporated by reference from the NCI IND # 70,005 and a letter of authorization is included as an attachment. (Attachment 4).

9. Previous Human Experience with the Investigational Agent

This section is incorporated by reference from the NCI IND # 70,005 and a letter of authorization is included as an attachment. (Attachment 4).

10. Additional Information

This section is incorporated by reference from the NCI IND # 70,005 and a letter of authorization is included as an attachment. (Attachment 4).

11. Attachments

The following lists the attachments to this IND application:

1) Investigator's Brochure
2) FDA Form 1572 with Full Clinical Protocol and Consent Form
3) Cardinal Health DMF and LOA
4) LOA referencing NIH IND

ATTACHMENT 1

Investigator's Brochure

INVESTIGATOR'S BROCHURE For:

[^{18}F]FLUOROMISONIDAZOLE, 1H-1-(3-[^{18}F]-FLUORO-2-HYDROXY-PROPYL)-2-NITRO-IMIDAZOLE, [^{18}F]FMISO

AN INVESTIGATIONAL POSITRON EMISSION TOMOGRAPHY (PET) RADIOPHARMACEUTICAL FOR INJECTION AND INTENDED FOR USE AS AN IN VIVO DIAGNOSTIC FOR IMAGING HYPOXIA IN TUMORS.

Investigational New Drug (IND) Application

Referenced IND # 76,042

David M Schuster, MD
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Department of Radiology and Imaging Sciences
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Atlanta, GA 30322
404-712-4859
Fax: 404-712-4860
dschust@emory.edu

Edition Number: 4
Approval Date: 11/09/2009

TABLE OF TABLES

TABLE OF FIGURES

II. [^{18}F]FMISO PRODUCT AGENT DESCRIPTION

1. AGENT DESCRIPTION

Fluorine-18 labeled misonidazole, 1H-1-(3-[^{18}F]-fluoro-2-hydroxy-propyl)-2-nitro-imidazole, or [^{18}F]FMISO, is a radiolabeled imaging agent that has been used for investigating tumor hypoxia with positron emission tomography (PET). The University of Washington pioneered the development and biodistribution evaluation of [^{18}F]FMISO. An ideal hypoxia-imaging agent should distribute independently of blood flow, which is best achieved when the partition coefficient of the tracer is close to unity. Under these circumstances, imaging can be done at a time when the intracellular tracer distribution has equilibrated with the tracer in plasma near the cells. [^{18}F]FMISO is an azomycin-based hypoxic cell sensitizer that has a nearly ideal partition coefficient and, when reduced by hypoxia, binds covalently to cellular molecules at rates that are inversely proportional to intracellular oxygen concentration, rather than by any downstream biochemical interactions.[1]

2. CHEMICAL STRUCTURE

[^{18}F]FMISO has not been marketed in the United States and, to the best of our knowledge, there has been no marketing experience with this drug in other countries. The radiopharmaceutical product, [^{18}F]FMISO is the only active ingredient and it is dissolved in a solution of ≤10 mL of 95% isotonic saline 5% ethanol (v:v). The drug solution is stored in at room temperature in a gray butyl septum sealed, sterile, pyrogen-free glass vial with an expiration time of 12 hours. The injectable dose of [^{18}F]FMISO for most studies will be ≤ 10 mCi of radioactive ^{18}F at a specific activity of greater than 125 Ci/mmol at the time of injection. In the dose of [^{18}F]FMISO only a small fraction of the FMISO molecules are radioactive. The amount of injected drug is ≤ 15 µg (≤ 80 nmol per dose) of FMISO. [^{18}F]FMISO is administered to subjects by intravenous injection of ≤ 10 mL.

There is no evidence that nonradioactive and radioactive FMISO molecules display different biochemical behavior.

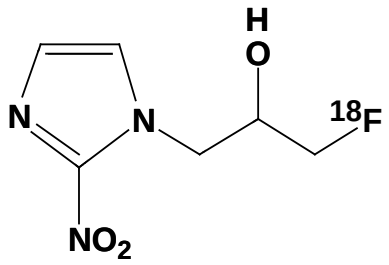

Figure 1. The chemical structure of [^{18}F]-fluoromisonidazole
1H-1-(3-[^{18}F]-fluoro-2-hydroxy-propyl)-2-nitro-imidazole

3. FINAL PRODUCT SPECIFICATIONS

The name of the drug is 1H-1-(3-[^{18}F]-fluoro-2-hydroxy-propyl)-2-nitro-imidazole, or [^{18}F]-fluoromisonidazole, ([^{18}F]FMISO). FMISO is the only active ingredient and it is formulated in a solution of ≤10 mL of 95% 0.15 M saline: 5% ethanol (v:v). The drug product is stored at room temperature in a gray butyl septum sealed, sterile, pyrogen-free glass vial with an expiration time of 12 hours. The injectable dose of [^{18}F]FMISO is ≤ 0.10 mCi/kg not to exceed 10 mCi with a specific activity greater than 125 Ci/mmol at the time of injection. The amount of injected drug is ≤ 15 μg (≤ 80 nmol) of FMISO. [^{18}F]FMISO is administered to subjects by intravenous injection of ≤10 mL. In the dose of [^{18}F]FMISO, only a small fraction of the FMISO molecules are radioactive. There is no evidence that nonradioactive and radioactive FMISO molecules display different biochemical behavior.

The product components are listed in Table 1, the impurities in Table 2, and the final product specifications in Table 3

Table 1. Final Product Components per single injected dose

COMPONENTS	Characterization	Amount in Injectate
[^{18}F]FMISO, 1H-1-(3-[^{18}F]-fluoro-2-hydroxy-propyl)-2-nitro-imidazole	Same as for [^{19}F]FMISO	≤ 10 mCi
[^{19}F]FMISO, 1H-1-(3-[^{19}F]-fluoro-2-hydroxy-propyl)-2-nitro-imidazole	NCS#292930	≤ 15 μg
Ethanol, absolute	USP	5% by volume
Saline for injection	USP	0.15 M

Table 2. Final Product Impurities per single injected dose

IMPURITIES	Acceptance Criteria	Highest Values in 9 Qualification Runs
Kryptofix® [2.2.2]	< 50 μg/mL	None detected
Acetonitrile	< 400 ppm	< 50 ppm
Acetone	< 5000 ppm	< 313 ppm
Other UV absorbing impurities	≤ 35 μg	4.9 μg (1 hr post synthesis)

Table 3. Final Product Specifications

TEST	SPECIFICATION
Chemical Purity (particulates)	Clear and Colorless
pH	6-8
Residual Kryptofix® [2.2.2]	< 50 µg/ mL Kryptofix®
Radiochemical Purity (HPLC)	> 95%
Chemical Purity (HPLC)	FMISO ≤ 15 µg per injected dose
	≤ 35 µg per dose other UV absorbing impurities eluted >3 min (327, 280 or 254 nm)
Radiochemical Purity (TLC)	R_f = >0.5 Purity ≥ 95%
Residual Solvent Levels	Acetone < 5000 ppm Acetonitrile < 400 ppm
Radionuclidic Purity	Measured half-life 100-120 minutes
Bacterial Endotoxin Levels	< 175 EU per dose
Sterility	no growth observed in 14 days , must also pass filter integrity test

III. INTRODUCTION

[^{18}F]-fluoromisonidazole ([^{18}F]FMISO) is a radiolabeled imaging agent that has been used for investigating tumor hypoxia with positron emission tomography (PET). [^{18}F] decays by positron emission. FMISO binds covalently to cellular molecules at rates that are inversely proportional to intracellular oxygen concentration. In hypoxic cells, FMISO is trapped, which is the basis for the use of this tracer to measure hypoxia. Because tissue oxygenation may serve as a marker of perfusion, response to radiotherapy and chemotherapy, tumor grade, and prognosis, development of a PET imaging agent for tumor hypoxia is a potentially valuable avenue of investigation.

Positron emission tomography (PET) is a quantitative tomographic imaging technique, which produces cross-sectional images that are composites of volume elements (voxels). In PET images, the signal intensity in each voxel is dependent upon the concentration of the radionuclide within the target tissue (e.g., organ, tumor) volume. To obtain PET imaging data, the patient is placed in a circumferential detector array.

Patients undergo two separate components in a typical PET imaging procedure. One component is a transmission scan via a germanium rod source or, in the case of PET-CT, by CT imaging of the body region(s) of interest. The second component of the study is the emission scan which can be a dynamic imaging acquisition over a specific area of interest, or multiple acquisitions over the whole body. The typical PET study takes about 20 minutes to 2 hours to perform depending upon the nature of the acquisitions and the areas of the body that are imaged.

The [^{18}F]FMISO radiotracer (≤ 10 mCi) is administered by intravenous injection. Imaging can commence immediately upon injection for a fully quantitative study over one area of the body. More often only a static image is acquired for a 20-minute interval beginning between 100 and 150 minutes post injection.

IV. PHARMACOLOGY

1. PHYSICAL CHARACTERISTICS

Fluoromisonidazole is a small, water-soluble molecule with a molecular weight of 189.14 Daltons. It has an octanol:water partition coefficient of 0.41, so that it would be expected to reflect plasma flow as an inert, freely-diffusible tracer immediately after injection, but later images should reflect its tissue partition coefficient in normoxic tissues.

2. MECHANISM OF ACTION

[^{18}F]FMISO is an azomycin-based hypoxic cell sensitizer that has a nearly ideal partition coefficient and, when reduced by hypoxia, binds covalently to cellular molecules at rates that are inversely proportional to intracellular oxygen concentration, rather than by any downstream biochemical interactions[1]. The covalent binding of nitroimidazoles is due to bioreductive alkylation based on reduction of the molecule through a series of 1-electron steps in the absence of oxygen[2]. Products of the hydroxylamine, the 2-electron reduction product, bind stably in cells to macromolecules such as DNA, RNA, and proteins. In the presence of oxygen, a futile cycle results in which the first 1-electron reduction product, the nitro radical anion, is re-oxidized to the parent nitroimidazole, with simultaneous production of an oxygen radical anion. FMISO is not trapped in necrotic tissue because mitochondrial electron transport is absent. The normal route of elimination for FMISO is renal. A small fraction of [^{18}F]FMISO is glucuronidated and excreted through the kidneys as the conjugate.

V. TOXICOLOGY AND SAFETY

1. MECHANISM OF ACTION FOR TOXICITY

Therapeutic Implications of Hypoxia. Tumor physiology differs from that of normal tissue in several significant ways. Circumstances within tumor tissue can result in hypoxia when growth outpaces angiogenesis or when the oxygen demands of accelerated cellular proliferation exceed local oxygen concentrations. Because hypoxia increases tumor radioresistance, it is important to identify patients whose disease poses this risk for therapeutic failure, lest hypoxic cells survive radiotherapy while retaining their potential to proliferate[3,4]. The selectivity of nitroimidazoles for hypoxic conditions has been demonstrated in rat myocytes[5,6], the gerbil stroke model[7,8], pig livers[9,10], rat

livers[11,12] and dog myocardium[13,14], as well as numerous cancer studies in cell cultures, animals and human trials[15,16].

The mechanism of action of FMISO is common to all nitroimidazoles and is based on the chemical reduction that takes place in hypoxic tissue, covalently binding the chemical to macromolecules in that tissue. The specificity of the reaction is enhanced by the fact that both the reduction and the binding occur within the same cell[17,18]. The reduction reaction, depicted in Figure 2, is reversible at the first step, depending upon the oxygenation status of the tissue, so that some FMISO eventually returns to the circulation and is excreted[19]. The reduction of the nitro group on the imidazole ring is accomplished by tissue nitroreductases that appear to be plentiful and therefore do not represent a rate-limiting factor[1]. The 1-electron reduction product (labeled as "II" in Figure 2) may be further reduced to "III" or it may competitively transfer its extra electron to O_2 and thus reform "I." This binding takes place at a rate that is inversely related to cellular oxygen concentration[6].

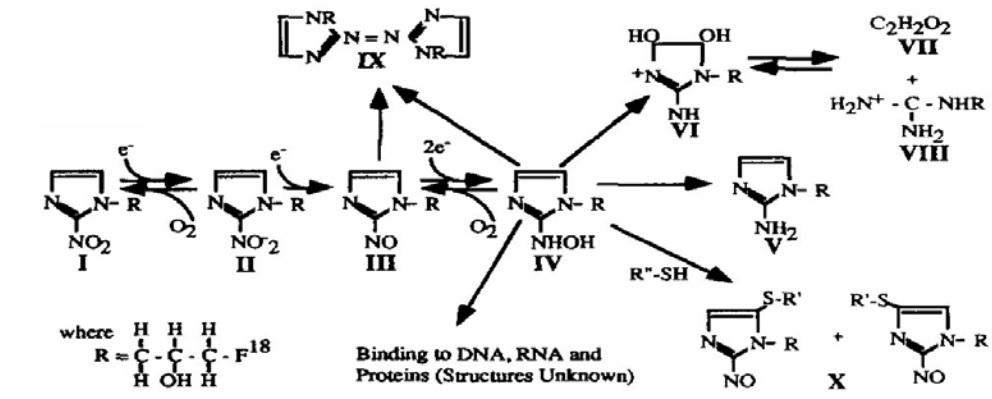

Figure 2. Metabolism of 2-nitroimidazoles.
See text (above figure) for further details

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Nitroimidazoles bind to hypoxic tissue, serving as hypoxia markers. They potentiate the cytotoxic effects of some chemotherapeutic agents such as the nitrosoureas, melphelan and cyclophosphamide[20,21]. Identifying hypoxic tissue has therapeutic implications for multiple disease states including stroke, myocardial ischemia, and is of particular value in cancer radiotherapy, as hypoxic cancer tissue is relatively radioresistant[22]. These chemical properties suggested the possibility of clinically imaging hypoxic tissue in vivo. Misonidazole, or a related compound, could be labeled with a radioisotope, and could bind to oxygen-deprived cells covalently, providing a positive image of hypoxia via PET. Fluoromisonidazole (Figure 1) has several properties that make it a potentially useful imaging agent. In contrast to the prototype molecule, misonidazole, FMISO can be labeled at the end of the alkyl side chain with ^{18}F, a positron emitter with a 110 minute half-life[23,24]. Fluorine-carbon bonds are highly stable and so the radioactive ^{18}F would be expected to remain on the molecule of interest.

MISO and fluoromisonidazole (FMISO) are 2-nitroimidazoles with nearly identical octanol:water partition coefficients, making them sufficiently lipophilic that they readily diffuse across cell membranes and into tissues[25], yet maintain a volume of distribution essentially equal to total body water[26]. They are less than 5% protein bound, allowing efficient transport from blood into tissues[17]. The distribution kinetics of 2-nitroimidazoles fit a linear two-compartment open model, except that high plasma concentrations after therapeutic level (gram) injections appear to saturate elimination processes in both mice and humans and proceed to non-linear kinetics.

Metabolism and Elimination. *In vitro,* MISO can be reduced using zinc, iron in HCl, xanthine oxidase and NADH[1]. In HeLa and CHO (hamster ovary) cells, reduction appears only under hypoxic conditions. Comparison with MISO indicates that the reduction reaction is similar, but slightly slower for FMISO[1]. FMISO achieves higher tumor:blood and tumor:muscle concentration ratios than MISO in murine tumors[27].

In vivo, under normal oxygen tension, MISO is metabolized primarily in the liver to its demethylated form but FMISO is not a substrate for this reaction. Additionally, ~7% (in humans) to ~14% (in mice) is conjugated to glucuronide, and small amounts (<5%) are converted to aminoimidazole. Substantial amounts of MISO are recoverable in feces. Fecal bacteria are able to reduce misonidazole only in the absence of oxygen. At treatment level dosing, the plasma half-lives of both FMISO and MISO range from 8 – 17.5 hours[28]. Parent molecule and glucuronide metabolites are primarily excreted in the urine[29,30,31].

FMISO Mouse Studies. Biodistribution studies in mice have used different transplanted tumors and compared [^{3}H]FMISO with the [^{18}F]FMISO. The only normal organs with significant uptake were those associated with nitroimidazole metabolism and excretion, i.e. liver and kidney. Mice bearing a variety of tumors of different sizes received a single injection of [^{3}H]FMISO and were sacrificed at 4 hr[32]. The results are shown in Table 4. For small KHT tumors, the tumor to blood ratios (T:B) of 2.3-2.9 were sufficiently high to allow tumor detection with imaging. Larger KHT tumors, with a reported hypoxic fraction >30%, had higher T:B ratios. RIF1 tumors in C3H mice have a hypoxic fraction of ~1.5% and had the lowest tumor:blood ratios: 1.7-1.9. This correlation between T:B ratios and hypoxic fraction was encouraging, but did not hold true across all tumor types. C3HBA mammary adenocarcinomas of the same size as the RIF1 and small KHT tumors, had hypoxic fractions of 3-12%, but had the highest T:B ratios, 4.0-4.7. Within tumor type, increasing hypoxia was associated with increased uptake of labeled FMISO, but comparisons across tumor types were more difficult, perhaps because of heterogeneity within the tumors.

Table 4. Biodistribution of [^{3}H]fluoromisonidazole in C3H mice32

Tumor	Drug dose	Tumor: Blood ratios	Tumor volumes. mm^{3*}	Estimated hypoxic fraction$^+$
KHT	5 mmol/kg	2.41	175 ± 16	7-12%
KHT	5 mmol/kg	2.29	110 ± 25	
KHT	20 mmol/kg	2.76	159 ± 39	
KHT	20 mmol/kg	2.86	123 ± 37	
KHT	5 mmol/kg	5.58	580 ± 26	>30%
KHT	5 mmol/kg	8.34	574 ± 66	
RIF1	5 mmol/kg	1.69	158 ± 23	~1.5%
RIF1	20 mmol/kg	1.76	159 ± 15	
RIF1	20 mmol/kg	1.86	136 ± 37	
C3HBA	5 mmol/kg	4.66	101 ± 13	3-12%
C3HBA	5 mmol/kg	3.96	137 ± 37	

* Tumor volumes are mean ± standard deviation for 5 tumors/group. Animals sacrificed at 4 hr.
+ Hypoxic fractions are taken from[33] for tumors of comparable size.

In individual KHT tumors or RIF1 tumors, there was no correlation between regional flow and regional FMISO retention at 4 hr after tracer injection. The r^2-values for KHT and RIF1 tumors were 0.0 and 0.05, respectively. Regional blood flow did not correlate with FMISO retention in normal tissues that retained high levels of FMISO, specifically in liver (a principal site of nitroimidazole metabolism) and kidney (the main route of excretion) nor in tissues such as muscle and brain.

The mouse biodistribution studies described above provided useful information about relative tumor FMISO distribution at a single time post-injection and demonstrated T:B ratios adequate for PET imaging. Tumor bearing rats have also been imaged dynamically to provide biodistribution data for all tissues after sacrifice. The well-characterized 36B10 transplantable rat glioma was grown subcutaneously in Fischer rats[34] to obtain time activity data for tumors and blood up to 2 hr after FMISO injection. These studies showed that tumors steadily accumulated [^{3}H]FMISO activity that exceeded levels in blood after ~20 min.

Dogs with spontaneous osteosarcomas, a tumor that is frequently radio-resistant, have also been imaged after injection of [^{18}F]FMISO. These images allowed the investigator to draw regions of interest around tumor and normal tissue in each imaging plane. Timed blood samples were also drawn and plasma was counted in a gamma well so that, after decay correction, imaging and blood data could be converted to units of μCi/g. Blood time activity curves for dogs were similar when presented in comparable

units[32]. Time activity curves for blood, muscle and for a region from a forelimb osteosarcoma in one dog are shown in Figure 3.

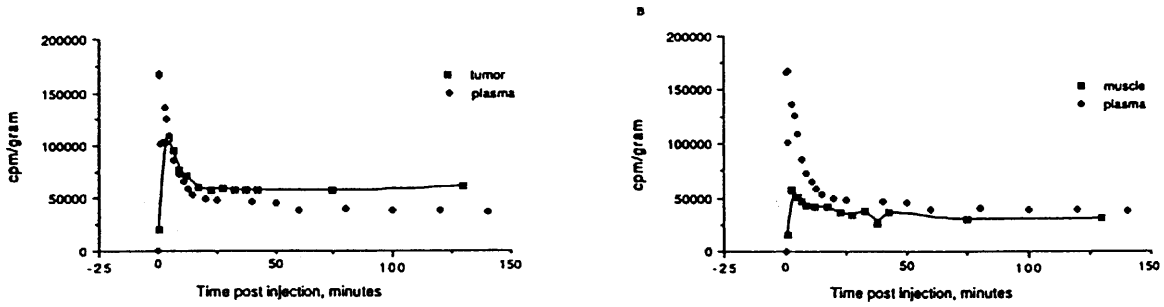

Figure 3. FMISO blood and tissue clearance curves in a dog with osteosarcoma

Muscle equilibrated with blood after 60 min, while the selected tumor region continued to accumulate FMISO above blood levels. The mean plasma half-time, calculated from five dogs, was 284±20 min for the slow component. The dog studies showed marked regional variation in FMISO uptake. These imaging studies with dogs confirmed the feasibility of imaging and suggested that multi-plane images in individual tumors would be necessary to assess regional variation in tumor hypoxia.

2. FMISO CELL TOXICITY STUDIES

Early studies evaluating the biological behavior of FMISO used several model systems with varying levels of complexity. The studies performed *in vitro* employed cells in monolayer cultures and multi-cellular spheroids. Multicellular spheroids are aggregates of cells that grow in culture and mimic small nodular tumors. Cell uptake and distribution studies in spheroids were done using [^{3}H]FMISO[35].

The *in vitro* studies of tumor cells and rodent fibroblasts measured the O_2-dependency of FMISO uptake and the time course of uptake at O_2 levels approaching anoxia. Uptake of FMISO by cells growing in monolayer cultures depended strongly on oxygen concentration, with maximum uptake under anoxic conditions and a decrease to 50% of maximum binding at levels between 700 to 2300 ppm in several different cell lines (Table 4a). The O_2-dependency of binding was a mirror image of the curve for sensitization to radiation by O_2, an advantageous characteristic for a hypoxia tracer intended to assess radiobiologically significant levels of hypoxia.

Table 5. Inhibition of [^{3}H]FMISO Binding by Oxygen *in vitro*[36]

Cell Line	O_2 concentration to inhibit binding by 50% (ppm)
RIF1	720
V79	1400
EMT6	1500
CaOs1	2300

Uptake of FMISO by multi-cellular spheroids provided visual and quantitative measures of hypoxia. Autoradiographs of 0.8 mm V79 spheroids after 4 hr incubation with [^{3}H]FMISO revealed heavily labeled cells in an intermediate zone between the well oxygenated periphery and the necrotic center. Uptake in anoxic spheroids matched that in anoxic monolayer cultures; oxygenated spheroids did not accumulate tracer, and hypoxic spheroids had intermediate uptake.

Whitmore et al. performed preliminary toxicity studies on MISO using Chinese hamster ovary cells [37]. Uncharacterized toxic products suspected of being either nitroso or hydroxylamine derivatives formed only under hypoxic conditions and were capable of sensitizing both hypoxic and aerobic cells to the damaging effects of radiation. These products have been further characterized by Flockhart and are differently distributed depending upon the species. In humans the demethylated molecule never exceeds 10% of the total MISO, and the amine never exceeds 2% in extracellular fluid[31]. The demethylation reaction is not possible with FMISO, which lacks a methoxy substituent.

3. ANIMAL TOXICITY STUDIES: MISO and FMISO

The literature provides a few animal studies of the toxicity of nitroimidazoles. The octanol/water partition coefficients for MISO and FMISO are 0.43 and 0.41, respectively; the LD50's in adult male Balb/C mice for MISO and FMISO are 1.8 mg/g (1.3-2.6) and 0.9 mg/g, respectively[38]. The serum half-lives of orally administered MISO and FMISO in mice were 2.3 hrs (range 1.87-2.92) and 2.0 hrs (range 1.79-2.24), respectively. A subsequent study of LD50's in 21 to 32 g, nine-month old, female C3H/HeJ mice gave toxicities of 0.62 to 0.64 mg/g for FMISO[39]. The long component of the plasma half-life of FMISO in humans is similar to MISO (8-17 hrs). FMISO is cleared primarily through the kidneys. Its volume of distribution is large, approximating that of total body water. Favorable tumor-to-normal tissue ratios for imaging are obtained at low doses of administered drug. These ratios were obtained in 15 kg dogs with a dose of 1 mg/kg.

After oral dosing exceeding a schedule-dependent cumulative threshold, misonidazole induces a peripheral neuropathy in humans, although such dosing far exceeds the PET imaging dose requirements. Because FMISO will be administered intravenously, the neurotoxicity of intravenous administration was evaluated in rats using a battery of routine clinical, neurofunctional, biochemical, and histopathologic screening methods[40]. Male Sprague-Dawley rats were administered intravenous doses of misonidazole at 0

(vehicle control), 100, 200, 300, or 400 mg/kg daily for 5 days per week for 2 weeks. Animals were evaluated for functional and pathological changes following termination of treatment and at the end of 4 weeks. During the dosing phase, hypoactivity, salivation, rhinorrhea, chromodacryorrhea, rough pelage and ataxia were observed at 400 mg/kg and body weight gain of the 300 and 400 mg/kg groups was significantly decreased relative to the vehicle controls (24% and 49% respectively) and related to reductions in food consumption of 8% and 23%. Although most 400 mg/kg animals appeared normal immediately after the dosing regimen, rotorod testing precipitated a number of clinical signs including: ataxia, impaired righting reflex, excessive rearing, tremors, vocalization, circling, head jerking, excessive sniffing and hyperactivity. All animals recovered and appeared normal through study termination. There were no treatment-related effects on motor activity, acoustic startle response, rotorod performance, forelimb group strength, toe and tail pinch reflexes, tibial nerve beta-glucuronidase activity or tail nerve conduction velocity. No microscopic changes were detected in peripheral nerves. Necrosis and gliosis were seen in the cerebellum and medulla of the 400 mg/kg animals after treatment and gliosis in these same brain regions was observed in the 300 and 400 mg/kg groups at a month after dosing. These results show that intravenous administration of misonidazole to rats causes dose-limiting central nervous system toxicity without effects on peripheral nervous tissue.

4. HUMAN TOXICITY STUDIES: MISO

Human studies of nitroimidazoles date back to the 1970's when several nitroimidazole derivatives were tested as oxygen mimetics in clinical research trials involving tumors that were presumed to be hypoxic. The goal was to sensitize them to cytotoxic levels of photon radiation so that they retained the beneficial 3-fold enhancement ratio characteristic of normoxic tissues[41,42,43]. Our knowledge of the toxic effects of 2-nitroimidazoles in humans is based principally on misonidazole, a close analog of fluoromisonidazole (Figure 1), and studies that used doses that were considered effective to enhance the cytotoxicity of radiotherapy. These human studies, no longer in progress, have been reviewed[44]. There have been no reported harmful effects until cumulative doses exceeded a few grams, which is vastly larger than the dosing required for PET imaging.

Gray reported preliminary human pharmacokinetic measurements using six healthy volunteers[45]. Subjects received single oral doses ranging from 1 g to 4 g. The peak serum level at 2 hours was 65 µg/mL and the drug serum half-life was 13.1 ± 4.0 hrs. A linear relationship was demonstrated between administered dose and serum level. Based on animal studies, a serum level of 100 µg/mL was considered necessary for effective radiosensitization and the oral dose calculated to achieve that serum level was 6.5 g. Single oral doses of 4-10 g were administered to 8 patients with advanced cancer and a life expectancy limited to 12 months. All patients experienced some degree of nausea, vomiting and anorexia for 24 hours. One of the eight had insomnia. At 10 g the nausea and vomiting were extreme, and the anorexia lasted for a week. Peak serum

levels were obtained between 1 and 3 hrs. The serum half-life ranged from 9-17 hrs with the median at 14 hrs.

Clinical studies employing multiple dosing of MISO have also been reported and peripheral neuropathy (PN) was the manifestation of toxicity that became dose limiting with daily doses of 3-5 g/m2. The results of a sequential dose reduction study46 are shown in Table 6:

Table 6. Clinical toxicity of misonidazole

Dose (g/m^2)	Doses/wk.	Weeks	Affected Patients	Total Patients	% Pts. with peripheral neuropathy
3-5	5	3	12	16	75
2	2	3	2	6	33
0.4-0.8	3-5	3-6	1	6	16

This data demonstrates the dose proportionality of the drug's primary toxicity during chronic administration at doses that far exceed those used in PET imaging. Limiting the total dose and giving no more than two doses in one week minimized toxicity.

Significantly lower peripheral neuropathic (PN) toxicity for therapeutic doses has been observed with weekly dosing schedules: 1 of 12 with PN at 1-2 g/m^2 for 6 weeks[47] and 0 of 10 at 3 g/m^2 for 4 weeks[48]. This is presumably due to the fact that the drug, which has a long serum half-life, is allowed to clear completely from the body. Dische had a similar experience, noting that calculations by surface area produce the most consistent correlation of oral dose to plasma level and that the maximum recommended safe dose was 12 g/m^2 over no less than 18 days[49]. Neuropathies were generally, but not always, reversible when the drug was discontinued.

There have been two fatalities attributed to the drug[50]. Both patients had advanced malignant disease and died in convulsions: One patient received 51 g in 6 fractions over 17 days, and the other patient received 16 g in 2 doses over 3 days.

The above data supports the conclusion that FMISO's primary toxicity is likely to be peripheral neuropathy, which is dependent upon frequency and dose level. There is no evidence to suggest that FMISO poses a risk for PN when administered as an imaging agent for PET as described herein. The risk for PN in fact appears to be minimized or absent even at therapeutic doses that far exceed those necessary for PET imaging.

5. [^{19}F]FMISO HUMAN TOXICITY

A search for articles dealing with the human toxicity of fluoromisonidazole (FMISO) yields no results. Therefore this assessment relies on animal studies and similarities among related chemical entities. The octanol/water partition coefficients for MISO and

FMISO are 0.43 and 0.41, respectively; the LD50's in adult male Balb/C mice for MISO and FMISO are 1.8 mg/g (1.3-2.6) and 0.9 mg/g, respectively[38] and in CH3 mice the LD50 is 0.6 mg/g for FMISO[39]. Using the relative toxicity factors from Paget (1965)[51] of 1.0 for mice and 9.8 for humans, the projected LD_{50} values are:

LD_{50} values	Misonidazole	Fluoromisonidazole
Concentration for human	0.184 g/kg	0.06-0.09 g/kg
Dose for 70 kg subject	12.86 g	6.43 g

The MISO values by this calculation are conservative when compared with the findings in early human trials (see Section 7, MISO Human Safety Studies). The serum half-lives of orally administered MISO and FMISO in mice were 2.3 hrs (range 1.87-2.92) and 2.0 hrs (range 1.79-2.24), respectively. The long component of the plasma half-life of FMISO in humans is similar to MISO (8-17 hrs). FMISO is cleared primarily through the kidneys.

The maximum dose to humans reported in imaging protocols was 1 mg/kg or 70 mg for a 70 kg subject; no adverse events have been reported. These studies are reported in Part VII. This is about 0.1% of the projected LD_{50}. Total patient imaging doses of the current radiopharmaceutical formulation contain ≤ 15 µg of fluoromisonidazole and less than 35 µg of other nitroimidazole derivatives. This is <0.001% of the projected LD50. The drug has had no toxic effects at these doses based upon a review of 5400 patients included in MISO studies[44] and over 269 patients studied with tracer doses of [^{18}F]FMISO, as summarized in this document (Section 9).

6. [^{18}F]FMISO HUMAN TOXICITY

Since the half-life of fluorine-18 is only 110 minutes, toxicity studies are not possible with the radiolabeled agent. The misonidazole data presented and the [^{19}F]FMISO calculations presented above in sections 4 and 5 should be the basis for both animal and human toxicity characterization and conclusions. The radiation dose associated with [^{18}F]FMISO is discussed separated in Part VI.

7. MISO HUMAN SAFETY STUDIES

Misonidazole for Therapy. In addition to their role as imaging agents, nitroimidazoles have been studied as therapeutic radiosensitizers (oxygen mimetics). These studies of over 7000 patients in 50 randomized trials have been reviewed[44]. Oral MISO was the agent in 40 of the trials involving about 5400 patients. The maximum doses used were 4 g/m^2 in a single dose and 12 g/m^2 as a total dose. The most common serious/dose limiting side effect was peripheral neuropathy with a latency period of several weeks.

The neuropathy was prolonged and, in some cases, irreversible. Nausea, vomiting, skin rashes, ototoxicity, flushing and malaise have also been reported at therapeutic dosing levels that vastly exceed imaging dose requirements. While these molecules are no longer used as clinical radiosensitizers, the results show the range of human experience with nitroimidazoles, and, in particular, support a reliable trend towards safety at imaging range dosing.

A 1978 study of oral misonidazole (MISO) as a radiosensitizing agent in human astrocytoma found good absorption, peak plasma levels between 1 and 4 hours and a half-life between 4.3 and 12.5 hours. Doses limited to 12 g/m^2 produced some nausea and vomiting but no serious side effects[48]. In an earlier study, Gray found a wide variation in tumor/plasma distribution ratios in six cases of advanced human metastatic breast cancers and soft tissue sarcomas[45]. The maximum dose in this study was 10 g, which caused a week of anorexia. Patients receiving up to 140 mg/kg tolerated the drug well.

8. [^{19}F]FMISO HUMAN SAFETY STUDIES

We are unaware of, nor did a literature search show, any human studies of [^{19}F]FMISO safety in humans beyond the carrier [^{19}F]-FMISO associated with the [^{18}F]FMISO human studies described below.

9. [^{18}F]FMISO HUMAN SAFETY STUDIES

[^{18}F]FMISO is a radiolabeled imaging agent that has been used for investigating tumor hypoxia with PET. It is composed of ≤ 15 µg of fluoromisonidazole labeled with ≤ 10 mCi of radioactive ^{18}F at a specific activity >1 Ci/mg at the time of injection. The drug is the only active ingredient and it is formulated in ≤ 10 mL of 5% ethanol in saline for intravenous injection. The radiochemical purity of the [^{18}F]FMISO is >95%.
Hypoxia imaging in cancer was reviewed in several recent publications[22,52,53,54].
[^{18}F]FMISO is a robust radiopharmaceutical useful in obtaining images to quantify hypoxia using PET imaging[55,56,57]. It is the most commonly used agent for PET imaging of tissue/tumor hypoxia[58,52,53,54,59,60,61].

Positron emission scanning with ^{18}F-FMISO has been studied over the past ten years in Australia, Switzerland, Denmark, Germany, China and in the United States under RDRC approval or its equivalent. Several published studies from the United States are from the University of Washington in Seattle. Since 1994 up to 4 injections of FMISO, each followed by a PET scan, have been performed in Seattle alone on approximately 300 patients; data have been published on over 133 of these. [^{18}F]FMISO has been used to image ischemic stroke, myocardial ischemia and a wide variety of malignancies. Although the papers listed in Table 8 total nearly 700 patients, we have taken a conservative approach in the text to reduce possible duplication. Nonetheless as many as 4 ^{18}F-FMISO injections and PET scans have been performed in over 600 different

patients represented in the published papers as listed in Part VII, Previous Human Experience. Administered doses ranged from approximately 3 to 30 mCi (100-1100 MBq). As would be expected based upon the above safety assessment of the agent when dosed and used for imaging, no adverse events have been attributed to ^{18}F-FMISO in any of these reports. One patient with advanced nasopharyngeal cancer experienced a Grade 3 febrile neutropenia and a Grade 1 mucositis and stomatitis that were definitely related to multiple chemotherapy agents and unrelated to FMISO.

10. FMISO GENOTOXICITY AND MUTAGENICITY

Multiple studies have found genetic transformations due to misonidazole and related nitroimidazoles using in vitro assays. The murine C3H/10T½ cell line (mouse embryo fibroblast) has a normal spontaneous transformation frequency of $<10^{-5}$ but these cells undergo oncogenic transformation in vitro when exposed to chemical and physical agents. The frequency of transformants with 3 days exposure to 1 mM drug was $2.27 \pm 0.38 \times 10^{-4}$ for FMISO and $4.55 \pm 0.95 \times 10^{-4}$ for misonidazole[62]. Although these values are about three to five times the background rate, this level of drug exposure would require about 10 grams of drug in a human. Imaging studies will inject ≤ 15 µg, or about 0.00015%.

FMISO and MISO were mutagenic when assayed by the AMES protocol using specific Salmonella typhimurium strains. MISO showed an increasing growth of revertants from 0 at 1 µg drug per plate to ~1500 at 100 µg per plate and ~6,000 at 1,000 µg per plate containing 0.1 mL of tester strain bacteria; FMISO showed fewer revertants , ~1,000 at 100 µg drug per plate and only ~600 revertants at 10 µg per plate[63]. In other cell lines, the frequency of unscheduled DNA synthesis was used as an index of genotoxicity. In this assay, [^{3}H]-thymidine incorporation in units of dpm/µg of DNA is used to quantify DNA synthesis. For a 1 mM dose of FMISO, the rate was 54 ± 6 for hepatocytes, 187 ± 14 for BL8 (nontransformed) cells and 217 ± 11 for JB1 (transformed) cells[64], with very similar values for MISO). For comparison, the control rate of DNA synthesis was 54 ± 4, 179 ± 15 and 158 ± 14, respectively for the three cell lines. This work concluded that in hypoxic cells nitroimidazoles react much more with thiols than with DNA. While each of these three tests detected low level alterations to DNA, exposure was both several orders of magnitude greater than, and of longer duration than that required in PET imaging with [^{18}F]FMISO. Drug exposure for imaging studies is below the levels where any genotoxicity was observed.

11. ADVERSE EVENTS AND MONITORING FOR TOXICITY

No adverse events have been attributed to PET imaging/diagnostic administration of [^{18}F] FMISO at the levels described herein in well over 1,000 injections, based upon up to 4 injections administered to each of over 600 patients. Thus no adverse effects are expected as a result of the IV administration of [^{18}F]FMISO for typical PET imaging

applications such as tumor hypoxia. The proposed [^{18}F]FMISO imaging dose is less than 0.001% of the recommended safe intravenous dose.

For purposes of informed consent regarding reasonably foreseeable risks to subjects in trials utilizing [^{18}F]FMISO, the following potential adverse effects are considered extremely rare:

- Risks related to allergic reaction that may be life threatening
- Injection related risks that may include infection, or extravasation of the dose that may lead to discomfort, localized pain, temporary loss of local function, and self limited tissue damage,

These risks are minimized by the requirement that appropriately trained and licensed/certified personnel prepare, deliver and administer the agent. The subject should be monitored per institutional standards for PET imaging studies. Emergency equipment, procedures, and personnel should be in place per institutional standards for imaging performed with intravenous contrast.

Radiation from ^{18}F carries an associated risk to the patient. The organ and total body doses associated with FMISO PET imaging are comparable to or lower than those associated with other widely used clinical nuclear medicine procedures and are well below the maximum individual dose suggested for investigational radiopharmaceuticals by the FDA.

12. SAFETY AND TOXICITY OF THE OTHER COMPONENTS OF THE FINAL [^{18}F]FMISO DRUG PRODUCT

The [^{18}F]FMISO is purified by HPLC using an eluent of 5% ethanol, USP. The injected does is in up to 10 mL of 5% ethanol, or a maximum of 0.5 mL of ethanol. This is less than 5% of the amount of ethanol in one beer. In Registry of Toxic Effects of Chemical Substances (RTECS) the LD_{Lo} is given as 1.4 g/kg orally for producing sleep, headache, nausea and vomiting. Ethanol has also been administered intravenously to women experiencing premature labor (8 g/kg) without producing any lasting side effects[65] (Jung 1980). Based upon these reports and experience with hundreds of patients over the past decade receiving this amount of ethanol in injectates, ethanol should not pose any danger of toxicity in this study.

The other components of the final product solution are USP grade sterile water for injection and sterile saline. These are all nontoxic for USP grade injectables at the concentrations used. The final product is at pH 7 and the final injection volume is ≤10 mL.

The potential contaminants in the final [^{18}F]FMISO drug product are: acetone, acetonitrile, Kryptofix® [2.2.2], other reaction products. Residual solvents in the final

product are limited to 5,000 ppm (µg/mL) of acetone and 400 ppm of acetonitrile. Acetone is used to clean the TRACERLab FX_{F-N} system. Acetonitrile is used to dissolve the Kryptofix® [2.2.2] and is the solvent for the reaction. The permissible level of acetonitrile in the final product is ≤400 ppm, the USP permissible level of acetonitrile in 2-[^{18}F]FDG. The allowable level for acetone is <5,000 ppm. Acetone is a Class three solvent. This class of solvents includes no solvent known as a human health hazard at levels normally accepted in pharmaceuticals. Therefore this limit is based upon the FDA's Guidance for Industry ICH Q3C-Tables and List (November 2003 Revision 1), page 7, where it considers 5,000 ppm in 10 mL, 50 mg or less per day, of Class 3 residual solvents as an acceptable limit without additional justification.

The toxicity for Kryptofix® [2.2.2] has not been reported (RTECS Number Kryptofix® [2.2.2] MP4750000) although this reagent has been investigated as a therapeutic in mice for chelation therapy after strontium exposure. The FDA has proposed a maximum permissible level of 50µg/mL of Kryptofix® [2.2.2] in 2-[^{18}F]FDG, therefore this maximum permissible level will also apply to the [^{18}F]FMISO final product.

There are trace amounts of other reaction products in the final product. The principal trace impurity is 1-(2,3-dihydroxy)propyl-2-nitroimidazole but other impurities are possible. For this reason the upper limit is set at 35 µg for the total of other materials in the final injectate that are retained more than 3 minutes on C18 HPLC (Aquasil 2X150 mm at 0.3 mL/min) and have UV absorbance at 254, 280 or 327 nm. The 35 µg is determined by assuming that the UV absorbing compounds have the same molar extinction coefficient as FMISO.

VI. BIODISTRIBUTION AND RADIATION DOSIMETRY OF FMISO

^{18}F is a positron emitter with a half-life of 110 minutes. Intravenously injected [^{18}F]-FMISO distributes throughout the total body water space, crossing cell membranes, including the blood-brain-barrier, by passive diffusion. [^{18}F]FMISO is bound and retained within viable hypoxic cells in an inverse relationship to the O_2 concentration. The uptake of [^{18}F]FMISO in normal human tissues has been measured and used to estimate the radiation absorbed dose associated with the imaging procedure. Dosimetry studies were performed at the University of Washington and have been published in the peer-reviewed Journal of Nuclear Medicine[55].

Sixty men and women were subjects in the study,. Of these, 54 had cancer, three had a history of myocardial ischemia, two were paraplegic and one had rheumatoid arthritis. After injecting 3.7 MBq/kg (0.1 mCi/kg), urine and normal tissues distant from each subject's primary pathology were imaged repeatedly to develop time-activity curves for target tissues. All tissues demonstrated a rapid uptake phase and first-order near-logarithmic clearance curves. All tissues receive a similar radiation dose, reflecting the similarity of biodistribution to that of water. Total tissue uptake data were normalized

for a 1.0 MBq injection into a 70 kg man. The organ curves are shown in Figure 4 and Figure 5[55]:

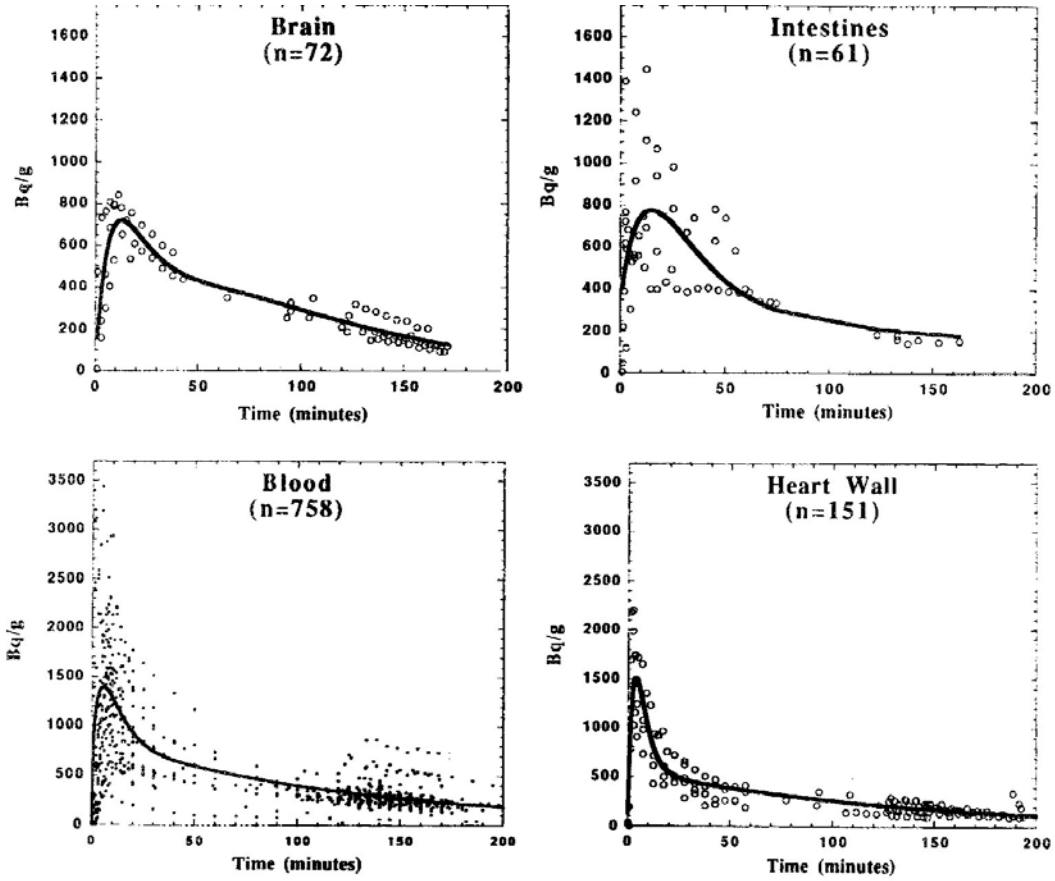

Figure 4. Activity of FMISO in 4 source organs with best fit used to determine AUC. The data are normalized to 1 MBq/70 kg bw.

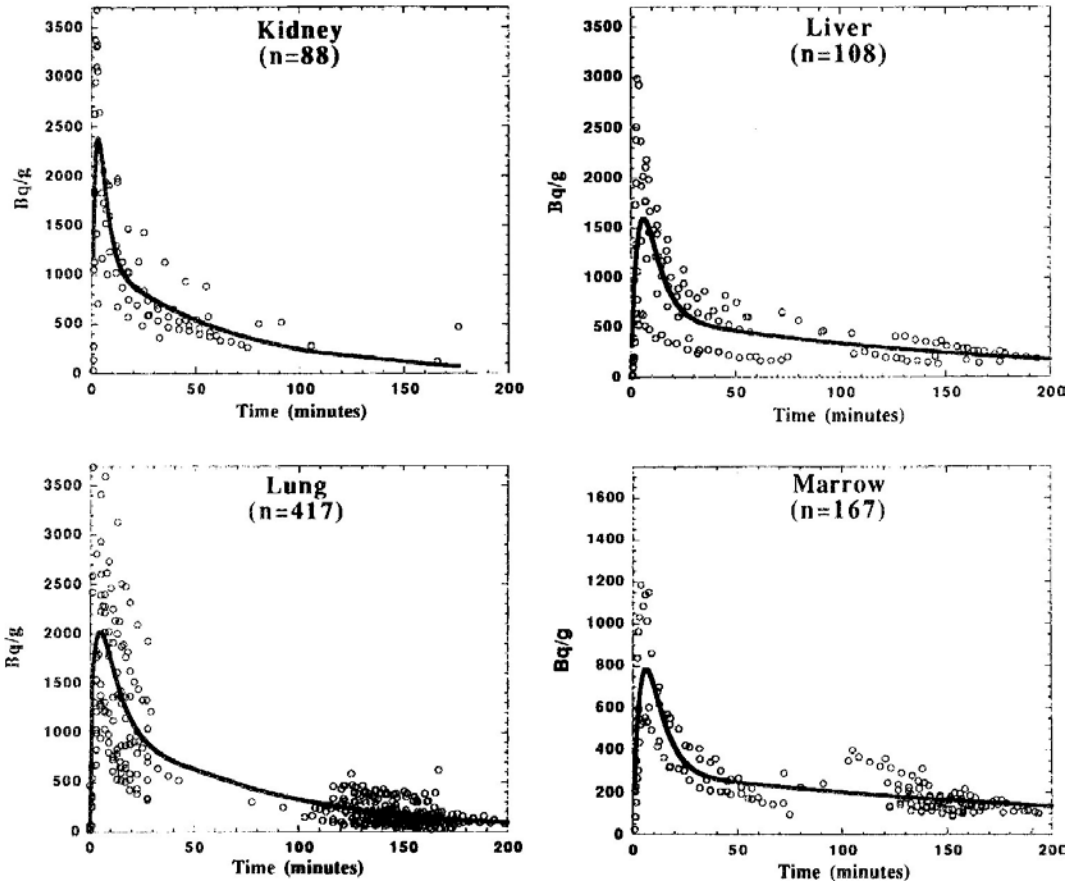

Figure 5. Activity of FMISO in four other source organs with best fit used to determine AUC. The data are normalized to 1 MBq/70 kg bw.

Radiation dose to the bladder wall varied with voiding interval from 0.021-0.029 mGy/MBq. ***Figure 6***[55] is a composite of the integrated ^{18}F urine activity of 42 samples from 20 studies. The line is the best fit to the data and was used to determine AUC for individual patients. Note that the mean total excretion is about 30 kBq, or 3% of the injected dose.

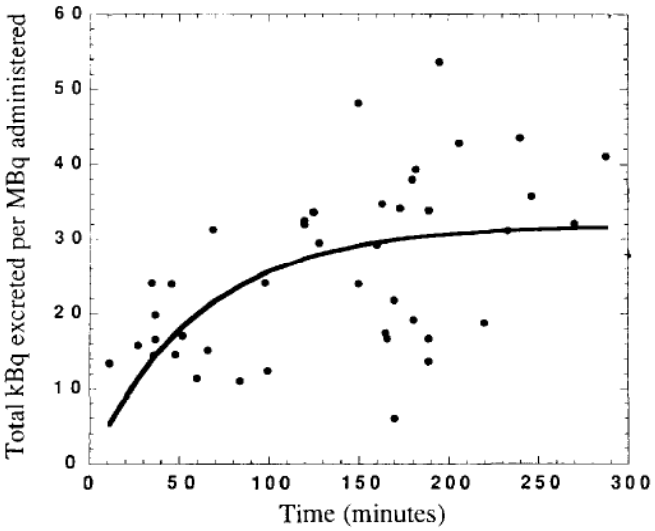

Figure 6. Bladder activity
from injection of 1 MBq of [^{18}F]FMISO/ 70 kg bw.

From these human data, radiation absorbed doses to organs was calculated using the MIRD schema and the results are shown in Table 7[55].

Table 7. Radiation Absorbed Dose to Organs

Tissue	Mean (mGy/MBq)	Mean (mrad/mCi)	Total / 7 mCi (mrad)
adrenals	0.0166	61.4	430
brain	0.0086	31.8	223
breasts	0.0123	45.5	319
gall bladder wall	0.0148	54.8	383
lower large intestine	0.0143	52.9	370
small intestine	0.0132	48.8	342
stomach	0.0126	46.6	326
upper large intestine	0.0140	51.8	363
heart wall	0.0185	68.5	479
kidneys	0.0157	58.1	407
liver	0.0183	67.7	474
lungs	0.0099	36.6	256
muscle	0.0142	52.5	368
ovaries	0.0176	65.1	456
pancreas	0.0179	66.2	464
red marrow	0.0109	40.3	282
bone surface	0.0077	28.5	199
skin	0.0048	17.8	124
spleen	0.0163	60.3	422
testes	0.0146	54.0	378
thymus	0.0155	57.4	401
thyroid	0.0151	55.9	391
urinary bladder wall	0.0210	77.7	544
uterus	0.0183	67.7	474
eye lens	0.0154	57.0	399
Total body	0.0126	46.6	325

Calculated total body dose for a 70 kg man injected with 3.7 MBq/kg was 0.013 mGy/MBq; for a 57 Kg woman it was 0.016 mGy/MBq. Effective dose equivalents were 0.013 mSv/MBq for men and 0.014 mSv/MBq for women. Ninety-seven percent of the injected radiation was homogenously distributed in the body, leaving only 3% for urinary excretion. Doses to smaller organs not directly determined by visualization, such as the lens, were calculated assuming average total-body concentrations. The absence of tracer visualized in images of those organs indicated that accumulation there was not increased.

The radiation exposure from [^{18}F]FMISO is equal to or lower than that of other widely used nuclear medicine studies. Increasing the frequency of voiding can reduce radiation dose to the normal organ receiving the highest radiation absorbed dose, the bladder

wall. Potential radiation risks associated with a typical PET study utilizing this agent are within generally accepted limits.

VII. [^{18}F]FMISO PREVIOUS HUMAN EXPERIENCE AND ASSESSMENT OF CLINICAL POTENTIAL

[^{18}F]FMISO is a radiolabeled imaging agent that has been used for investigating tumor hypoxia with PET. A hypoxia-imaging agent should be independent of blood flow, which is achieved when the partition coefficient of the tracer is close to unity and imaging is done at a time when the tracer distribution has equilibrated with its entry into the cells. [^{18}F]FMISO is an azomycin-based hypoxic cell sensitizer that has a nearly ideal partition coefficient and binds covalently to molecules at rates that are inversely proportional to intracellular O_2 concentration, rather than by some downstream biochemistry. It is composed of ≤ 15 µg of fluoromisonidazole labeled with ≤ 10 mCi of radioactive ^{18}F at a specific activity ≥1 Ci/mg at the time of injection. The drug is the only active ingredient and it is formulated in ≤ 10 mL of 5% ethanol in saline for intravenous injection. The radiochemical purity of the [^{18}F]FMISO is >95%.

Hypoxia imaging in cancer was reviewed in several recent publications[22,52,53,54]. [^{18}F]FMISO is a robust radiopharmaceutical useful in obtaining images to quantify hypoxia using PET imaging[55,56,57]. It is the most commonly used agent for PET imaging of hypoxia [58,52,53,54,59,60,61]. While its biodistribution properties do not result in high contrast images, they result in images at 2 hours after injection that unambiguously reflect regional partial pressure of oxygen, Po_2, and hypoxia in the time interval after the radiopharmaceutical was administered.

Positron emission scanning with [^{18}F]FMISO has been studied over the past ten years in Australia, Switzerland, Denmark, Germany and in the United States under RDRC approval or its equivalent. Several published studies from the United States are from the University of Washington in Seattle. Since 1994, approximately 300 patients have undergone FMISO PET scans in Seattle, at least 133 of whom are included in Table 8 of published studies. [^{18}F]FMISO has been used to image ischemic stroke, myocardial ischemia and a wide variety of malignancies.

Although published papers, as listed in Table 8, total 694 patients, we have elected to remain conservative in that duplication of some patients is possible. Nonetheless we are confident that over 600 unique patients have undergone up to 4 injections of the agent as described herein. The most recent papers, summarized briefly below, conservatively appear to represent at least 66 unique and recent patients, for example. Administered doses ranged from approximately 3 to 30 mCi (100 - 1100 MBq). No adverse events were noted in any of these papers, which are summarized in Table 8.

There have been several recent papers published on FMISO use as a PET imaging agent in humans. Representative papers from key groups in ongoing [F-18]FMISO PET imaging are summarized below.

In a paper published in 2009, Swanson[67] reported on 24 patients with glioblastoma who underwent T1Gd, T2, and 18F-FMISO studies either prior to surgical resection or biopsy, after surgery but prior to radiation therapy, or after radiation therapy. Abnormal regions seen on the MRI scan were segmented, including the necrotic center (T0), the region of abnormal blood-brain barrier associated with disrupted vasculature (T1Gd), and infiltrating tumor cells and edema (T2). The 18F-FMISO images were scaled to the blood 18F-FMISO activity to create tumor-to-blood ratio (T/B) images. The hypoxic volume (HV) was defined as the region with T/Bs greater than 1.2, and the maximum T/B (T/Bmax) was determined by the voxel with the greatest T/B value. They found that the HV generally occupied a region straddling the outer edge of the T1Gd abnormality and into the T2. A significant correlation between HV and the volume of the T1Gd abnormality that relied on the existence of a large outlier was observed. There was consistent correlation between surface areas of all MRI-defined regions and the surface area of the HV. The T/Bmax, typically located within the T1Gd region, was independent of the MRI-defined tumor size. Univariate survival analysis found the most significant predictors of survival to be HV, surface area of HV, surface area of T1Gd, and T/Bmax. They concluded that hypoxia may drive the peripheral growth of glioblastomas[67].

In a 2008 paper by Lin, seven patients with head and neck cancers were imaged twice with FMISO PET, separated by 3 days, before radiotherapy. Intensity-modulated radiotherapy plans were designed, on the basis of the first FMISO scan, to deliver a boost dose of 14 Gy to the hypoxic volume, in addition to the 70-Gy prescription dose. The same plans were then applied to hypoxic volumes from the second FMISO scan, and the efficacy of dose painting evaluated by assessing coverage of the hypoxic volumes using Dmax, Dmin, Dmean, D95, and equivalent uniform dose (EUD). The authors found similar hypoxic volumes in the serial scans for 3 patients but dissimilar ones for the other 4. There was reduced coverage of hypoxic volumes of the second FMISO scan relative to that of the first scan. The decrease was dependent on the similarity of the hypoxic volumes of the two scans. They concluded that the changes in spatial distribution of tumor hypoxia, as detected in serial FMISO PET imaging, compromised the coverage of hypoxic tumor volumes achievable by dose-painting IMRT. However, dose painting always increased the EUD of the hypoxic volumes[70].

In a study published in 2008, Roels et. al. investigated the use of PET/CT with fluorodeoxyglucose (FDG), fluorothymidine (FLT) and fluoromisonidazole (FMISO) for radiotherapy (RT) target definition and evolution in rectal cancer. PET/CT was performed before and during preoperative chemoradiotherapy (CRT) in 15 patients with resectable rectal cancer. They concluded that FDG, FLT and FMISO-PET reflect different functional characteristics that change during CRT in rectal cancer. FLT and FDG show good spatial correspondence, while FMISO seems less reliable due to the non-specific FMISO uptake in normoxic tissue and tracer diffusion through the bowel wall. FDG and FLT-PET/CT imaging seem most appropriate to integrate in preoperative RT for rectal cancer[75].

Nehmeh et. al. reported a study on 20 head and neck cancer patients in a 2008 paper. Of these, 6 were excluded from the analysis for technical reasons. All patients underwent an FDG study, followed by two (18)F-FMISO studies 3 days apart. The authors found that variability in spatial uptake can occur between repeat (18)F-FMISO PET scans in patients with head and neck cancer. Of 13 patients analyzed, 6 had well-correlated intratumor distributions of (18)F-FMISO-suggestive of chronic hypoxia. They concluded that more work is required to identify the underlying causes of changes in intratumor distribution before single-time-point (18)F-FMISO PET images can be used as the basis of hypoxia-targeting intensity-modulated radiotherapy[74].

In a 2008 paper Lee reported on a study that examined the feasibility of ((18)F-FMISO PET/CT)-guided IMRT with the goal of maximally escalating the dose to radioresistant hypoxic zones in a cohort of head and neck cancer (HNC) patients. (18)F-FMISO was administered intravenously for PET imaging. The CT simulation, fluorodeoxyglucose PET/CT, and (18)F-FMISO PET/CT scans were co-registered using the same immobilization methods. The tumor boundaries were defined by clinical examination and available imaging studies, including fluorodeoxyglucose PET/CT. Regions of elevated (18)F-FMISO uptake within the fluorodeoxyglucose PET/CT GTV were targeted for an IMRT boost. Additional targets and/or normal structures were contoured or transferred to treatment planning to generate (18)F-FMISO PET/CT-guided IMRT plans. The authors found that the heterogeneous distribution of (18)F-FMISO within the GTV demonstrated variable levels of hypoxia within the tumor. Plans directed at performing (18)F-FMISO PET/CT-guided IMRT for 10 HNC patients achieved 84 Gy to the GTV(h) and 70 Gy to the GTV, without exceeding the normal tissue tolerance. An attempt to deliver 105 Gy to the GTV(h) for 2 patients was successful in 1, with normal tissue sparing. The conclusion was that it was feasible to dose escalate the GTV(h) to 84 Gy in all 10 patients and in 1 patient to 105 Gy without exceeding the normal tissue tolerance. This information has provided important data for subsequent hypoxia-guided IMRT trials with the goal of further improving locoregional control in HNC patients[68].

Thorwarth et. al. published a 2008 paper on a dose painting strategy to overcome hypoxia-induced radiation resistance. 15 HNC patients were examined with 18F-FDG and dynamic 18F-FMISO PET before the start of a 70Gy radiotherapy. After approx. 20 Gy, a second dynamic 18F-FMISO scan was performed. The voxel based 18F-FMISO PET data were analyzed with a kinetic model, which allows for the determination of local tumor parameters for hypoxia and tissue perfusion. Their statistical analysis showed that only a combination of these two parameters predicted treatment outcome. They concluded that a translation of the imaging data into a reliable dose prescription can only be reached via a TCP model that includes these functional parameters. A model was calibrated using the outcome data of the 15 HNC patients. This model mapping of locally varying dose escalation factors to be used for radiotherapy planning. A planning study showed that hypoxia dose painting is feasible without a higher burden for the organs at risk[71].

Table 8. Published manuscripts reporting ^{18}F-FMISO human imaging studies

Year	Clinical Condition	n	mCi injected	MBq injected	Reference
2009	Brain Cancer	11	(7 mCi) 0.1 mCi/kg	260 (3.7 mCi/kg)	Szeto[66] (USA 2009)
2009	Brain Cancer	24	(7 mCi) 0.1 mCi/kg	260 (3.7 mCi/kg)	Swanson[67] (USA 2009)
2009	Head & Neck Cancer	28	10	370	Lee[68] (USA 2009)
2008	Brain Cancer	22	(7 mCi) 0.1 mCi/kg	260 (3.7 mCi/kg)	Spence[69] (USA 2008)
2008	Head & Neck Cancer	7	10	370	Lin[70] (USA 2008)
2008	Head & Neck Cancer	15	Not Reported	Not Reported	Thorwarth[71] (Germany 2008)
2008	Head & Neck Cancer	28	9.3-11	344-407	Lee[72] (USA, 2008)
2008	Head & Neck Cancer	3	10.8	~ 400	Thorwarth[73] (Germany, 2008)
2008	Head & Neck Cancer	20	9.3-11	344-407	Nehmeh[74] (USA, 2008)
2008	Rectal Cancer	10	8.9-11	330-398	Roels[75] (Belgium 2008)
2007	Advanced Head & Neck Cancer	14	9.4-12.2	350-450	Eschmann[76] (Germany 2007)
2007	Advanced Non-small cell lung cancer	4	7	259	Spence[77] (USA, 2007)
2007	Head & Neck Cancer	38	9.6	356	Gagel[78] (2007, Germany)
2007	Head & Neck Cancer	13	10.8	400	Thorwarth[79] (Germany, 2007)
2006	Head & Neck	24	9.7 $\pm$ 0.7	360 $\pm$ 25	Zimny[80] (Germany, 2006)
2006	Non-small cell lung cancer	21	10	370	Cherk[81] (Australia, 2006)
2006	Head and Neck Cancer	45	Not Reported	Not Reported	Rischin[82] (Australia, 2006)
2006	Head and Neck Cancer	73	10	Max 370 nom 260	Rajendran[83] (USA, 2006)
2006	Non-small cell lung cancer	8	8.9 $\pm$ 0.10	329 $\pm$ 36	Gagel[84] (Germany, 2006)

Year	Clinical Condition	n	mCi injected	MBq injected	Reference
2006	Glioma	17	0.5	18.5/kg nom 130	Cher[85] (Australia, 2006)
2005	Head & neck cancer	26	9.4-12.2	350-450	Eschmann[60] (Germany, 2005)
	Non-small cell lung cancer	14			
2004	Various brain tumors	11	3.3-11.4	123-421 Avg.= 291	Bruehlmeier [86] (Switzerland, 2004)
2004	Various cancers	49	0.1 mCi/kg	3.7/Kg nom 260	Rajendran[54] (USA, 2004)
2004	Head & neck cancer	16	7.9-0.9	292 ± 35	Gagel[87] (Germany, 2004)
2003	Ischemic Stroke	19	Not Reported	nom 130	Markus[88] (Australia, 2003)
2003	Soft tissue tumors	13	5.9-11.3	218-418 Avg.= 400	Bentzen[89] (Denmark, 2003)
2003	Soft tissue sarcoma	29	Not Reported	3.7/Kg nom 260	Rajendran[90] (USA, 2003)
2001	Brain tumors	13	Not Reported	Not Reported	Scott[91] (Australia, 2001)
2000	Ischemic Stroke	24	Not Reported	nom 130	Read[92] (Australia, 2000)
1996	Various cancers	37	Not Reported	3.7/Kg nom 260	Rasey[93] (USA, 1996)
1995	Non-small cell lung cancer	7	Not Reported	3.7/Kg nom 260	Koh[53] (USA, 1995)
1992	Various cancers	8	20-29.7	740-1100 (multiple studies)	Koh[94] (USA, 1992)
1992	Glioma	3	10	370	Valk[59] (USA, 1992)
	Total*	694			

*It is possible that some patients are represented more than once.

The overall conclusion, based upon the studies summarized above, is that [^{18}F]FMISO PET identifies hypoxic tissue that is heterogeneously distributed within human tumors[93]. It promises to help facilitate image-guided radiotherapy and to also guide the use of hypoxia-selective cytotoxins. These are two of several ways that this agent might help

circumvent the cure-limiting effects of tumor hypoxia. In addition, [^{18}F]FMISO has identified a discrepancy between perfusion, blood-brain barrier disruption, and hypoxia in brain tumors[86] and a lack of correlation between FDG metabolism and hypoxia in several types of malignancies[90]. Hypoxic tissue does not correlate either with tumor volume or vascular endothelial growth factor (VEGF) expression[22,54].

[^{18}F]FMISO PET was able to identify post-radiotherapy tumor recurrence by differential uptake of tracer. The standardized uptake value (SUV) ratio between recurrent tumor and muscle was >1.6, while that between tumor and normal mediastinum was >2.0[60]. One study concluded that [^{18}F]FMISO was not feasible for the detection of tumor hypoxia in human soft tissue tumors[89]. In ischemic stroke, [^{18}F]-FMISO was able to identify the areas of brain tissue into which a stroke had extended[88,92]. In addition to the FMISO imaging studies summarized above, alternative nitroimidazoles have been evaluated as imaging agents in single-center pilot studies. A 2001 study from Finland used [^{18}F]-fluoroerythro-nitroimidazole (^{18}F-FETNIM) to evaluate 8 patients with head and neck squamous cell cancer at doses of ~370 MBq without adverse effect[95] (Lehtio 2001). Other agents, fluoropropyl-nitroimidazole and fluorooctyl-nitroimidazole. have not proved as useful in visualizing hypoxic tissue[96] (Yamamoto 1999), probably because of their higher lipophilicity. A derivative that is more hydrophilic than FMISO, [^{18}F]-fluoroazomycin-arabinofuranoside (FAZA) had been recommended for further study[97] (Sorger 2003) and shows considerable clinical promise.

In human metastatic neck lymph nodes, comparison of FMISO tumor-to-muscle uptake ratio at 2 hours using the computerized polarographic needle electrode system (pO_2 histography) found average to high correlation, whereas no correlation was found with [^{18}F]-2-fluoro-2-deoxyglucose (FDG)[87]. A significant correlation was found between hypoxic tissue identified by FMISO and by immunohistochemical staining for both pimonidazole and carbonic anhydrase IX[98] (Dubois 2004).

Taken together, these imaging studies show that [^{18}F]FMISO is able to identify a unique feature of malignant and endangered tissues, hypoxia, thereby adding to the armamentarium of specific markers used to image tumors and potentially impact treatment for the benefit of individual patients. Low oxygenation status is often phenotypic of tumors that demonstrate a poor response to therapy, which justifies extensive investigation of the utility of agents like [^{18}F]FMISO to improve specific treatment regimens directed at hypoxic tumors.

The rationale for using a T:B ratio of 1.2 to separate normoxia from hypoxia is based on human and animal data. The initial animal results showed that normoxic myocardium ratios were near unity over a wide range of flows. In numerous other organs of normal mice, rats, rabbits and dogs, the mean of the distribution histogram was 1.035, median 0.96, for 1342 samples[99]. Therefore, a cut-off of 1.2 was selected, with confidence that any T:B ratio above that value was indicative of hypoxic tissue. This conclusion is further justified by the human study presented in Figure 7. In this patient with a primary brain tumor, the FDG image was co-registered with the FMISO image (left panel). In brain

regions far from the right frontal tumor, the T:B values for FMISO were uniformly less than 1.2, as depicted by the blue dots in the right panel, even though FDG SUV spanned a range from about 3 to 13. In the tumor area, a substantial fraction of the pixels were still in the normal range, but many values exceeded the cut-off as shown by the colored pixels in the FMISO image. A distribution histogram of the red data points shows a continuous distribution, reflecting the fact that the level of oxygenation is a continuum from normoxic to hypoxic. One consequence of this continuous scale is that FMISO images exhibit only modest contrast. However, the evidence that uptake is independent of blood flow and numerous other physiologic parameters, as described about, provides confidence that FMISO images uniquely identify tumors with prognostically significant levels of hypoxia.

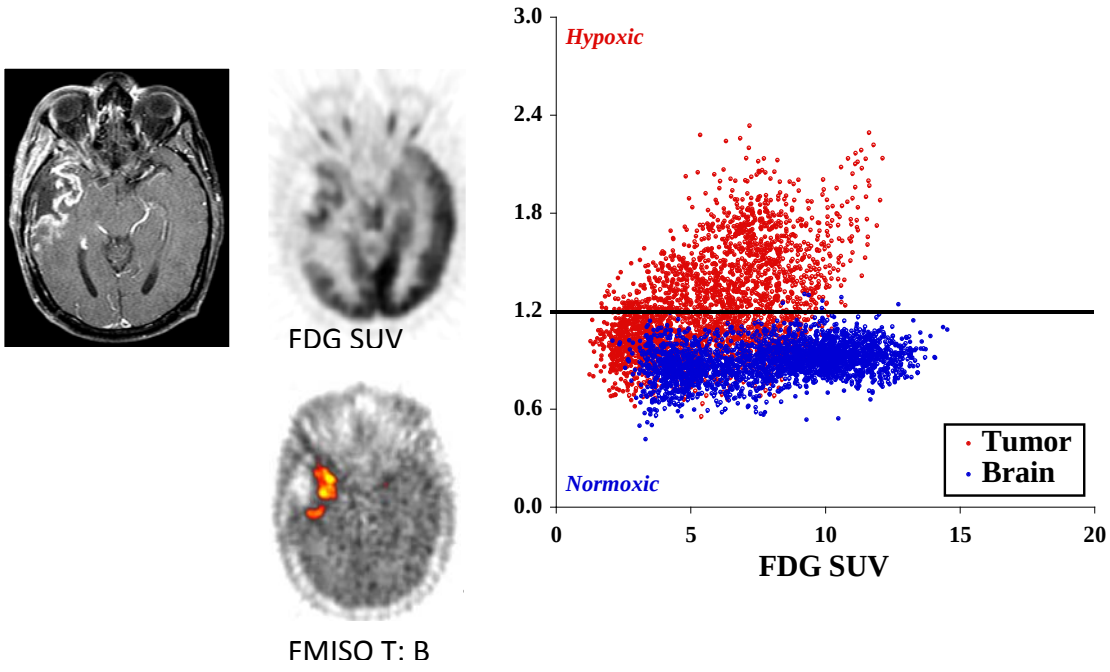

Figure 7. Right-frontal glioma post surgery.

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ATTACHMENT 2

FDA Form 1572 Including CVs, Protocol and Consent Form

DEPARTMENT OF HEALTH AND HUMAN SERVICES

PUBLIC HEALTH SERVICE

FOOD AND DRUG ADMINISTRATION

STATEMENT OF INVESTIGATOR

(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) PART 312)

(See instructions on reverse side.)

Form Approved: OMB No. 0910-0014.
Expiration Date: January 31, 2006.
See OMB Statement on Reverse.

NOTE: No investigator may participate in an investigation until he/she provides the sponsor with a completed, signed Statement of Investigator, Form FDA 1572 (21 CFR 312.53(c)).

1. NAME AND ADDRESS OF INVESTIGATOR

David Schuster, M.D.
Emory University Hospital
Room E152
1364 Clifton Rd., N.E.
Atlanta, GA 30322

2. EDUCATION, TRAINING, AND EXPERIENCE THAT QUALIFIES THE INVESTIGATOR AS AN EXPERT IN THE CLINICAL INVESTIGATION OF THE DRUG FOR THE USE UNDER INVESTIGATION. ONE OF THE FOLLOWING IS ATTACHED.

☒ CURRICULUM VITAE ☐ OTHER STATEMENT OF QUALIFICATIONS

3. NAME AND ADDRESS OF ANY MEDICAL SCHOOL, HOSPITAL OR OTHER RESEARCH FACILITY WHERE THE CLINICAL INVESTIGATION(S) WILL BE CONDUCTED.

Emory University Hospital
Emory Center for Systems Imaging
1364 Clifton Rd., N.E.
Atlanta, GA 30322

4. NAME AND ADDRESS OF ANY CLINICAL LABORATORY FACILITIES TO BE USED IN THE STUDY.

Emory University Hospital
Emory Center for Systems Imaging
1364 Clifton Rd., N.E.
Atlanta, GA 30322

5. NAME AND ADDRESS OF THE INSTITUTIONAL REVIEW BOARD (IRB) THAT IS RESPONSIBLE FOR REVIEW AND APPROVAL OF THE STUDY(IES).

Institutional Review Board
Emory University
1599 Clifton Road
5th Floor East
Atlanta, GA 30322

6. NAMES OF THE SUBINVESTIGATORS *(e.g., research fellows, residents, associates)* WHO WILL BE ASSISTING THE INVESTIGATOR IN THE CONDUCT OF THE INVESTIGATION(S).

Hyun Kim, MD

7. NAME AND CODE NUMBER, IF ANY, OF THE PROTOCOL(S) IN THE IND FOR THE STUDY(IES) TO BE CONDUCTED BY THE INVESTIGATOR.

Tumor Hypoxia Imaging in Support of Radiofrequency Ablation (RFA) Success Prediction (RASP) Study for Metastatic Colorectal Liver Lesions

8. ATTACH THE FOLLOWING CLINICAL PROTOCOL INFORMATION:

☐ FOR PHASE 1 INVESTIGATIONS, A GENERAL OUTLINE OF THE PLANNED INVESTIGATION INCLUDING THE ESTIMATED DURATION OF THE STUDY AND THE MAXIMUM NUMBER OF SUBJECTS THAT WILL BE INVOLVED.

☒ FOR PHASE 2 OR 3 INVESTIGATIONS, AN OUTLINE OF THE STUDY PROTOCOL INCLUDING AN APPROXIMATION OF THE NUMBER OF SUBJECTS TO BE TREATED WITH THE DRUG AND THE NUMBER TO BE EMPLOYED AS CONTROLS, IF ANY; THE CLINICAL USES TO BE INVESTIGATED; CHARACTERISTICS OF SUBJECTS BY AGE, SEX, AND CONDITION; THE KIND OF CLINICAL OBSERVATIONS AND LABORATORY TESTS TO BE CONDUCTED; THE ESTIMATED DURATION OF THE STUDY; AND COPIES OR A DESCRIPTION OF CASE REPORT FORMS TO BE USED.

9. COMMITMENTS:

I agree to conduct the study(ies) in accordance with the relevant, current protocol(s) and will only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, rights, or welfare of subjects.

I agree to personally conduct or supervise the described investigation(s).

I agree to inform any patients, or any persons used as controls, that the drugs are being used for investigational purposes and I will ensure that the requirements relating to obtaining informed consent in 21 CFR Part 50 and institutional review board (IRB) review and approval in 21 CFR Part 56 are met.

I agree to report to the sponsor adverse experiences that occur in the course of the investigation(s) in accordance with 21 CFR 312.64.

I have read and understand the information in the investigator's brochure, including the potential risks and side effects of the drug.

I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study(ies) are informed about their obligations in meeting the above commitments.

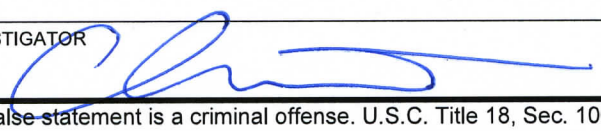
I agree to maintain adequate and accurate records in accordance with 21 CFR 312.62 and to make those records available for inspection in accordance with 21 CFR 312.68.

I will ensure that an IRB that complies with the requirements of 21 CFR Part 56 will be responsible for the initial and continuing review and approval of the clinical investigation. I also agree to promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others. Additionally, I will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.

I agree to comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements in 21 CFR Part 312.

INSTRUCTIONS FOR COMPLETING FORM FDA 1572
STATEMENT OF INVESTIGATOR:

1. Complete all sections. Attach a separate page if additional space is needed.
2. Attach curriculum vitae or other statement of qualifications as described in Section 2.
3. Attach protocol outline as described in Section 8.
4. Sign and date below.
5. FORWARD THE COMPLETED FORM AND ATTACHMENTS TO THE SPONSOR. The sponsor will incorporate this information along with other technical data into an Investigational New Drug Application (IND).

10. SIGNATURE OF INVESTIGATOR	11. DATE
	9/1/2011

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Please **DO NOT RETURN** this application to this address.

Study protocol. Tumor Hypoxia Imaging in Support of Radiofrequency Ablation (RFA) Success Prediction (RASP) Study for Metastatic Colorectal Liver Lesions

Location of Study: Subject evaluation and PET imaging will be performed at Emory University Hospital in Atlanta, GA.
Estimated Duration: 5 Years
Maximum Number of Subjects: 50. No controls.
Clinical Uses: Metastatic Colorectal Liver Cancer.
Characteristics of Subjects: All ages over 18. Male and Female. All Performance Levels.

Description of the project
The goal of this research is to investigate the biomarker of tumor hypoxia utilizing the PET radiotracer of F-18 fluoromisonidazole (FMISO) in oncologic patients. The study will include patients with metastatic colorectal liver cancer with correlative investigations in tumor markers of hypoxia.

F-18 FMISO PET is known to correlate with hypoxia in tumors of the head and neck. The role of F-18 FMISO PET in imaging hypoxia in primary and metastatic liver disease has not been established. Our hypothesis is that F-18 FMISO PET will correlate with tumor hypoxia in patients with metastatic colorectal liver lesions as a biomarker to predict ultimate complete response to RFA.

Study aims are:
1. To investigate F-18 FMISO PET imaging for metastatic colorectal liver cancer and correlate to conventional F-18 FDG PET-CT.
2. To investigate F-18 FMISO PET imaging for metastatic colorectal liver cancer and correlate uptake parameters to ultimate response to radiofrequency ablation as measured with conventional imaging and clinical parameters.

Impact of research, including significance and probability of success
Hypoxia is known to contribute to resistance to chemotherapy and radiation. The relationship of hypoxia to resistance to radiofrequency ablation techniques has not been studied. In preclinical models, antiangiogenic molecularly targeted therapies and image-guided targeted therapy can inhibit tumor growth and normalize tumor vascularity, leading to decreased hypoxia. Currently there is no proven in-vivo imaging biomarker for tumor hypoxia. Advanced conventional imaging method such as DCE-MR is an indirect marker of tumor perfusion and/or capillary permeability but not proven for tumor hypoxia. Imaging hypoxia in liver tumors will allow for development of a biomarker for anti-angiogenic therapy and will facilitate planing external and selective intra-arterial radiotherapy and/or modify current RFA techniques to target areas of resistance due to hypoxia.
Successful accomplishment of the stated goals will also lay the grounds for future:
a. Application of F-18 MISO as biomarker in other primary and metastatic liver cancers
b. Application of F-18 MISO as biomarker in non-liver solid organ cancers
c. Application of F-18 MISO as adjuvant to planing loco-regional therapy to account for areas of potential resistance due to hypoxia.

Experimental Approach and Methods:

Patient Selection

Recruitment: All patients will be recruited form the Interventional Radiology Clinic of Dr. Kevin Kim at Emory University Hospitals.

Inclusion Criteria

- Patient with histologically confirmed metastatic colorectal carcinoma to liver eligible for RFA therapy.

- Two weeks or greater since biopsy
- Ability to lie still for up to 30 minutes for PET scanning
- Age >18
- Willingness to provide written informed consent
- Negative serum or urine pregnancy test within 24 hours

Exclusion Criteria

- Not meeting above criteria

Procedures for Screening and Enrollment

Written informed consent will be obtained before subject participation in the study. No procedures will be performed before written informed consent is obtained. Participants will be assigned an identification number for screening purposes; data collected during the screening process will be recorded using that number.

A screening visit will take place not more than 6 weeks before imaging. The following procedures will be performed at visit 1:

- Obtain written informed consent
- Inclusion/exclusion criteria review
- Vital signs measurements
- Medication history review
- Pregnancy based on serum or urine pregnancy test obtained within 24 hours prior to injection of F-18 FMISO.

F-18 FMISO injection and imaging session activities

The following procedures will be performed during F-18 FMISO injection and imaging visits:

- Baseline vital signs (record TPR & BP) before the start of F-18 FMISO infusion
- F-18 FMISO, (0.1 mCi/kg) (maximum 370 MBq, 10 mCi) injected intravenously with PET/CT imaging as detailed below
- Adverse event inquiry
- Baseline vital signs (record TPR & BP) immediately following imaging study

Follow-up Telephone contact

A telephone contact one day post the last imaging session will be made to assess for any adverse events.

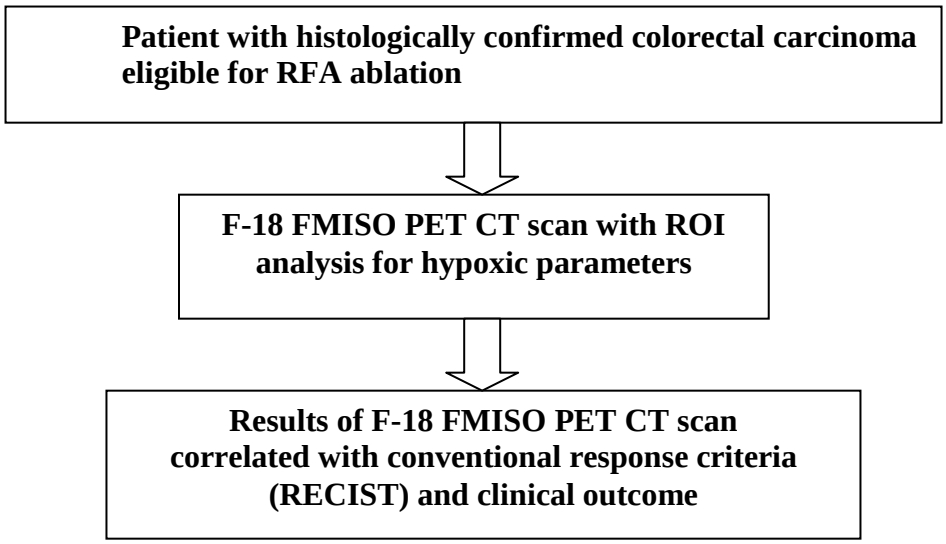
Study Activities and Visits

Visit 1- Consenting, enrollment, and baseline assessments, imaging session- bolus infusion and serial whole body imaging
Visit 2- Phone contact 1 day after injection

Safety Assessments

Safety will be evaluated by the following:
Adverse events
Vital signs performed at pre-injection baseline and immediately after the imaging study.
Phone contact 1 day after injection

Schema:



Imaging Procedures

F-18 FMISO PET Production: The radiotracer will be produce under contract with Cardinal Health, a commercial radiopharmacy. DMF and LOA attached in application.

FMISO-PET/CT:18F-fluoromisonidazole at a dose of 3.7 MBq/kg (0.1 mCi/kg) (maximum 370 MBq, 10 mCi) will be injected IV. The patient will be imaged on a state of the art PET-CT scanner (GE MV690, GE MV600, GE DST, Siemens Biograph 40). A low-dose CT scan without contrast for the PET/CT will be performed for attenuation correction and anatomic correlation. Emission acquisition typically encompassing 1-2 table positions to image the entire liver will begin 110 ± 10 minutes after FMISO injection. Participants will be imaged in the supine position.

Scans will be corrected for randoms, scatter using the models implemented by the supplied GE PET software, and attenuation as estimated by the CT image. Data will be reconstructed using the manufacturer provided order subset estimation maximization (OSEM) algorithm with no applied decay correction. Image analysis will be performed with software developed by the authors running on a GE AW or MimVista workstation.

Data Analysis

A 3-dimensional region of interest (ROI) will be defined on the FMISO-PET/CT scan as correlated with the already acquired standard of care contrast CT and/or FDG PET the candidate RFA lesions in each liver lobe. SUVmax, total lesion activity, and uptake volume will be determined for each index lesion. SUVmean will also be determined from a representative uninvolved region of each lobe of the liver as well as aorta. The ratios of SUVmax/liver SUVmean, SUVmax/blood pool SUVmean, hypoxic volume/total anatomic volume, and hypoxic volume/metabolic FDG volume will also be calculated. These parameters will be recorded and used to determine changes between baseline and follow-up in terms of various hypoxic parameters for index lesions, but also to correlate with RECIST response criteria, and ultimately patient outcome.

Description of Case Report Form:
Case report form will include standard patient demographics including name, age, sex, medical record number, history, pathologic proof, and results of other imaging including but not limited to CT, MR and FDG PET. All RFA candidate lesions in each lobe will be identified on the CRF. These will have recorded: SUVmax, total lesion activity, and uptake volume. Total anatomic volume of each lobe will be recorded. Metabolic FDG volume from each index lesion (from separate FDG PET study) will also be recorded on this

form. Background structures will also have SUVmax and SUVmean recorded including uninvolved region of each lobe of the liver as well as aorta.

Radiation Methodology

The use of F-18 as a radioactive tracer is ideal for imaging with nuclear medicine cameras for PET imaging. F-18 is a safe, routinely used agent for cancer (2-FDG) scanning; it has a relatively short half-life (110 minutes) and is associated with low levels of radiation exposure to the subject. Several F-18 radiopharmaceutical are in clinical use for diagnostic nuclear medicine studies in the US and Europe. Whole-body F-18 imaging is a safe procedure. Patients must remain still during the scan, but most state-of-the-art imaging systems are designed to reduce head motion and patient discomfort.

Potential Risks and Benefits

Risks: Toxic pharmacologic effects of F-18 FMISO PET CT scan are not anticipated given that it has been widely studied with no reported adverse events. The radiopharmaceutical will produced by Cardinal Health, a commercial radiopharmacy. Rigorous testing will ensure radiochemical purity, quality, identity, sterility, and lack of pyrogenicity prior to administration.

Consent: Informed consent will be obtained from all subjects. A copy of the consent has been attached to this application. The consent will be obtained by one of the study staff after the research protocol and the risk of participating in the study have been fully explained. This consent will be obtained prior to enrolling any of the subjects in the study. A copy of the consent form will be provided to all subjects.

Potential Benefits: There are no benefits that a healthy subject could have from entering this study

Statistical Analysis

Standard statistical analysis will be performed including but not limited to T testing, ANOVA and other tests of statistical variance by one of two Radiology Department statisticians.

Adverse Event Reporting

Any patient death that may be due to the study procedure (i.e. severe radiotracer reaction), unanticipated problem, or protocol deviation/non-compliance would be promptly reported to the Emory IRB office. Additionally any patient death not associated with the study procedure or serious anticipated event (i.e. radiotracer allergy) will be reported to the Emory IRB and FDA upon continuing review. This radiotracer will be studied under IND with FDA guidance. No serious adverse events have been reported per the attached IB.

Data and Safety Monitoring Plan (DSMP):

Patients will be monitored by the technologists and study nurse before and after the studies for any adverse events/reactions. They will be given contact phone numbers to call if they experience any problems (i.e. problems with the IV site, any allergic reaction symptoms). They will be followed routinely by their referring physician with clinical exams, and the PI will work with the co-investigators and referring physicians to ensure that the patients continue to follow up as scheduled.

Any serious adverse events (see above) will be communicated by the PI to the Emory IRB using standard adverse event reporting forms. A data safety monitoring board is not necessary.

Emory University
Consent to be a Research Subject

Title: Tumor Hypoxia Imaging in Support of Radiofrequency Ablation (RFA) Success Prediction (RASP) Study for Metastatic Colorectal Liver Lesions

Principal Investigator: David Schuster, MD

Sponsor: National Institute of Health

Introduction

You are being asked to be in a medical research study. This form is designed to tell you everything you need to think about before you decide to consent (agree) to be in the study or not to be in the study. **It is entirely your choice. If you decide to take part, you can change your mind later on and withdraw from the research study.** The decision to join or not join the research study will not cause you to lose any medical benefits. If you decide not to take part in this study, your doctor will continue to treat you.

Before making your decision:

- Please carefully read this form or have it read to you
- Please listen to the study doctor or study staff explain the study to you
- Please ask questions about anything that is not clear

You can take a copy of this consent form, to keep. Feel free to take your time thinking about whether you would like to participate. You may wish to discuss your decision with family or friends. Do not sign this consent form unless you have had a chance to ask questions and get answers that make sense to you. By signing this form you will not give up any legal rights.

A description of this clinical trial will be available on www.ClinicalTrials.gov, as required by U.S. law. This website will not include information that can identify you. At most the website will include a summary of the results. You may search this website at any time.

Study Overview

The purpose of this study is to see if an investigational radioligand, FMISO (18F-fluoromisonidazole) used during PET scans (Positron Emission Tomography) can help doctors see if a tumor is getting oxygen. Radiation and chemotherapy do not appear to work as well on tumors with low oxygen levels. We are studying if the procedure you are about to undergo, radiofrequency ablation (RFA), has the same problems with tumors with low oxygen levels.

This clinical trial will study body images from PET scans using the research radioligand, FMISO. A radioligand is a molecule that carries a small amount of radioactive substance into the body, The images show color where the FMISO emits radiation, the PET scanner can pick up the radiation being released to create a picture from within the body. When the study doctors take pictures of the body using the FMISO and the PET scanner, they hope to see how well the tumor is getting oxygen. If the tumor is not getting enough oxygen, then the treatments that can destroy it might not work well. The more doctors know about how the amount of oxygen a tumor gets effects treatment, the more likely they are to give a patient the right treatment from the beginning. This study will add to doctors' knowledge of how tumors, low oxygen, and treatments are related.

FMISO is not yet approved by the Food and Drug and Administration (FDA) for routine use in people diagnosed with metastatic liver cancer. It is currently being used in clinical trials with humans. This trial's results will add to the evidence

available on this agent as the FDA decides whether it should be used regularly to help people with cancer. This trial will be done at Emory Hospital and enroll about 50 subjects.

Procedures:
The scans will be performed at the Emory Center for PET located in the Nuclear Medicine Department on the first floor of the Emory University Hospital or in the Winship Cancer Institute. The entire procedure will last about 3 hours. Before the PET scan, you will be asked to not eat or drink for four hours. This will allow the FMISO to get in your blood system easier. You will meet with a technologist and doctor who are approved to work on this study, and who will be performing the procedures on you. An intravenous tube called a catheter (IV) will be inserted in a vein in your arm to be used for injection of the FMISO. You will then receive a slow injection through the IV tube of the FMISO. After this, you will wait in a quiet room for 2 hours in order for the FMISO to enter into your liver.

After 2 hours, you will lay down on a mobile couch that will slide into the scanner. The scanner has the appearance of a large box containing a large round opening into which your body is placed. An initial "transmission" scans lasting about 1 minute in which the couch will move will be done. This transmission scan is similar to a CAT scan and is used to correct for the effect of your body on the PET scan in order to produce better images. This transmission scan is done on the PET scanner and will look no different to you. A set of PET scans (pictures) will be done over 20 minutes. The couch will move. When finished, the IV will be removed. You will be able to leave the PET Center after this time. You will continue with your care as planned.

Vital signs
Your temperature, pulse, respiration, and blood pressure will be taken before and after the injection of FMISO.

Follow up

You will see your treating doctor at regular intervals according to her/his recommendations and usual practice. Information gathered by your treating doctor as part of your normal follow-up visits will be given to your study doctor or research staff so they can find out more about your health.

Your treating doctor will be asked to inform the study doctor or research staff about your health and your disease status until the end of the study (up to five [5] years after you completed your treatment and had your last FMISO PET scan). The study doctors will want to collect follow-up images (standard of care MRI and CT scans) during this time. Your follow-up care will be decided between you and your treating doctor.

Risks and Discomforts
The procedures described in this study may cause all, some, or none of the side effects listed here. These are common procedures that are considered relatively safe. Previously unknown side effects can also occur. If new side effects are reported, you will be told. You will be watched closely to see if any of these side effects are happening. It is also important that you give us accurate and complete information about your past medical history.

FMISO:
In previously studied patients who receive the same dose as you would, we have not noticed any major side effects nor did the patients complain of any as a direct result of the tests. But if you notice anything differently, please feel free to contact the investigators (contact number given below).

FMISO, when it is given in a few small doses, like those being used in this study, is not known to cause any problems for humans.

Intravenous Catheter:

One tube will be placed in your vein (arm or hand.) It is called an intravenous catheter or IV. It is placed under sterile conditions by piercing the skin and underlying vein with a needle, over which is threaded the IV catheter and then the needle is withdrawn. When the catheter is placed or removed, the site of insertion may become sore or bruised. Rarely, bleeding or infection can occur at this site; however, this is highly unlikely. A small gauze pad or bandage is placed over the site after the IV catheter is removed. This is similar to what happens when one donates blood.

Radiation Exposure:

This research study involves exposure to radiation from PET/CT scans, similar to those routinely used for medical purposes. This radiation dose is not necessary for your medical care and will occur only as a result of your participation in this study. The radiation dose that you will receive is estimated to be equal to or less than the annual radiation exposure limit allowed for persons who are occupationally exposed to radiation (for example, x-ray technologist, radiologist). The principal risk associated with a radiation dose is the possibility of developing a radiation-induced cancer later in life. The risk for radiation-induced cancer from this study is minimal. The risk from radiation exposure of this magnitude is considered to be comparable to other everyday risks. Women who may be pregnant should not participate in this study because of possible effects of radiation exposure on their unborn child. Both men who may later father children and women of childbearing potential should be aware that exposure to radiation poses a very slight risk of genetic mutation in the next generation.

Vein Puncture

You could experience bruising, pain, and rarely infection at the vein puncture site for the blood draw. Care will be taken to minimize these risks.

Reproductive Risk

If you are pregnant or nursing or plan to become pregnant during the course of the study, you cannot take part in this research study. We do not know the effects on the fetus, breastfeeding baby, or mother-to-be, and this study may cause harm. Because the PET, CT and MRI scans and the investigational radioligand FMISO in this study can affect an unborn or nursing baby, you should not become pregnant or breastfeed, or father a baby, while on this study.

You and your study doctor should discuss taking precautions. If you or your partner does become pregnant, you will need to tell your study doctor immediately. If you are unsure of your pregnancy status on the day of your imaging scans for the trial, you will need to tell your study doctor and have a pregnancy test before any of the day's study procedures.

If you are a man: the effect of the study drug on sperm is not known

New Information:

It is possible that the researchers will learn something new during the study about the risks of being in it. If this happens, they will tell you about it so you can decide if you want to continue to be in this study or not. You may be asked to sign a new consent form that includes the new information if you decide to stay in the study.

Benefits:

This study is not designed to benefit you directly. Your condition may improve while you are in this study but it may not, and it may even get worse. This study is designed to learn more about the study drug. The study results may be used to help other patients in the future.

Compensation

You will not be offered payment for being in this study.

Other Treatment Outside this Study:

You may choose to not take part in this study. You could have PET, CT and MRI scans done without participating in this study. If you decide not to take part, there will be no penalty or loss of benefits to which you are otherwise entitled. Please talk with your treating doctor about this and other options.

Confidentiality:

Certain offices and people other than the researchers may look at your medical charts and study records. Government agencies, Emory employees overseeing proper study conduct may look at your study records. Study sponsors may also look at your study records. These offices include Food and Drug Administration, the Office for Human Research Protections, the study sponsor, the Emory Institutional Review Board, the Emory Office of Research Compliance and the Office for Clinical Research. Emory will keep any research records we produce private to the extent we are required to do so by law. A study number rather than your name will be used on study records wherever possible. Your name and other facts that might point to you will not appear when we present this study or publish its results.

Study records can be opened by court order or produced in response to a subpoena or a request for production of documents unless a Certificate of Confidentiality is in place for this study.

Research Information Will Go Into the Medical Record:
If you are or have been an Emory Healthcare patient, you have an Emory Healthcare medical record. If you are not and have never been an Emory Healthcare patient you do not have one. Please note that an Emory Healthcare medical record will be created for you if you have any services or procedures done by an Emory provider or facility for this study.

If you agree to be in this study, a copy of the consent form and HIPAA patient form that you sign will be placed in your Emory Healthcare medical record. Emory Healthcare may create study information about you that can help Emory Healthcare take care of you. For example, the results of study tests or procedures. These useful study results will be placed in your Emory Healthcare medical record. Anyone who has access to your medical record will be able to have access to all the study information placed there . The confidentiality of the study information in your medical record will be protected by laws like the HIPAA Privacy Rule. On the other hand, some state and federal laws and rules may not protect the research information from disclosure.

Emory does not control results from tests and procedures done at other places. So these results would not be placed in your Emory Healthcare medical record. And they will not likely be available to Emory Healthcare to help take care of you. Emory also does not have control over any other medical records that you may have with other healthcare providers. Emory will not send any test or procedure results from the study to these providers. So if you decide to be in this study, it is up to you to let them know.

The researchers will review the results of certain study tests and procedures **only** for the **research**. The researchers will **not** be looking at these results to make decisions about your personal health or treatment. For this study, those things include

- All PET scans with FMISO;

For safety reasons, however, some basic information will be placed in your Emory medical record:

- The fact that you are enrolled in a research study and you gave informed consent to join it
- Contact information for the researcher who is in charge of the study
- A description of health care that would be called for in case of medical problems you may have arising from the study; and
- A description of when and how health care providers may get research information, upon request, that they may need to give you medical care.

We encourage you to let your health care provider know if you decide to take part in this study. That way they can have extra information that can help them to make decisions about your health care.

In Case of Injury:

If you get ill or injured from being in the study, Emory would help you to get medical treatment. Emory and the sponsor have not, however, set aside any money to pay you or to pay for this medical treatment. The only exception is if it is

proved that your injury or illness is directly caused by the negligence of an Emory or sponsor employee. "Negligence" is the failure to follow a standard duty of care.

If you become ill or injured from being in this trial, your insurer will be billed for your treatment costs. If you do not have insurance, or if your insurer does not pay, then you will have to pay these costs.

If you believe you have been injured by this research, you should contact Dr. David Schuster, at (404) 712-4859. You should also let any health care provider who treats you know that you are in a research study.

Costs

If you take part in this study, you may have to pay extra costs. The amount you may have to pay depends on several things:

First, whether or not you have health insurance. If you do have health insurance:

The insurance may or may not pay for clinical trials.

If the insurance pays for clinical trials, the amount paid will be different depending on the insurance coverage you have.

You will have to pay for any co-payments, deductibles or co-insurance amounts that your insurance coverage requires. Emory and the sponsor will not pay for these.

If you do have insurance, you should contact the insurance provider and tell them you want to be in this clinical trial. Ask them what they will pay for and what they will not pay for.

If you do not have insurance, Emory will review your case as part of its program for low-income patient care. The standard policies of that program will apply. The program will figure out if you have to pay any costs for taking part in the study and what those costs will be.

Items that the Sponsor will Provide Free-of-Charge:

You or your insurance company will not be charged for the following parts of this research study:

- One (1) PET scan with FMISO;

Withdrawal from the Study:

You have the right to leave a study at any time without penalty. For your safety, however, you should consider the study doctor's advice about how to go off the study.

The study doctor and sponsor also have the right to take stop your participation in this study without your consent if:

- They believe it is in your best interest;
- You were to object to any future changes that may be made in the study plan;
- or for any other reason.

Contact Information

Contact Dr. David Schuster at (404) 712-4859

- if you have any questions about this study or your part in it,
- if you feel you have had a research-related injury or a bad reaction to the study drug, or
- if you have questions, concerns or complaints about the research

Contact the Emory Institutional Review Board at 404-712-0720 or 877-503-9797 or irb@emory.edu:

- if you have questions about your rights as a research participant.

- if you have questions, concerns or complaints about the research.

You may also let the IRB know about your experience as a research participant through our Research Participant Survey at http://www.surveymonkey.com/s/6ZDMW75

Consent

Please, print your name and sign below if you agree to be in this study. By signing this consent form, you will not give up any of your legal rights. We will give you a copy of the signed consent, to keep.

_____
Name of Subject

_____ _____
Signature of Subject Date Time

_____ _____
Signature of Person Conducting Informed Consent Discussion Date Time

As part of this study, a sample of your tumor tissue obtained from a biopsy or surgery that resulted in the diagnosis of a brain tumor will be sent and stored at ACRIN designated pathology laboratory for analysis as part of this study and for future correlative research.

If you agree to the collection of this sample and storage of the sample, please sign below.

_____ _____
Signature of Subject Date

CURRICULUM VITAE

Revised: 8/5/2011

1. Name: David M. Schuster, M.D.

2. Office Address:

Department of Radiology and Imaging Sciences
Division of Nuclear Medicine and Molecular Imaging
Emory University Hospital, Room E152
1364 Clifton Road
Atlanta, GA 30322

Telephone: 404-712-4859 **Fax:** 404-712-4860 **Pager:** 404-686-5500 (#11161)

3. E-mail Address: dschust@emory.edu

4. Citizenship: US Citizen

5. Current Titles and Affiliations:

a. Academic appointments:

1. Primary appointments:

Assistant Professor, Radiology	2001-present

2. Joint and secondary appointments:

Core Member of the Discovery and Developmental Therapeutics Program, Winship Cancer Institute	2007-present

b. Clinical appointments:

Clinical Director of Positron Emission Tomography	2002-2008
Director, Nuclear Medicine and Molecular Imaging	2006-present

6. Previous Academic and Professional Appointments:

Instructor, Tufts University School of Medicine	1992-1996

7. Previous Administrative and/or Clinical Appointments:

Staff Radiologist at Boston VA Medical Center with teaching Appointment at Tufts University	1992-1996
Staff Radiologist; Asheville, North Carolina VA Medical Center	1997-2001

8. Licensures/Boards:

Georgia Medical License	1996-present
North Carolina Medical License	1998-present
Massachusetts Medical License	1988-1997
DEA certificate	1991-present

9. Specialty Boards:

Diplomate, American Board of Radiology	1992-present
American Board of Radiology Special Competence in Nuclear Radiology	1997-present
Diplomate, American Board of Nuclear Medicine (passed American Board of Nuclear Medicine 10-year recertification, 2007)	1997-2017

10. Education:

B.S., Rensselaer Polytechnic Institute, Troy, New York	1984
M.D., Albany Medical College, Union University	1987

11. Postgraduate Training:

Internship, Internal Medicine, (Program Director: Steven Frisch, MD) Albany Medical Center, Albany, New York	1987-1988
Residency, Diagnostic Radiology, (Program Director: Robert Sarno, MD) Tufts University, Boston, Massachusetts	1988-1992
Fellowship, Nuclear Radiology (Program Director: Naomi Alazraki, MD) Emory University School of Medicine, Atlanta, Georgia	1995-1996

12. Committee Memberships:

a. **National and International**:

Society of Nuclear Medicine Coding and Reimbursement Committee	2002-2004
RSNA Radiology Research Study Section	2011
American Imaging Management Specialty Physician Advisory Panel	2011
SNM Physicians from Academic Institutions Working Group	2011

b. **Regional and State:**

Society of Nuclear Medicine - Southeastern Chapter Council	2005-2009

c. **Institutional:**

i. Emory University:

Emory University Radiation Safety Committee	2004-present
Emory University Public Art Committee	
Member:	2007-present
Co-Chair:	2009-present
Emory University Visual Arts Gallery Committee	2010-present

ii. Emory University School of Medicine:

Radiology Medical Student Course Task Force	2001-2005
Infrastructure Committee for the School of Medicine Strategic Plan	2009-2010

iii. Emory Department of Radiology:

Radiology Resident/Education Selection Committee	2001-2005
Emory Nuclear Medicine Research Committee	2001-present
Nuclear Medicine Resident/Education Selection Committee	2001-present
Radiology Professional Development Committee	2002-2004
Radiology Strategic Planning Committee	2006-present
Radiology Clinical Operations Committee	2006-present

Radiology Vice-Chair for Research Search Committee	2007-2009
Radiology Research Leadership Council	2009-present

13. Consultantships:

Scientific Advisor for Nihon Medi-Physics Co., Ltd	5/2003-11/2003

14. Manuscript Reviewer:

Journal of Nuclear Medicine	2004-present
American Journal of Kidney Diseases	2010-present

15. Honors and Awards:

Cum Laude, Rensselaer Polytechnic Institute	1984
Alpha Omega Alpha	1987
Cum Laude, Albany Medical College	1987
Teaching Award at Tufts University/Boston VA for establishing a Radiology resident learning center	1995
Excellence in Public Service Award for helping to establish "Clot Busters" Team Asheville, North Carolina VA Medical Center	2000
Society of Nuclear Medicine - Tetalman Award for recognition for young investigator and teacher	2002
Society of Nuclear Medicine - Education and Research Foundation Pilot Grant	2003
Society of Nuclear Medicine - Award for a Top Three Clinical Paper in Journal of Nuclear Medicine	2008
Georgia Cancer Coalition Distinguished Cancer Clinician and Scientist	2009-present
Emory University Volunteer Creativity and Arts Award for contribution to furthering the arts at Emory University	2010

16. Society Memberships:

a.	Society of Nuclear Medicine	1997-present
b.	American College of Radiology	1992-present
c.	Radiological Society of North America	1992-present
d.	American Roentgen Ray Society	1992-present
e.	Academy of Molecular Imaging	2002-present

17. Research Focus:

My research focuses on molecular and nuclear imaging, with a special emphasis on improving cancer diagnosis and staging using novel radiotracers and positron emission tomography cancer imaging, including the use of image fusion techniques. A specific concentration of my research is amino acid transport imaging for oncologic applications. I also maintain active research interests in the field of medical informatics and integrative medicine.

18. Grant Support:

a. **Active Support:**

i. Federally Funded:

National Institutes of Health
1 R01 CA 129356-01
anti-[18F]FACBC PET-CT for the Detection and Staging of Recurrent Prostate Carcinoma
Total direct: $244,333.
Dates: 09/1/07-08/31/12, Effort: 2.4 calendar
Role: PI

National Institutes of Health
P 50 CA 128301 (PI: Carolyn C. Meltzer)
Emory Molecular and Translational Imaging Research Center
(Project #1: anti-[18F]FACBC PET-CT for Characterization of Primary Prostate Carcinoma)
Total Direct: $970,940
Dates: 09/24/08-08/31/13, Effort: 1.2 calendar
Role: Co-Investigator, Research Project PI

National Institutes of Health
1 R01 CA121320-01 (PI: Mark Goodman)
Leucine Type Amino Acid Transport in Gliomas
Total direct: $18,079, Effort: 0.6 calendar
Dates: 09/01/07-06/30/12
Role: Co-Investigator

National Institutes of Health
1RO1 CA156755 (PI: Bowei Fei)
Molecular Imaging Directed, 3D Ultrasound-guided, Biopsy System
Total direct: $210,228, Effort: 0.6 calendar
Dates: 1/1/11-12/31/15
Role: Co-Investigator

ii. Contracts:

Nihon Medi-Physics Co., Ltd.
PI: David M. Schuster, M.D.
A Pilot Study of anti-[18F]FACBC PET-CT for Pulmonary Nodules
Total direct: $172,685
Dates: 05/28/08-05/28/11, Effort: 1.2 calendar
Role: PI

iii. Other Funding:

Georgia Cancer Coalition
GCC Distinguished Cancer Clinician and Scientist
Total Direct: $454,545
Dates: 07/01/2009-06/30/2014, Effort: 2.4 calendar
Role: PI

b. Previous Support:

Society of Nuclear Medicine Research & Education Fund/Grant
(PI: David M. Schuster)
Renal Tumor Imaging Utilizing Fusion PET-CT with 18F-FACBC: A Pilot Study of a Novel Radiotracer
Total Direct: $7,000
Dates: 09/27/02-09/12/04
Role: PI

Nihon Medi-Physics
(PI: David M. Schuster)
Pharmacokinetics and Pharmacodynamics of 18F-FACBC in Prostate Cancer
Total Direct: $273,112.00
Dates: 12/1/03-11/30/04
Role: PI

Nihon Medi-Physics
(PI: Mark M Goodman)
Biodistribution and Human Dosimetry of anti-[18F]FACBC
Total Direct: $26,470
Dates: 03/01/06-07/01/06
Role: Co-PI

Nihon Medi-Physics
(PI: Mark M Goodman)
Imaging Analysis of Amino Acid Metabolism in Intracranial Tumors Using PET and 18F-FACBC
Total Direct: $176,806.00
Dates: 08/02/02-08/30/04
Role: Co-PI

18. Clinical Service Contributions: Responsibilities include

As Division Director of Nuclear Medicine and Molecular Imaging, my leadership role focuses on administering a multi-hospital university division including clinical, research, financial, and educational oversight. Responsibilities include integration and growth of Divisional services at Emory University Hospital, The Emory Clinic, Emory Midtown (Crawford-Long), Emory Johns Creek Hospital, Grady Hospital, and the Atlanta VA Medical Center. Significant accomplishments include success of positron emission tomography clinical services at Emory University Hospital, successful transition of Nuclear Medicine services at Emory Midtown to the academic model, successful implementation of a positron emission tomography clinical-research fellowship, and growth of grant funded salary support including NIH sponsored R-01 and P-50 grants.

19. Formal Teaching:

a. Medical Student Teaching:

16 Emory University medical student lectures and seminars (1-2 per year)	2001-2009
General teaching and supervision of medical students	2001-present
Formulated special teaching CD and program for the Medical Student Clerkship for Nuclear Imaging and Therapy	2006

b. Graduate Program

46 Emory University Diagnostic Radiology resident and fellow lectures (4-5 per year)	2001-present
General teaching and supervision of Radiology residents and fellows	2001-present
32 Emory University Nuclear Medicine resident and fellow lectures	2001-present

(3-4 per year)

General teaching and supervision of Nuclear Medicine residents and fellows 2001-present

Formulated special review of literature and teaching CD for the Emory PET rotation 2006

c **Other Teaching:**

Organized Weekly Atlanta VA Pulmonary Conference 2001-2002

20. Supervisory Teaching:

a. **Residency Program (Supervised Projects)**

Gregory Ravizzini, M.D. 2004
Project: Central line injection artifact simulating paratracheal adenopathy on FDG PET imaging
Current Position: Diagnostic Radiology Resident, SUNY Health Science Center, Syracuse, NY

Minh Nguyen, M.D. 2004
Project: CT with histopathologic correlation of FDG uptake with pulmonary granuloma and pleural plaque caused by remote talc pleurodesis
Current Position: Diagnostic Radiology Resident, University of Miami, Miami, FL

Mathew S. Hartman, M.D. 2004
Project: False positive uptake in granulomatous disease with FDG PET-CT
Current Position: Staff Radiologist, Allegheny General Hospital, Pittsburgh, PA

Zachary Collins, M.D. 2004
Project: Comparison of SPECT/CT bone scans versus traditional SPECT Bone scans in Perioperative Evaluation of Vertebral Compression Fractures
Current Position: Faculty, University of Kansas Medical Center, KS

Kush Kumar, M.D. 2005
Project: Incremental benefit of SPECT+CT bone scans over conventional planar and SPECT bone scans in vertebroplasty
Current Position: Staff Physician, Nuclear Medicine, VA Medical Center, Dublin, GA

Mary Koshy, M,D, 2005
Project: Comparison of CT- and FDG-PET-defined gross tumor volume in intensity-modulated radiotherapy for head-and-neck cancer.
Current Position: Staff Physician, Florida Radiation Oncology Group, Jacksonville, FL

Sunit Sebastian, M.D. 2006, 2007
Project: Do oral and intravenous contrast have a role in PET-CT studies of the abdomen and pelvis?

Current Position: Assistant Professor of Radiology and Director, Body Imaging
University of Mississippi Medical Center, Jackson, MS

Thomas B. Reilly, M.D. 2007
Project: Sarcoid-like reaction in the spleen following chemotherapy for non-Hodgkin's lymphoma
Current Position: Vascular Interventional Fellow.

Valeria Moncayo, MD 2011
Project: OctreoScan SPECT-MR.
Current Position: Nuclear Medicine Residency,
Emory University Hospital; Atlanta, GA

CJ Harrison, MD 2011
Project: Intracranial Falx Metastasis Detected with PET-CT.
Current Position: Radiology Residency,
Emory University Hospital; Atlanta, GA

b. Post-doctoral

i. <u>Positron Emission Tomography Clinical Research Fellows</u>

Yamin Dou, MD 2001 – 2002
Project: Intensive Didactic and Practicum on PET Interpretation and Clinical Relevance.
Current Position: Staff Radiologist,
Lahey Clinic; Burlington, MA

Scott C. Bartley, MD 2001-2002
Project: Intensive Didactic and Practicum on PET Interpretation and Clinical Relevance.
Current Position: Staff Physician,
VA Medical Center/Emory University Hospitals; Atlanta, GA

Fabio P. Esteves, MD 2002 – 2003
Project: Intensive Didactic and Practicum on PET Interpretation and Clinical Relevance.
Current Position: Staff Physician,
Emory University Hospitals; Atlanta, GA

Christopher Swingle, MD 2003 – 2004
Project: 1) Intensive Didactic and Practicum on PET Interpretation and Clinical Relevance. 2) Xanthogranulomatous pyelonephritis characterized on PET/CT.
Current Position: Staff Physician,
SSM/St. Mary's Health Center; Richmond Heights, MO

Arturo Lira, MD, 2004 – 2005
Project: Intensive Didactic and Practicum on PET Interpretation and Clinical Relevance.
Current Position: Private Prcatice,
Amarillo, Texas

Sergei Roumiantsev, MD 2005 – 2006
Project: Intensive Didactic and Practicum on PET Interpretation and Clinical

Relevance.
Current Position: Private Practice,
Saudi Arabia

Michael Starsiak, MD 2006 – 2007
Project: 1) Intensive Didactic and Practicum on PET Interpretation and Clinical Relevance. 2) PET/CT scan in the diagnosis of cholangiocarcinoma
Current Position: Nuclear Medicine Physician
Bethesda Naval Hospital, Bethesda, MD

Julio Sepulveda, MD 2007-2008
Project: 1) Intensive Didactic and Practicum on PET Interpretation and Clinical Relevance. 2) The significance of a fatty hilum within an FDG avid lymph node. 3) Posterior Bladder Layering of Excreted F-18 FDG on PET/CT
Current Position: Diagnostic Radiology Resident
University of Puerto Rico, School of Medicine San Juan, PR

Wanzhen Zeng, MD 2007-2008
Project: 1) Intensive Didactic and Practicum on PET Interpretation and Clinical Relevance. 2) The significance of a fatty hilum within an FDG avid lymph node. 3) Posterior Bladder Layering of Excreted F-18 FDG on PET/CT
Current Position: Assistant Professor of Medicine,
Ottawa Hospital, Ottawa, ON

Vitaliy Gavrikov, MD 2008-2009
Project: 1) Intensive Didactic and Practicum on PET Interpretation and Clinical Relevance. 2) Rb-82 Positron Emission Tomography for Post Therapy Brain Tumor Evaluation: A Pilot Study
Current Position: Private practice,
Atlanta, GA

Asad Nasir, MD, 2008-2009
Project: 1) Intensive Didactic and Practicum on PET Interpretation and Clinical Relevance. 2) Rb-82 Positron Emission Tomography for Post Therapy Brain Tumor Evaluation: A Pilot Study
Current Position: Private practice,
Clearwater, FL

Ramisa Ehsan, MD, 2011-present
Project: 1) Intensive Didactic and Practicum on PET Interpretation and Clinical Relevance. 2) In vivo assessment of Folate Receptor (FR) expression using 99mTc-EC20 SPECT/CT (FolateScan) imaging in Squamous Cell Carcinoma of Head and Neck (SSCHN) using Immunohistochemistry (IHC) and Western Blot Assessment (WBA) as reference: A Pilot Study
Current Position: PET/CT Clinical Research Fellow,
Emory University Hospitals, Atlanta, GA

Xuexian S Yan, MD, 2011-present
Project: 1) Intensive Didactic and Practicum on PET Interpretation and Clinical Relevance. 2) Respiratory Gated PET and CT. SUV Measurements Below the Diaphragm.
Current Position: PET/CT Clinical Research Fellow,
Emory University Hospitals, Atlanta, GA

ii. <u>Molecular Imaging Research Associates</u>

Bital Savir-Baruch, MD 2008-2010
Projects: 1) Clinical trials of anti-1-amino-3-[18F]fluorocyclobutane-1-carboxylic acid (anti-[18F]FACBC) PET-CT in recurrent prostate cancer, primary prostate cancer, and solitary pulmonary nodules.
Current Position: Surgical Resident,
Emory University Hospitals, Atlanta, GA

Rianot Amzat, MD 2010-present
Projects: 1) Clinical trials of anti-1-amino-3-[18F]fluorocyclobutane-1-carboxylic acid (anti-[18F]FACBC) PET-CT in recurrent prostate cancer, primary prostate cancer, and solitary pulmonary nodules. 2) Rb-82 Positron Emission Tomography for Post Therapy Brain. 3) FACPC PET for Pancreatic Carcinoma
Current Position: Senior Research Associate,
Emory University, Atlanta, GA

Pooneh Taleghani, MD 2010-present
Projects: 1) Clinical trials of anti-1-amino-3-[18F]fluorocyclobutane-1-carboxylic acid (anti-[18F]FACBC) PET-CT in recurrent prostate cancer, primary prostate cancer, and solitary pulmonary nodules. 2) Rb-82 Positron Emission Tomography for Post Therapy Brain. 3) FACPC PET for Pancreatic Carcinoma
Current Position: Senior Research Associate,
Emory University, Atlanta, GA

iii. <u>Post-Doctoral Research Fellows</u>

Jonathon A Nye, PhD 2005-2007
Projects: 1) Biodistribution and Radiation Dosimetry of the Synthetic Nonmetabolized Amino Acid Analogue Anti-18F-FACBC in Humans. 2) Initial Experience with the Radiotracer Anti-1-Amino-3-18F-Fluorocyclobutane-1-Carboxylic Acid with PET/CT in Prostate Carcinoma. 3) Initial Experience with the Radiotracer anti 1 amino 3 [18F]fluorocyclobutane-1-carboxylic acid (anti-[18F]FACBC) with PET in Renal Carcinoma.
Current Position: Assistant Professor of Radiology,
Emory University, Atlanta, GA

Shengyong Wu, MD, Ph.D 2010-present
Projects: 1) Myocyte Regeneration in Myocardial Hypertrophic Rats with ^{18}F-FACBC. 2) Leucine Type Amino Acid Transport in Gliomas
Current Position: Molecular Imaging Fellow,
Emory University, Atlanta, GA

22. Lectureships, Seminar Invitations, and Visiting Professorships:

a. International

Visiting Professor 2/2000
International Atomic Energy Agency UN Medical Mission
Hanoi, Vietnam

Invited lecture: "Limitations & Pitfalls of PET-CT in the Head and Neck" 5/2005

American Society of Neuroradiology
Toronto, Canada

Invited lecture: "FACBC PET: From Bench to Bedside" 9/2010
8th International Symposium for Future Drug Discovery and Medical Care
Hokkaido University, Hokkaido, Japan

Invited lecture: "FACBC PET: From Bench to Bedside" 9/2010
Post-Conference Satellite Meeting of the
8th International Symposium for Future Drug Discovery and Medical Care
World Trade Center, Tokyo, Japan

b. National

Invited lecture: "Avoiding Pitfalls in Imaging of the Head and Neck" 9/2005
American Association of Otolaryngology
Los Angeles, California

Invited lecture: "Practical PET/CT of the Abdomen" 11/2006
Radiological Society of North America Refresher Course
Chicago, Illinois

Invited lecture: "Limitations & Pitfalls of PET-CT in the Head and Neck" 9/2006
American Society of Head and Neck Radiology
Orlando, Florida

Invited lecture: "PET Breast Imaging" 2/2006
Institute for Advanced Medical Education Breast Cancer Course
Atlanta, Georgia

Invited lecture: "Practical PET/CT of the Abdomen" 11/2007
Radiological Society of North America Categorical Course
Chicago, Illinois

Invited lecture: "Tracer Development, from Bench to Bedside" 10/2007
Southeastern Chapter Society of Nuclear Medicine
Atlanta, Georgia

Invited lecture: "Practical PET/CT of the Abdomen" 11/2008
Radiological Society of North America Categorical Course
Chicago, IL

Invited lecture: "Breast Cancer Imaging with Nuclear Medicine" 11/2008
School of Breast Oncology National Course
Atlanta, Georgia

Invited lecture: "anti-[^{18}F] FACBC" 6/2008
National Institutes of Health Conference on Imaging of Prostate Carcinoma
Rockville, Maryland

Invited lecture: "Practical PET/CT of the Abdomen" 2/2008
Radiological Society of North America Highlights Course
Orlando, Florida

Invited lectures: "Cardiac PET/CT Imaging" 2/2009
"PET-CT in the Head and Neck"
"PET Imaging in Lymphoma"
"PET Imaging in Melanoma"
"Practical PET/CT of the Abdomen and GI Tract"
CT Radiology PET Update Course
San Juan, Puerto Rico

Invited lecture: "Practical PET/CT of the Abdomen and GI Tract" 9/2009
Southeastern Chapter Society of Nuclear Medicine
Birmingham, Alabama

Invited lecture: "Clinical Utility of PET Scanning in Breast Cancer" 11/2009
School of Breast Oncology National Course
Atlanta, Georgia

Visiting Professor 11/2009
Invited lectures: "Expect the Unexpected"
"Practical PET/CT of the Abdomen and GI Tract"
"Clinical Utility of PET Scanning in Breast Cancer"
Albert Einstein College of Medicine
New York, New York

Invited lecture: "Clinical Utility of PET Scanning in Breast Cancer" 11/2010
School of Breast Oncology National Course
Atlanta, Georgia

Invited lecture: 1/2011
"Amino Acid Transport Imaging in Prostate Carcinoma: anti-3-[^{18}F]FACBC and Other PET Radiotracers"
SNM Multimodality Molecular Imaging of Prostate Cancer Symposium
Palm Springs, California

Invited lectures: "PET-CT in the Head and Neck" 2/2011
"PET Imaging in Lymphoma"
"SPECT/CT – PET/CT"
"Benign Thyroid and Parathyroid"
Albert Einstein College Nuclear Medicine Update
San Juan, Puerto Rico

Invited lecture: "Metastases: Beyond the Bone Scan" 4/2011
ASTRO Cancer Imaging and Radiation Therapy Symposium
Atlanta, Georgia

Visiting Professor 5/2011
Invited lectures: "PET-CT in the Head and Neck"
"Clinical Utility of PET Scanning in Breast Cancer"
"Mother of All Nuclear Medicine Board Reviews"
Kansas City Radiological Society
Kansas City, Kansas

c. Local

Invited lecture: "CPT Code Potpourri: What You Don't Know…" 12/1999
Emory University Nuclear Medicine Update Course
Atlanta, Georgia

Invited lecture: "Radiology in Critical Care" 9/1999
VAMC Critical Care Course
Asheville, North Carolina

Invited lecture: "Radiology in Critical Care" 9/1999
VAMC Critical Care Course
Asheville, North Carolina

Invited lectures: "PET Imaging in Lymphoma" 7/2003
"PET Imaging in Melanoma"
"PET and the Thyroid"
"Limitations & Pitfalls of PET-CT in the Head and Neck"
Emory University Nuclear Medicine Update Course
Sea Island, Georgia

Invited lecture: "PET-CT: The First Six Months" 4/2003
Emory University Radiology Grand Rounds
Atlanta, Georgia

Invited lectures: "PET Imaging in Lymphoma" 7/2004
"PET Imaging in Melanoma"
"PET and the Thyroid"
"Limitations & Pitfalls of PET-CT in the Head and Neck"
Emory University Nuclear Medicine Update Course
Sea Island, Georgia

Invited lectures: "PET Imaging in Lymphoma" 7/2005
"PET Imaging in Melanoma"
"PET and the Thyroid"
"Limitations & Pitfalls of PET-CT in the Head and Neck"
Emory University Nuclear Medicine Update Course
Hilton Head, South Carolina

Invited lecture: "Molecular Imaging in Breast and Prostate Cancer" 11/2006
Emory University Winship Cancer Institute Seminar
Atlanta, Georgia

Invited lectures: "PET Imaging in Lymphoma" 7/2006
"PET Imaging in Melanoma"
"PET and the Thyroid"
"Limitations & Pitfalls of PET-CT in the Head and Neck"
Emory University Nuclear Medicine Update Course
Amelia Island, Florida

Invited lectures: "PET Imaging in Lymphoma" 7/2007
"PET Imaging in Melanoma"
"PET and the Thyroid"

"Limitations & Pitfalls of PET-CT in the Head and Neck"
Emory University Nuclear Medicine Update Course
Amelia Island, Florida

Invited Lecture: "Tracer Development, from Bench to Bedside" 11/2007
Emory University Research in Progress Seminar (RIPS)
Atlanta, Georgia

Invited lectures: "PET Imaging in Lymphoma" 7/2008
"PET Imaging in Melanoma"
"PET and the Thyroid"
"Limitations & Pitfalls of PET-CT in the Head and Neck"
Emory University Nuclear Medicine Update Course
Amelia Island, Florida

Invited lecture: "Clinical Utility of PET Scanning in Breast Cancer" 5/2010
Emory University Multidisciplinary Breast Tumor Conference
Atlanta, Georgia

Invited lecture: "Division of Nuclear Medicine and Molecular Imaging" 12/2010
Emory University Research in Progress Seminar (RIPS)
Atlanta, Georgia

Invited lecture: "FACBC PET: From Bench to Bedside" 12/2010
Emory University Radiology Grand Rounds
Atlanta, Georgia

23. Bibliography:

a. Published and accepted research articles (clinical, basic science, other) in refereed journals (mentorship of first author designated by asterisk):

1) Laussucq S, **Schuster D**, Alexander WJ, Thacker WL, Wilkinson HW, Spika JS. False positive DNA probe test for legionella species associated with a cluster of respiratory illnesses. *Journal of Clinical Microbiology* 1988;26(8):1442-1444.

2) Redd SC, **Schuster DM**, Quan J, Plikaytis BD, Spika JS, Cohen ML. Legionellosis in cardiac transplant recipients – results of a nationwide survey. *Journal of Infectious Diseases* 1988;Sep;158(3):651-653.

3) **Schuster DM,** Pedrosa MC, Robbins AH. Magnetic resonance cholangiography. *Abdominal Imaging* 1995;20:353-356.

4) **Schuster DM.** The interface of radiology within a combined "complementary-allopathic" medicine framework. *Journal of Alternative and Complementary Medicine* 1995;4(1):333-337.

5) **Schuster DM,** Gale ME. The malady of incomplete, inadequate, and inaccurate radiology requisition histories: a computerized treatment. *American Journal of Roentgenology* 1996;167:855-859.

6) **Schuster DM.** The integrative hospital explored via acupuncture. *Journal of Alternative and Complementary Medicine* 1996;4(2):503-514.

7) **Schuster DM,** Scheidt K. Artifactual perfusion defect from a hypertrophic first costosternal articulation. *Clinical Nuclear Medicine* 1997;22:642.

8) **Schuster DM,** Mukundan S, Small W, Fajman W. The use of the diagnostic radionuclide ascites scan to facilitate treatment decisions for hepatic hydrothorax. *Clinical Nuclear Medicine* 1998;23:16-18.

9) **Schuster DM,** Alazraki N. Esophageal scarring causing false positive uptake on I-131 whole body imaging. *Clinical Nuclear Medicine* 1998;23:334
10) **Schuster DM.** One possible future. *Journal of Alternative and Complementary Medicine* 1998;4:255-256.

11) **Schuster DM**. Malignant supraclavicular lymph node visualization during Tc-99m HDP bone imaging. *Clinical Nuclear Medicine* 2000;25(5):376-377.

12) **Schuster DM,** Chapman WE, Ahl ET, Ahearne P. Jejunal diverticular hemorrhage localized by red blood cell scintigraphy. *Clinical Nuclear Medicine* 2001;26(11):936-937

13) **Schuster DM,** Hall SE, Couse CB, Swayngim DS, Kohatsu KY. Involving users in the implementation of an imaging order entry system. *Journal of the American Medial Informatics Association* 2003;10(4):315-21.

14) *Nguyen M, Varma V, Perez R, **Schuster DM**. CT with histopathologic correlation of FDG uptake in a patient with pulmonary granuloma and pleural plaque caused by remote talc pleurodesis. *American Journal of Roentgenology* 2004;182:92-94.

15) *Swingle CA, Baumgarten DA, **Schuster DM**. Xanthogranulomatous pyelonephritis characterized on PET/CT. *Clinical Nuclear Medicine* 2005;30(11):728-9.

16) *Ravizzini G, Nguyen M, **Schuster DM**, Halkar RK. Central line injection artifact simulating paratracheal adenopathy on FDG PET imaging. *Clinical Nuclear Medicine* 2004;29(11):735-7.

17) Koshy M, Paulino AC, Howell R, **Schuster D**, Halkar R, Davis LW. F-18 FDG PET-CT fusion in radiotherapy treatment planning for head and neck cancer. *Head and Neck* 2005;27(6):494-502.

18) Paulino AC, Koshy M, Howell R, **Schuster D**, Davis LW. Comparison of CT- and FDG-PET-defined gross tumor volume in intensity-modulated radiotherapy for head-and-neck cancer. *International Journal of Radiation Oncology and Biology Physics* 2005;61(5):1385-92.

19) Bawa M, Sidhu G, Galt JR, **Schuster DM**, Halkar, RK. Choroidal melanoma with hematogenous spread to the liver: F-18 FDG PET/CT findings. *Clinical Nuclear Medicine* 2006;31(6):347-8.

20) Chen AY, Vilaseca I, Hudgins PA, **Schuster D**, Halkar R. PET-CT vs contrast-enhanced CT: what is the role for each after chemoradiation for advanced oropharyngeal cancer? *Head and Neck* 2006;28(6):487-95.

21) Sharma J, Mazzaglia P, Milas M, Berber E, **Schuster DM**, Halkar R, Siperstein A, Weber CJ. Radionuclide imaging for hyperparathyroidism (HPT): which is the best technetium-99m sestamibi modality? *Surgery* 2006;140(6):856-63.

22) **Schuster DM**, Votaw JR, Nieh PT, Yu W, Nye JA, Master V, Bowman FD, Issa MM, Goodman MM. Initial experience with the radiotracer anti-1-amino-3-18f-fluorocyclobutane-1-carboxylic acid with PET/CT in prostate carcinoma. *Journal of Nuclear Medicine* 2007;48(1):56-63 (Featured on Journal Cover).

23) Nye JA, **Schuster DM**, Yu W, Camp VM, Goodman MM, Votaw JR. Biodistribution and radiation dosimetry of the synthetic nonmetabolized amino acid analogue anti-18F-FACBC in humans. *Journal of Nuclear Medicine* 2007;48(6):1017-20.

24) *****Reilly TB, **Schuster DM**, Starsiak MD, Kost CB, Halkar RK. Sarcoid-like reaction in the spleen following chemotherapy for non-Hodgkin's lymphoma. *Clinical Nuclear Medicine* 2007;32(7):569-71.

25) **Schuster DM**, Halkar RK, Esteves FP, Garcia EV, Cook CD, Syed MB, Bowman FD, Votaw JR. Investigation of emission-transmission misalignment artifacts on rubidium-82 cardiac PET with adenosine pharmacologic stress. *Molecular Imagining and Biology* 2008;10(4):201-8.

26) *Zeng W, Styblo T, Li S, Sepulveda JN, **Schuster DM**. Breast angiosarcoma: FDG PET findings. *Clinical Nuclear Medicine* 2009;34(7):443-5.

27) **Schuster DM,** Nye JA, Nieh PT, Votaw JR, Halkar RK, Issa MM, Yu W, Sepulveda J, Zeng W, Young A. Goodman MM. Initial experience with the radiotracer anti 1 amino 3 [18F]fluorocyclobutane-1-carboxylic acid (anti-[18F]FACBC) with PET in renal carcinoma. *Molecular Imaging and Biology* 2009;11(6):434-8.

28) Jani AB, Fox TH, Whitaker D, **Schuster DM**. Case study of anti-1-amino-3-F-18 fluorocyclobutane-1-carboxylic acid (anti-[F-18] FACBC) to guide prostate cancer radiotherapy target design. *Clinical Nuclear Medicine* 2009;34(5):279-84.

29) Esteves FP, Nye JA, Khan A, Folks RD, Halkar RK, Garcia EV, **Schuster DM**, Lerakis S, Raggi P, Votaw JR. Prompt-gamma compensation in Rb-82 myocardial perfusion 3D PET/CT. *Journal of Nuclear Cardiology* 2010;17(2):247-53.

30) Schreibmann E, Nye JA, **Schuster DM**, Martin DM, Votaw J, Fox T. MR-based attenuation correction for hybrid PET-MR brain imaging systems using deformable image registration. *Medical Physics* 2010;37(5):2101-9.

31) *Savir-Baruch B, **Schuster DM**, Jarkas N, Master VA, Nieh PT, Halkar RK, Nye JA, Lewis MM, Crowe RJ, Voll RJ, Camp VM, Bellamy LM, Roberts DL, Goodman MM. Pilot evaluation of anti-1-amino-2-[(18)F] FACPC) PET-CT in recurrent prostate carcinoma. *Molecular Imaging and Biology* 2010 Oct 26. [Epub ahead of print]

32) *Zeng W, Sepulveda JN, Nye J, Votaw JR, Nieh PT, Carew J, **Schuster DM**. Posterior bladder layering of excreted 18F-FDG on PET/CT. *Nuclear Medicine Communications* 2010;31(10):859-63.

33) Esteves FP, Khan A, Correia LC, Nye JA, Halkar RK, **Schuster DM**, Stillman A, Raggi P. Absent coronary artery calcium excludes inducible myocardial ischemia on computed

tomography/positron emission tomography. *International Journal of Cardiology* 2011;147(3):424-7.

34) **Schuster DM**, Savir-Baruch B, Nieh PT, Master VA, Halkar RK, Rossi PJ, Lewis MM, Nye JA, Yu W, Bowman FD, Goodman MM. Recurrent prostate carcinoma detection with anti-1 amino 3 [^{18}F]flurocyclobutane-1-carboxylic acid (*anti*-[^{18}F]FACBC) PET-CT and ^{111}Indium-capromab-pendetide SPECT-CT. *Radiology* 2011;259(3):852-61.

35) *Amzat R, Taleghani P, Savir-Baruch B, Nieh PT, Master VA, Halkar RK, Lewis MM, Faurot M, Bellamy LM, Goodman MM, **Schuster DM**. Unusual presentations of metastatic prostate carcinoma as detected by (*anti*-1-amino-3- [^{18}F] FACBC) PET-CT. *Clinical Nuclear Medicine*. In Press.

36) Nye J, Nashwa J, **Schuster DM**, Savir-Baruch B, Voll RJ, Camp VM, Goodman MM. Biodistribution and Human Dosimetry of Enantiomer-1 of the Synthetic Leucine Analog Anti-1-amino-2-fluorocyclopentyl-1-carboxylic acid (*anti*-2-[^{18}F]FACPC-1). *Nuclear Medicine and Biology*. 2011 Jul 6. [Epub ahead of print]

37) Oka S, Okudaira H, Yoshida Y, **Schuster DM**, Goodman MM, Shirakami Y. Transport mechanisms of trans-1-amino-3-[^{14}C]fluorocyclobutane-1-carboxylic acid in prostate cancer cells. *Nuclear Medicine and Biology.* In Press.

38) *Moncayo V, Martin D, Sarmiento J, Zybtek B, Fox T, **Schuster DM**. In-111Octreoscan SPECT-MRI fusion for the detection of pancreatic insulinoma. *Clinical Nuclear Medicine*. In Press.

39) McConathy J, Yu W, Jarkas N, **Schuster DM**, Soe W, Goodman MM. Radiohalogenated non-natural amino acids as PET and SPECT tumor imaging agents. *Medicinal Research Reviews.* 2011 Jul 26. [Epub ahead of print]

b. Manuscript submitted:

1) Piduru SM, **Schuster DM**, Barron BJ, Dhanasekaran R, Lawson DH, Kim HS. Prognostic Value of F-18 FDG PET-CT in Predicting Survival in Patients with Unresectable Metastatic Melanoma to Liver Undergoing Yttrium-90 (Y90) Radioembolization. Submitted *American Journal of Roentgenology*.

c. Review articles:

1) **Schuster DM**, Alazraki N. Gallium and other agents in diseases of the lung. *Seminars in Nuclear Medicine* 2002;32(3):193-211.

2) **Schuster DM**, Halkar RK. Molecular imaging in breast cancer. *Radiologic Clinics of North America* 2004;42(5):885-908.

3) *Esteves FP, **Schuster DM**. Halkar RK. Gastrointestinal tract malignancies and positron emission tomography: an overview. *Seminars in Nuclear Medicine*. 2006; 36(2):169-81.

d. Book and syllabus chapters:

1) **Schuster DM**, Mosley CK. 2007. Practical PET CT of the abdomen and pelvis. In Wahl RL (Ed), *Categorical Course in Diagnostic Radiology: Clinical PET and PET/CT Imaging*. Oak Brook, IL: RSNA. p. 71-81.

2) **Schuster DM**, Martin DR. 2008. Molecular imaging in individualized cancer management. In Leyland-Jones B (Ed), *Pharmacogenetics of Breast Cancer: Towards the Individualization of Therapy*. New York, NY: Informa Healthcare. p. 291-307.

3) Goodman MM**, Schuster DM**, Savir-Baruch B. 2011. Radiolabeled amino acids for prostate cancer imaging. In McConathy J and Goodman MM (Eds). *Radiolabeled Amino Acids for Tumor Imaging with PET and SPECT*. In Press.

e. Books edited and written:

1) Taylor A, **Schuster DM**, Alazraki N. *A Clinician's Guide to Nuclear Medicine*. Society of Nuclear Medicine, Reston VA, 2000.

2) Taylor A, **Schuster DM**, Alazraki N. *A Clinician's Guide to Nuclear Medicine*, 2nd Edition. Society of Nuclear Medicine, Reston VA, 2006.

f. Other Publications:

i. Abstracts:

1) Pedrosa MC, **Schuster DM,** Robbins AH. Magnetic resonance cholangiography: a useful derivative of routine abdominal MRI. *Gastroenterology* 1995;108(4):A432.

2) Wilson DA, Halkar RK, Galt JR, **Schuster DM**, Scheidt KA, Fajman WJ. Nonuniform attenuation: not just in myocardial perfusion imaging. *Journal of Nuclear Medicine* 1998; 5:276P.

3) **Schuster DM,** Goar SL, Kohatsu KY. Differential utilization of advanced imaging studies between physicians and mid-level health care providers. *American Journal of Roentgenology* 2000;174:74-75.

4) **Schuster DM,** Sorensen CA, Fredrickson LA, Kohatsu KY, Gale ME. Zero tolerance for missed results: an automated imaging results notification system. *American Journal of Roentgenology* 2000; 174:19.

5) **Schuster DM,** Gale ME, Fredrickson LA, Sorensen CA, Kohatsu KY. Report as email: imaging results notification system. *American Journal of Roentgenology* 2000;174:19-20.

6) **Schuster D.M**., Votaw J.R., Halkar R.K., McConathy J., Crowe R.J., Olson J., Goodman M.M. Uptake of the synthetic pet amino acid radiotracer 1-amino-3-[^{18}F]fluorocyclobutane-1-carboxylic acid (^{18}F-FACBC) within primary and metastatic brain cancer compared with 18F-fluorodeoxyglucose (^{18}F-FDG). *Journal of Nuclear Medicine* 2003;5:167p.

7) **Schuster D.M.,** Votaw J.R., Halkar R.K., McConathy J., Crowe R.J., Olson J., Goodman M.M. Validation of human estimated radiation dosimetry from animal data for the synthetic

PET amino acid radiotracer 1-amino-3-[^{18}F]fluorocyclobutane-1-carboxylic acid (^{18}F-FACBC). *Journal of Nuclear Medicine* 2003; 5:322p.

8) *Nguyen MX, Ravizzini GC, Bartley S, **Schuster DM**, Halkar, RK. Does SPECT/CT imaging provide additional benefits over traditional planar and SPECT imaging of hyperfunctioning parathyroids? Annual Meeting of the Radiological Society of North America, 2003.

9) *Hartman MS, **Schuster DM**, Tigges S, Gal AA, Gruden JF. False positive uptake in granulomatous disease with FDG PET-CT. *American Journal of Roentgenology* 2004;182 (4):49.

10) Collins ZS, Nguyen MX, Bartley SC, **Schuster DM**, Halkar RK. Comparison of SPECT/CT bone scans versus traditional SPECT bone scans in perioperative evaluation of vertebral compression fractures. Annual Meeting of the Radiological Society of North America, 2004.

11) Koshy M, Paulino AC, Howell R, **Schuster D**, Halkar R, Davis L. Volumetric analysis of the PET-CT defined target in intensity modulated radiotherapy for head and neck cancer. International Journal Of Radiation Oncology Biology Physics 2004;60(1):S492.

12) Koshy M, Paulino AC, Howell R, **Schuster D**, Halkar R, Davis L. Influence of F-18FDG PET-CT fusion on radiotherapy treatment planning for head and neck cancer. Journal Of Clinical Oncology 2004;22(14):496S.

13) Kumar K CZ, Nguyen M, Bartley SC, **Schuster DM**, Halkar RK. Incremental benefit of SPECT+CT bone scans over conventional planar and SPECT bone scans in vertebroplasty. *Journal of Nuclear Medicine* 2005; 46:79P.

14) **Schuster DM**, Halkar HK, Esiashvili S, Garcia EV, Syed M, White M, Cooke CD, Votaw JR. Clinically significant emission-transmission misalignment artifacts on RB-82 cardiac PET are minimized with adenosine pharmacologic stress. *Journal of Nuclear Medicine* 2005; 46:267P.

15) **Schuster DM**, Votaw JR, Halkar RK, Baumgarten DA, Issa MM, Marshall FF, Nieh PT, Ritenour CW, Ogan K, Amin MB, Goodman M.M. Amino acid transport in renal masses as measured by uptake of the synthetic PET amino acid radiotracer 1-amino-3-[18F]fluorocyclobutane-1-carboxylic acid (18F-FACBC). *Journal of Nuclear Medicine* 2005; 46:384P.

16) **Schuster DM**, Votaw JR, Nieh PT, et al. Initial experience with the radiotracer anti 1 amino 3 [18F] fluorocyclobutane-1-carboxylic acid (anti-[18F] FACBC) with PET/CT in newly diagnosed prostate cancer. *Journal of Nuclear Medicine* 2006;47(1):224P.

17) Sebastian S, Kalra MK, **Schuster DM**, Blake ML. Do oral and intravenous contrast have a role in pet-ct studies of the abdomen and pelvis? Annual Meeting of the Radiological Society of North America, 2006.

18) *Han Y, Starsiak M, Parekh S, **Schuster DM**, Cai Q. PET/CT scan in the diagnosis of cholangiocarcinoma-a preliminary study. Poster for Digestive Disease Week: The American Association for the Study of Liver Diseases (AASLD), The American Gastroenterological Association (AGA), The American Society for Gastrointestinal Endoscopy (ASGE), The Society for Surgery of the Alimentary Tract (SSAT). Los Angeles, 2006.

19) Nye JA , **Schuster DM**, Yu W, Camp VM, Olson J, Goodman MM, Votaw JR. 2007. Whole body PET dosimetry of the synthetic leucine analogue 1-amino-3-[18F] fluorocyclobutane-1-

carboxylic acid (anti-[18F] FACBC) in humans. *Journal of Nuclear Medicine* 2007:48(2):132P.

20) Sebastian S, Blake MA, Blodgett TM, **Schuster DM**, Small WC, Meltzer CC. Use of oral and intravenous contrast in PET-CT studies: To be, or not to be. *Journal of Nuclear Medicine* 2007:48(2):210p.

21) Fox T, Schreibmann E, Lauenstein T, **Schuster D**, Martin D. Deformable image registration using FDG-PET/MRI for metastatic breast cancer detection. *Medical Physics* 2007; 34(6): 2396.

22) Esteves F, Nye J, Khan A, **Schuster DM**, Halkar R, Carew J, Votaw J. Prompt gamma compensation in adenosine stress Rb-82 myocardial perfusion 3D PET/CT – Impact on specificity and normalcy rate. *Journal of Nuclear Medicine* 2008:49(1):2-3p.

23) *Sepulveda J, Zeng W, Carew J, **Schuster DM**. The significance of a fatty hilum within an FDG avid lymph node. *Journal of Nuclear Medicine* 2008:49(1):251-252p.

24) **Schuster DM**, Savir-Baruch B, Nieh PT, Votaw JR, Nye JA, Master V, Halkar H, Bowman FD, Goodman MM. Initial report of a clinical trial of anti-1 amino 3 [18F]fluorocyclobutane-1-carboxylic acid (anti-[18F]FACBC) PET-CT in recurrent prostate cancer. *Journal of Nuclear Medicine* 2009:50(Suppl. 2):136p.

25) Montilla JL, Kim H, **Schuster DM**, Barron B. Tc99m-MAA and Y-90 SIRT SPECT/CT: from therapy planning to therapeutic intervention; how we do it. 35th Annual Scientific Meeting of the Society of Interventional Radiology, March, 2010, Tampa, FL (Poster)

26) Williams R, McIntosh EB, Montilla JL, **Schuster DM**, Barron J, Kim HS, Pre-Y-90 SIRT shunt study for metastatic liver tumor: is it necessary? 35th Annual Scientific Meeting of the Society of Interventional Radiology, March, 2010, Tampa, FL

27) *Savir-Baruch B, **Schuster DM**, Jarkas N, Master V, Nieh PT., Halkar RK., Nye JA, Lewis MM, Roberts DL, Goodman MM. Pilot evaluation of 1-amino-2-[18F]fluorocyclopentane-1-carboxylic acid (anti-2-[18F]FACPC) PET-CT in recurrent prostate carcinoma. *Journal of Nuclear Medicine* 2010;51(Suppl. 2):237P.

28) **Schuster DM**, Savir-Baruch B, Nieh PT, Master V, Halkar H, Rossi PJ, Lewis MM, Yu W, Bowman FD, Goodman MM. Report of a clinical trial of anti-1 amino 3 [18F]fluorocyclobutane-1-carboxylic acid (anti-[18F]FACBC) PET-CT in recurrent prostate carcinoma. *Journal of Nuclear Medicine* 2010:51(Suppl.2):127p.

29) Yang X, **Schuster DM**, Master V, Nieh P, Fenster A, Fei B. Automatic 3D segmentation of ultrasound images using atlas registration and statistical texture prior. SPIE Medical Imaging 2011: Visualization, Image-Guided Procedures, and Modeling, February, 2011, Lake Buena Vista, FL.

30) Piduru SM, **Schuster DM**, Barron BJ, Dhanasekaran R, Lawson DH, Kim HS. F-18 FDG PET-CT and bremsstrahlung SPECT-CT in predicting survival in patients with unresectable metastatic melanoma to liver undergoing yttrium-90 (Y-90) radioembolization: a preliminary study. Cancer Imaging and Radiation Therapy Symposium of ASTRO/RSNA, April, 2011, Atlanta, GA.

31) *Amzat R, Taleghani P, Savir-Baruch B, Miller DL, Beitler JL, Bellamy LM, Nye JA, Yu W, Goodman W, Goodman MM, **Schuster DM**. Pilot study of the utility of anti-1-amino-3-

[18F]fluorocyclobutane-1-carboxylic acid (anti-3-[18F] FACBC) PET-CT for the non-invasive imaging of lung nodules. *Journal of Nuclear Medicine* 2011:52(Suppl.1):1884.

32) **Schuster D**, Fei B, Fox T, Osunkoya AO. Histopathologic Correlation of Prostatic Adenocarcinoma on Radical Prostatectomy with Pre-Operative Anti-18F Fluorocyclobutyl-Carboxylic Acid Positron Emission Tomography/Computed Tomography. Modern Pathology 2011;24:222A-223A.

ii. Letters to the Editor:

1) Redd SC, **Schuster DM**, Quan J, Plikaytis BD, Spika JS, Cohen ML. Legionellosis in cardiac transplant recipients: results of a nationwide survey. *Journal of Infectious Diseases* 1988;158(3):651.

2) **Schuster DM**, Achong DM, Knox TA, Fawaz KA. Duodenal perforation by a biliary endoprosthesis: evaluation by hepatobiliary scintigraphy. *Journal of Clinical Gastroenterology* 1992;15(2):177.

3) **Schuster DM**. Indeterminate adrenal masses. *Journal of Nuclear Medicine* 2000;41(5):963.

CURRICULUM VITAE
Emory University School of Medicine

Hyun S. "Kevin" Kim, MD, FSIR

BIOGRAPHICAL

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Citizenship: United States

APPOINTMENTS AND POSITIONS

CURRENT TITLES AND AFFILIATIONS
1. Academic Appointments

2008 – Present	Emory University School of Medicine Atlanta, Georgia	Associate Professor of Radiology in Tenure Track
2009 – Present	Emory University School of Medicine Atlanta, Georgia	Secondary appointment, Associate Professor of Surgery
2009 – Present	Emory University School of Medicine Atlanta, Georgia	Secondary appointment, Associate Professor of Hematology and Oncology
2009 – Present	Emory University School of Medicine Atlanta, Georgia	Faculty Member Winship Cancer Institute
2008 – Present	Johns Hopkins University School of Medicine Baltimore, Maryland	Volunteer Faculty, Departments of Radiology, Surgery, Gynecology and Obstetrics

2. Clinical Appointments

2008 – Present	Emory Healthcare	Attending Physician
2008 – Present	Children's Healthcare of Atlanta	Attending Physician
2008 – Present	Grady Healthcare	Attending Physician

3. Other Appointments

2008 – Present	Emory University School of Medicine Atlanta, Georgia	Director, Division of Interventional Radiology and Image guided Medicine
2008 – Present	Emory University School of Medicine Atlanta, Georgia	Director of Interventional Radiology and Image guided Medicine Research
2008 – Present	Emory University School of Medicine Atlanta, Georgia	Director of Interventional Oncology
2008 – Present	Emory Healthcare Emory University Hospital Emory Crawford Long Hospital Grady Memorial Hospital Children's Healthcare of Atlanta at Egleston	Chief, Interventional Radiology

PREVIOUS ACADEMIC AND PROFESSIONAL APPOINTMENTS

1999 – 2000	Johns Hopkins University School of Medicine Baltimore, Maryland	Instructor of Radiology
2001 – 2008	Johns Hopkins University School of Medicine Baltimore, Maryland	Assistant Professor of Radiology and Surgery
2007 – 2008	Johns Hopkins University School of Medicine Baltimore, Maryland	Assistant Professor of Gynecology and Obstetrics

PREVIOUS ADMINISTRATIVE AND/OR CLINICAL APPOINTMENTS

2001	Johns Hopkins University School of Medicine Baltimore, Maryland	Associate Director of Fellowship in Vascular & Interventional Radiology
2001 - 2005	Johns Hopkins University	Director of Fellowship in

	School of Medicine Baltimore, Maryland	Vascular & Interventional Radiology
2001 - 2005	Johns Hopkins University School of Medicine Baltimore, Maryland	Director of Outreach Education/ / Medical Student/Resident Education
2001 – 2008	Johns Hopkins University School of Medicine Baltimore, Maryland	Director of Gynecologic Interventions
2001 – 2008	Johns Hopkins Hospital Baltimore, Maryland	Attending Physician

CERTIFICATION AND LICENSURE

MEDICAL OR OTHER PROFESSIONAL LICENSURE:

Texas Medical License #K0504 (Current status: inactive)		1996-1999
Maryland Medical License #D0054562		4/7/99 – 9/30/10
Georgia Medical License #061261		6/6/08 – 8/31/09
Federal DEA	BK5228122	4/23/98-12/31/10
Maryland DPS	60100953 M48129	1/30/97-9/30/08

SPECIALTY CERTIFICATION:

Diplomate, American Board of Radiology	5/19/1999-Permanent
Certificate of Added Qualifications in Vascular & Interventional Radiology American Board of Radiology	11/11/02-11/11/12

EDUCATION AND TRAINING

UNDERGRADUATE:

1988-1991	University of California at Berkeley Berkeley, California	B.A., Molecular & Cell Biology

GRADUATE:

1991 - 1993	Harvard University Harvard School of Dental Medicine & Medical School

	First two years of Medical School Curriculum Boston, Massachusetts	
1993 - 1995	Medical College of Virginia School of Medicine Richmond, Virginia	M.D.
2002 - 2004	Johns Hopkins University School of Medicine **&** Carey Business School Baltimore, Maryland	Certificate in Business of Medicine

POST-GRADUATE:

1995 - 1999	UT MD Anderson Cancer Center- University of Texas Medical School Houston, Texas	Diagnostic Radiology Residency
1999 - 2000	Johns Hopkins University School of Medicine Baltimore, Maryland	Fellowship in Cardiovascular & Interventional Radiology

SERVICE

COMMITTEE MEMBERSHIPS

1. National/International

Professional Education Committee Society of Interventional Radiology	2006-Present
Executive Committee: Continuing Medical Education Committee American Roentgen Ray Society	2007-Present
CME Approval Subcommittee-Interventional Section of Education American Roentgen Ray Society	2007-Present
Publication Advisory Committee Society of Interventional Radiology	2009-Present

2. Institutional

Appointment and Promotions Committee, Department of Radiology Emory University School of Medicine	2008-Present
Executive Committee, Department of Radiology	2008-Present

Emory University School of Medicine

Ad hoc Education Committee, Department of Radiology Emory University School of Medicine	2008-Present
Ad hoc Residency Selection Committee, Department of Radiology Emory University School of Medicine	2008-2009
Hospital Planning Committee, Emory Healthcare	2008-Present
New Clinic Planning Committee, Emory Clinic	2008-Present

EDITORIAL ACTIVITIES

Manuscript Reviewer:

Cardiovascular Interventional Radiology	2004-present
Southern Medical Journal	2004-present
Catheterization and Cardiovascular Interventions	2005-present
European Journal of Vascular and Endovascular Surgery	2006-present
American Journal of Obstetrics & Gynecology	2007-present
Journal of the Pancreas	2007-present
Clinical Medicine: Oncology	2007-present
Thrombosis Journal	2007-present
Society of Interventional Radiology News Editorial Board	2007-present
Journal of Women's Health	2008-present
Journal of Vascular and Interventional Radiology	2008-present
American Journal of Roentgenology	2008-present
Fertility and Sterility	2008-present
Journal of Urology	2009-present
Cancer	2009-present
Yonsei Medical Journal	2009-present

HONORS AND AWARDS

Harvard Medical School Student Research Fellowship	1992-1993
Harvard University Scholarship	1991-1993
Children's Hospital, Boston, Neonate Research Fellowship for Medical Students	1992
Certificate of Merits, RSNA Meeting	1997
Magna Cum Laude, ARRS Meeting	1998
Teacher of the Year CVDL – Interventional Radiology Johns Hopkins University School of Medicine	2001-2002
William Gatewood Research Fellowship	2005-2006
Fellow of the Society of Interventional Radiology	2008

ACTIVITIES IN PROFESSIONAL AND SCIENTIFIC SOCIETIES

MEMBERSHIP

The Johns Hopkins Medical and Surgical Association	1999-Present
Society of Interventional Radiology	1999-Present
Cardiovascular and Interventional Radiological Society of Europe	1999-Present
American College of Radiology	1999-Present
Radiological Society of North America	1999-Present
American Roentgen Ray Society	1999-Present
American Heart Association – Council on Radiology	1999-Present
American University Radiologists	2008-Present
International Society of Gastrointestinal Oncology	2008-Present
The European Association for the Study of the Liver	2009-Present
American Society of Clinical Oncology	2009-Present
North American NeuroEndocrine Tumor Society	2009-Present

Southeastern Angiographic Society 2009-Present

ORGANIZATION OF NATIONAL/INTERNATIONAL CONFERENCES

9/2000	Faculty and Proctor, Practicum in Interventional Radiology at Johns Hopkins Johns Hopkins Medical Institutions, Baltimore, MD.
5/2001	Faculty and Proctor, Practicum in Interventional Radiology at Johns Hopkins Johns Hopkins Medical Institutions, Baltimore, MD.
6/2001	Faculty, "At the Crest on the Wave: A Retreat Exploring Controversies on the Cutting Edge of Interventional Radiology" the 8th annual Penn-Hopkins-Maryland Conference on Interventional Radiology
2002	Moderator for Legs for Life Workshop at the 27th Annual Scientific Meeting of the Society of Cardiovascular and Interventional Radiology Meeting, April, 2002, Baltimore, MD
2002	Moderator for Carotid Stenting Workshop at the 27th Annual Scientific Meeting of the Society of Cardiovascular and Interventional Radiology Meeting, April, 2002, Baltimore, MD
6/2002	Course Director (IR) of the State of the art Glue Embolization (Sponsor: Cordis), Johns Hopkins Hospital
10/2002	Course Director (IR) of the Johns Hopkins Practicum in Embolothearpy at The Johns Hopkins Medical Institutions, Baltimore, MD.
11/2002	Course Director (IR) of the State of the art Glue Embolization (Sponsor: Cordis), Johns Hopkins Hospital
6/2003	Course Director (IR) of the State of the art Glue Embolization (Sponsor: Cordis) Johns Hopkins Hospital
11/2003	Course Director (IR) of the State of the art Glue Embolization (Sponsor: Cordis) Johns Hopkins Hospital
2003-2008	Chair, Scientific Committee, Korean American Medical Association
2003	Course Director of the Johns Hopkins Practicum in Embolothearpy at the Johns Hopkins Medical Institutions, Baltimore, MD.
2004	Moderator for Legs for Life Workshop at the 29th Annual Scientific Meeting of the Society of Interventional Radiology Meeting, April, 2004, Phoenix, AZ
2004	Course Director of the 25th Korean American Medical Association Annual Scientific Meeting, Cambridge, MD

2005	Course Director of the 26th Korean American Medical Association Annual Scientific Meeting, Williamsburg, VA
2007	Moderator for Varicose Vein Workshop at the 32th Annual Scientific Meeting of the Society of Interventional Radiology Meeting, March 2007, Seattle, WA
2007	Moderator for Scientific Session (Interventional oncology) at the Annual Scientific Meeting of the American Roentgen Ray Society Meeting, May 2007, Orlando, FL
2008	Moderator for Varicose Vein Workshop at the 33rd Annual Scientific Meeting of the Society of Interventional Radiology Meeting, March 2008, Washington, DC
2008	Chair for Interventional Radiology Section at the 12th Asian Oceanic Congress of Radiology, October 2008, Seoul, Korea

RESEARCH FOCUS

Dr. Kim is an interventional radiologist and image guided medicine physician who specializes in image-guided interventional oncology. His research interests and publications have centered on investigating more effective and less invasive novel treatments in the fields of Image-guided therapies in Oncology, Venous Hematologic Disease and Women's Health, Venous Disease. More specifically, transcatheter therapies for liver cancer, percutaneous ablations, MRI-guided interventions, high intensity focused ultrasound ablations, thrombolysis and new thrombectomy treatments are of his interests. He has successfully completed and is conducting multiple scientific trials with external fundings. His works have contributed greatly to making these therapies readily available to patients who suffer from these diseases. Translational research with development of new novel minimally invasive technologies with high impact in the clinical arena is the focus of his career.

GRANT SUPPORT

ACTIVE SUPPORT

Grant Title:	MR guided Radifrequency Ablation of Sheep Uterus: Assessment of MR Guidance and Monitoring Techniques, RF Ablation Protocol and Histopathologic Correlation
Funding Agency:	Gatewood Fellowship, Johns Hopkins University
Role:	Principal Investigator
Dates:	2005 - Present
Total Direct Cost:	$10,000

Grant Title:	MR guided Cryoablation Of Uterine Leiomyomata: A Clinical Trial With Histopathological Correlation
Funding Agency:	Society of Interventional Radiology Foundation
Role:	Principal Investigator
Dates:	2007 - Present
Total Direct Cost:	$25,000

PENDING GRANT

Grant Title:	Molecular Characterization of Uterine Tissue Thermal Therapy
Funding Agency:	NIH R01
Role:	Co-Principal Investigator, 10% effort/salary
Total Direct Cost:	$1.2M

Grant Title:	MRI guided High Intensity Focused Ultrasound for Tumor Ablation
Funding Agency:	Philips Medical Systems
Role:	Principal Investigator, 25% effort/salary
Total Direct Cost:	$300,000

PREVIOUS SUPPORT

Grant Title:	MR Guided Focused Ultrasound Fibroid Ablation of Uterine Fibroids (Protocol UF002) at the Johns Hopkins Hospital
Funding Agency:	InSightec
Role:	Principal Investigator, 25% effort/salary
Dates:	2002 - 2003
Total Direct Cost:	$154,500

Grant Title:	MR Guided Focused Ultrasound Fibroid Surgery of Uterine Fibroids (Protocol UF005) at the Johns Hopkins Hospital
Funding Agency:	InSightec
Role:	Principal Investigator, 25% effort/salary
Dates:	2003 - 2005
Total Direct Cost:	$232,020

Grant Title:	Uterine Fibroid Registry Core Site by CIRREF at the Johns Hopkins Hospital
Funding Agency:	CIRREFF
Role:	Principal Investigator
Dates:	2002 - 2005
Total Direct Cost:	No grant support

Grant Title:	MR Guided Focused Ultrasound Fibroid Surgery in the Treatment of Uterine Fibroids; Long Term Follow-up at the Johns Hopkins Hospital
Funding Agency:	InSightec
Role:	Principal Investigator, 10% effort/salary
Dates:	2004 - 2008
Total Direct Cost:	$159,547

CLINICAL SERVICE CONTRIBUTIONS

Clinical Program Building / Leadership:

2001 - 2008 Led establishment of 1st multidisciplinary fibroid center
Johns Hopkins Medical Institutions

- Established multidisciplinary approach to a disease once thought of as only surgical cure
- Contributed to design of the center and treatment approach
- Trained radiologists and gynecologist in planning the treatments for best efficacy and safety

2001 - 2008 Director of Gynecologic Interventions
Johns Hopkins Medical Institutions

- Established minimally invasive non-surgical treatments for a variety of diseases
- Established the service from none to one of the most successful practice in the region
- Secured exponential growth non-invasive percutaenous interventional services
- Trained radiologists and gynecologist in planning the treatments for best efficacy and safety

2001 - 2003 Principle director of Legs for Life Program
Johns Hopkins Medical Institutions

- Successfully established outreach/awareness program
- Successfully establish screening program with high patient satisfaction

2002 - 2005 Led clinical evaluation of clinical applications of MR-g Focused Ultrasound
Johns Hopkins Medical Institutions

- Established clinical efficacy of High Intensity Focused Ultrasound in a variety of applications
- Contributed to design of subsequent High Intensity Focused Ultrasound
- Trained radiologists in the use of this new technology

2003 - 2006 Founding member and on the board of directors, Cosmetic Center
Johns Hopkins Medical Institutions

- Establish the 1st of such multidisciplinary center at Johns Hopkins
- Secured exponential growth in non-invasive venous interventional services
- Developed complementary program of education and outreach for community physicians
- Optimized service in support of outstanding patient satisfaction in a competitive environment

2008 - Present Director of Interventional Radiology and Image guided Medicine
Emory University School of Medicine
Chief of Interventional Radiology Services
Emory Healthcare
Emory University Hospital
Emory University Hospital Midtown
Wesley Woods Geriatric Center
Children's Healthcare at Egleston
Grady Memorial Hospital
Emory Winship Cancer Institutte

- *Growth of overall clinical volumes of year*
- *Oversaw expansion and renovation of IR infastructure*
- *Complete overhaul of IR practice for patient safety, quality and service*
- *Complete overhaul of educational programs in IR*
- *Development and implementation of practice quality improvement programs*

TEACHING

Educational Program Building / Leadership:

Medical Student Education

- Established the education of Interventional Radiology in a systemic method to 2nd through 4th year medical students as a part of the standard Hopkins curriculum
- Establish elective program to introduce interventional radiology research to medical students
- Personally mentored and guided 13 Hopkins medical students to some of the most prestigious Diagnostic Radiology residency programs

Fellowship Education

- Successfully recruited new fellows at a time of severe radiologist shortages
- Successfully retained one of the largest IR fellowship at time of severe radiologist shortages
- Personally taught, guided and mentored 50 IR fellows
- Facilitated fellow development
- Develop and maintained the fellowship as one of the most prestigious and most sought-after nation-wide.

Faculty preceptor for Johns Hopkins Fellowship in Vascular and Interventional Radiology — 1/1/01-Present

Faculty preceptor for Johns Hopkins Residency in Diagnostic Radiology – CVDL Rotation — 1/1/01-Present

Faculty preceptor for Johns Hopkins Medical Student Radiology Electives — 1/1/01-Present

Faculty preceptor for advanced clinical and research electives for medical students Cardiovascular and Interventional Radiology
Johns Hopkins University School of Medicine — 1/1/01-Present

FORMAL TEACHING

Medical Student Teaching:

1. Introduction to Cardiovascular and Interventional Radiology; Medical Students MS III & IV [Course Director: Dr. Magid], Johns Hopkins School of Medicine, Baltimore, MD, 2000-2001 academic year:
September 11, 2000, September 18, 2000, October 10, 2000, October 17, 2000, November 7, 2000, November 30, 2000, January 3, 2001, January 10, 2001, February 7, 2001, February 9, 2001, February 20, 2001, February 27, 2001, April 10, 2001, April 18, 2001, May 8, 2001, May 17, 2001

2. Introduction to Cardiovascular and Interventional Radiology; Medical Students MS III & IV [Course Director: Dr. Magid], Johns Hopkins School of Medicine, Baltimore, MD, 2001-2002 academic year:
September 27, 2001, October 2, 2001, October 22, 2001, October 29, 2001, November 6, 2001, November 8, 2001, November 16, 2001, February 5, 2002, February 7, 2002, February 19, 2002, February 20, 2002, March 14, 2002, April 16, 2002, April 17, 2002, May 17, 2002

3. Introduction to Cardiovascular and Interventional Radiology; Medical Students MS III & IV [Course Director: Dr. Magid], Johns Hopkins School of Medicine, Baltimore, MD, 2002-2003 academic year:
September 10, 2002, October 22, 2002, November 25, 2002, February 10, 2003, February 11, 2003, March 12, 2003, April 14, 2003

4. Introduction to Cardiovascular and Interventional Radiology; Medical Students MS III & IV [Course Director: Dr. Magid], Johns Hopkins School of Medicine, Baltimore, MD, 2003-2004 academic year:
September 15, 2003, September 24, 2003, February 13, 2004, February 23, 2004, April 1, 2004, April 12, 2004, April 29, 2004, May 17, 2004

5. Introduction to Cardiovascular and Interventional Radiology; Medical Students MS III & IV [Course Director: Dr. Magid], Johns Hopkins School of Medicine, Baltimore, MD, 2004-2005 academic year:
Sept. 16, 2004, Oct. 13, 2004, Oct. 20, 2004, Nov. 3, 2004, Nov. 17, 2004, Jan. 24, 2005, Feb. 7, 2005, Feb. 17, 2005, March 7, 2005, April 11, 2005, April 21, 2005, May 16, 2005, May 25, 2005

6. Future of Interventional Radiology, Emory MIII-VI
Interventional Radiology and Image Guided Medicine
Emory University School of Medicine, Atlanta, GA, Jan 18, 2009

Graduate/Resident/Fellow Teaching:

1. Senior Diagnostic Radiology Board Review
The Russell H. Morgan Department of Radiology and Radiological Science
Johns Hopkins University School of Medicine, Baltimore, MD, January 25, 2001

2. Uterine Fibroid Embolization
Johns Hopkins CVDL Lecture Series [Course Director: Sally Mitchell]
The Russell H. Morgan Department of Radiology and Radiological Science
Johns Hopkins Medical Institutions, Baltimore, MD, April 24, 2001

3. Pulmonary Angiography and Caval Filters
Johns Hopkins CVDL Lecture Series [Course Director: Sally Mitchell]
The Russell H. Morgan Department of Radiology and Radiological Science
Johns Hopkins Medical Institutions, Baltimore, MD, September 4, 2001

4. Percutaneous Management of Abscess/Pseudocyst, Advanced Pancreatic Intervention, Johns Hopkins CVDL Lecture Series [Course Director: Sally Mitchell]
The Russell H. Morgan Department of Radiology and Radiological Science
Johns Hopkins Medical Institutions, Baltimore, MD, October 9, 2001

5. Renal Artery PTA/Stent, Johns Hopkins CVDL Lecture Series [Course Director: Sally Mitchell]
The Russell H. Morgan Department of Radiology and Radiological Science
Johns Hopkins Medical Institutions, Baltimore, MD, November 13, 2001

6. State of the Art TIPS, Johns Hopkins CVDL Lecture Series [Course Director: Sally Mitchell]
The Russell H. Morgan Department of Radiology and Radiological Science
Johns Hopkins Medical Institutions, Baltimore, MD, October 30, 2001

7. Current Status of IVC Filter Filtration, Johns Hopkins Resident Lecture Series [Course Director: Stan Siegleman]
The Russell H. Morgan Department of Radiology and Radiological Science,
Johns Hopkins Medical Institutions, Baltimore, MD, January 25, 2001

8. Pseudocyst Management , Johns Hopkins CVDL Lecture Series [Course Director: Sally Mitchell]
The Russell H. Morgan Department of Radiology and Radiological Science,
Johns Hopkins Medical Institutions, Baltimore, MD, November 12, 2002

9. Advanced TIPS , Johns Hopkins CVDL Lecture Series [Course Director: Sally Mitchell]
The Russell H. Morgan Department of Radiology and Radiological Science,
Johns Hopkins Medical Institutions, Baltimore, MD, February 4, 2002

10. Portal Hypertension, Johns Hopkins CVDL Lecture Series [Course Director: Sally Mitchell]
The Russell H. Morgan Department of Radiology and Radiological Science
Johns Hopkins Medical Institutions, Baltimore, MD, January 28, 2002

11. Uterine Fibroid Embolization I, Johns Hopkins CVDL Lecture Series [Course Director: Sally Mitchell]
The Russell H. Morgan Department of Radiology and Radiological Science
Johns Hopkins Medical Institutions, Baltimore, MD, October 17, 2002

12. Uterine Fibroid Embolization II, Johns Hopkins CVDL Lecture Series [Course Director: Sally Mitchell]
The Russell H. Morgan Department of Radiology and Radiological Science
Johns Hopkins Medical Institutions, Baltimore, MD, October 31, 2002

13. Infertility and Fallopian Tube Recanalization, Johns Hopkins CVDL Lecture Series [Course Director: Sally Mitchell]
The Russell H. Morgan Department of Radiology and Radiological Science
Johns Hopkins Medical Institutions, Baltimore, MD, October 29, 2002

14. State of the Art Gynecologic Intervention
The Russell H. Morgan Department of Radiology and Radiological Science
Johns Hopkins Medical Institutions, Baltimore, MD, September 10, 2002

15. Venous Intervention, Johns Hopkins CVDL Lecture Series [Course Director: Sally Mitchell]
The Russell H. Morgan Department of Radiology and Radiological Science
Johns Hopkins Medical Institutions, Baltimore, MD, January 8, 2002

16. Fallopian Tube Recannalization, Johns Hopkins CVDL Lecture Series [Course Director: Sally Mitchell]
The Russell H. Morgan Department of Radiology and Radiological Science,
Johns Hopkins Medical Institutions, Baltimore, MD, January 31, 2002

17. Advanced Treatment in Uterine Fibroids, Johns Hopkins CVDL Lecture Series [Course Director: Sally Mitchell]
The Russell H. Morgan Department of Radiology and Radiological Science,
Johns Hopkins Medical Institutions, Baltimore, MD, July 15, 2002

18. Uterine Fibroid Embolization, Johns Hopkins Resident Lecture Series [Course Director: Stan Siegleman]
The Russell H. Morgan Department of Radiology and Radiological Science
Johns Hopkins Medical Institutions, Baltimore, MD, March 5, 2002

19. TIPS, Current Status, Johns Hopkins CVDL Lecture Series
[Course Director: Hyun S. Kim]
The Russell H. Morgan Department of Radiology and Radiological Science
Johns Hopkins Medical Institutions, Baltimore, MD, August 7, 2003

20. Percutaneous Treatment of Uterine Fibroids, Johns Hopkins CVDL Lecture Series [Course Director: Hyun S. Kim]
The Russell H. Morgan Department of Radiology and Radiological Science,
Johns Hopkins Medical Institutions, Baltimore, MD, August 5, 2003

21. Catheter directed Thrombolysis in PAOD, Johns Hopkins CVDL Lecture Series
[Course Director: Sally Mitchell]
The Russell H. Morgan Department of Radiology and Radiological Science
Johns Hopkins Medical Institutions, Baltimore, MD, May 15, 2003

22. Catheter directed Thrombolysis and Thrombolytics, Johns Hopkins CVDL Lecture Series [Course Director: Sally Mitchell]
The Russell H. Morgan Department of Radiology and Radiological Science,
Johns Hopkins Medical Institutions, Baltimore, MD, April 22, 2003

23. Uterine Fibroids Embolization, Current Concepts, Clinical Aspects of Reproductive Health [Course Director: Wanda Nicholson] The Johns Hopkins School of Public Health, Baltimore, MD, April 16, 2003

24. Catheter-directed Thrombolysis of DVT, Johns Hopkins CVDL Lecture Series [Course Director: Hyun S. Kim]
The Russell H. Morgan Department of Radiology and Radiological Science,
Johns Hopkins Medical Institutions, Baltimore, MD, September 21, 2004

25. Basic Uterine Fibroid Embolization, Johns Hopkins CVDL Lecture Series
[Course Director: Hyun S. Kim]
The Russell H. Morgan Department of Radiology and Radiological Science,
Johns Hopkins Medical Institutions, Baltimore, MD, August 3, 2004

26. Percutaneous Dialysis Catheter, Johns Hopkins CVDL Lecture Series
[Course Director: Hyun S. Kim]
The Russell H. Morgan Department of Radiology and Radiological Science
Johns Hopkins Medical Institutions, Baltimore, MD, July 27, 2004

27. New developments in percutaneous uterine fibroid treatments, Current Concepts, Clinical Aspects of Reproductive Health
[Course Director: Wanda Nicholson] The Johns Hopkins School of Public Health, Baltimore, MD, April 7, 2004

28. Uterine Fibroid Embolization, Johns Hopkins Resident Lecture Series [Course Director: Stan Siegleman]
The Russell H. Morgan Department of Radiology and Radiological Science
Johns Hopkins Medical Institutions, Baltimore, MD, November 30, 2005

29. Uterine Fibroid Embolization, Johns Hopkins CVDL Lecture Series
[Course Director: Kelvin Hong]
The Russell H. Morgan Department of Radiology and Radiological Science,
Johns Hopkins Medical Institutions, Baltimore, MD, August 24, 2005

30. Fallopian Tube Recannalization, Johns Hopkins CVDL Lecture Series
[Course Director: Hyun S. Kim]
The Russell H. Morgan Department of Radiology and Radiological Science,
Johns Hopkins Medical Institutions, Baltimore, MD, June 21, 2005

31. New Developments in Percutaneous Uterine Fibroid Treatments, Current Concepts, Clinical Aspects of Reproductive Health
[Course Director: Wanda Nicholson] The Johns Hopkins School of Public Health, Baltimore, MD, April 20, 2005

32. Chronic Pelvic Pain, Johns Hopkins CVDL Lecture Series [Course Director: Hyun S. Kim]
The Russell H. Morgan Department of Radiology and Radiological Science,
Johns Hopkins Medical Institutions, Baltimore, MD, March 15, 2005

33. New Developments in Percutaneous Uterine Fibroid Treatments, Current Concepts, Clinical Aspects of Reproductive Health
[Course Director: Wanda Nicholson] The Johns Hopkins School of Public Health, Baltimore, MD, April 19, 2006

34. Varicose Vein Treatment, Johns Hopkins CVDL Lecture Series
[Course Director: Kelvin Hong]
The Russell H. Morgan Department of Radiology and Radiological Science,
Johns Hopkins Medical Institutions, Baltimore, MD, February 21, 2006

35. Minimally Invasive Treatments, Graduate Course in Medical Illustration
[Course Director: Cory Sandone], the Johns Hopkins School of Medicine
Baltimore, MD, March to April, 2006

36. Varicose Vein Treatment, Johns Hopkins CVDL Lecture Series [Course Director: Kelvin Hong]
The Russell H. Morgan Department of Radiology and Radiological Science,

Johns Hopkins Medical Institutions, Baltimore, MD, November 1, 2006

37. Chronic Pelvic Pain Treatment, Johns Hopkins CVDL Lecture Series
[Course Director: Kelvin Hong]
The Russell H. Morgan Department of Radiology and Radiological Science,
Johns Hopkins Medical Institutions, Baltimore, MD, November 15, 2006

38. Current Concepts in IVC Filtration, Johns Hopkins CVDL Lecture Series
[Course Director: Kelvin Hong]
The Russell H. Morgan Department of Radiology and Radiological Science,
Johns Hopkins Medical Institutions, Baltimore, MD, February 28, 2007

39. Minimally Invasive Treatments, Graduate Course in Medical Illustration
[Course Director: Cory Sandone], Department of Art as Applied to Medicine
Johns Hopkins School of Medicine, Baltimore, MD, March to April, 2007

40. Minimally Invasive Treatments, Graduate Course in Medical Animation
[Course Director: Jennifer Friedman], Department of Art as Applied to Medicine
Johns Hopkins School of Medicine, Baltimore, MD, April to May, 2007

41. Current Concepts in Fibroids Treatment, Johns Hopkins CVDL Lecture Series
[Course Director: Kelvin Hong]
The Russell H. Morgan Department of Radiology and Radiological Science
Johns Hopkins Medical Institutions, Baltimore, MD, May 16, 2007

42. Current Concepts in DVT Thrombolysis, Johns Hopkins CVDL Lecture Series
[Course Director: Kelvin Hong]
The Russell H. Morgan Department of Radiology and Radiological Science,
Johns Hopkins Medical Institutions, Baltimore, MD, June 27, 2007

43. Minimally Invasive Treatments, Graduate Course in Medical Illustration
[Course Director: Cory Sandone], Department of Art as Applied to Medicine
Johns Hopkins School of Medicine, Baltimore, MD, February to April, 2008

44. Minimally Invasive Treatments, Graduate Course in Medical Animation
[Course Director: Jennifer Friedman], Department of Art as Applied to Medicine
Johns Hopkins School of Medicine, Baltimore, MD, February to May, 2008

45. Minimally Invasive Therapies for Fibroids, Johns Hopkins CVDL Lecture Series
[Course Director: Kelvin Hong]
The Russell H. Morgan Department of Radiology and Radiological Science
Johns Hopkins Medical Institutions, Baltimore, MD, April 2, 2008

46. Minimally Invasive Therapies for Varicose Veins, Johns Hopkins CVDL Lecture Series
[Course Director: Kelvin Hong]
The Russell H. Morgan Department of Radiology and Radiological Science
Johns Hopkins Medical Institutions, Baltimore, MD, April 23, 2008

47. Minimally Invasive Therapies for Pelvic Pains, Johns Hopkins CVDL Lecture Series
[Course Director: Kelvin Hong]
The Russell H. Morgan Department of Radiology and Radiological Science

Johns Hopkins Medical Institutions, Baltimore, MD, April 30, 2008

48. Catheter-Directed Thrombolysis Therapy for DVT, Johns Hopkins CVDL Lecture Series
[Course Director: Kelvin Hong]
The Russell H. Morgan Department of Radiology and Radiological Science
Johns Hopkins Medical Institutions, Baltimore, MD, May 21, 2008

49. Minimally Invasive Therapies for Fibroids, Johns Hopkins CVDL Lecture Series
[Course Director: Cliff Weiss]
The Russell H. Morgan Department of Radiology and Radiological Science
Johns Hopkins Medical Institutions, Baltimore, MD, July 30, 2008

50. Catheter-Directed Thrombolysis Therapy for DVT, Johns Hopkins CVDL Lecture Series
[Course Director: Cliff Weiss]
The Russell H. Morgan Department of Radiology and Radiological Science
Johns Hopkins Medical Institutions, Baltimore, MD, Aug 20, 2008

51. Introduction to Interventional Radiology Part I, Emory Radiology Lecture Series
[Course Director: Mark Mulins]
Emory University School of Medicine, Atlanta, GA, Sept 25, 2008

52. Introduction to Interventional Radiology Part II, Emory Radiology Lecture Series
[Course Director: Mark Mulins]
Emory University School of Medicine, Atlanta, GA, Sept 27, 2008

53. Future of Interventional Radiology, Emory IR & IGM Lecture Series
[Course Director: Gail Peters]
Interventional Radiology and Image Guided Medicine
Emory University School of Medicine, Atlanta, GA, Sept 11, 2008

54. Future of Interventional Radiology, Emory Radiology Retreat
[Course Director: Mary Newell]
Emory University School of Medicine, Atlanta, GA, Sept 26, 2008

55. Minimally Invasive Therapies for Uterine Fibroids, Emory IR & IGM Lecture Series
[Course Director: Gail Peters]
Interventional Radiology and Image Guided Medicine
Emory University School of Medicine, Atlanta, GA, Sept 18, 2008

56. Minimally Invasive Therapies for Varicose Veins, Emory IR & IGM Lecture Series
[Course Director: Gail Peters]
Interventional Radiology and Image Guided Medicine
Emory University School of Medicine, Atlanta, GA, Oct 2, 2008

57. Current Treatments of HCC Part I, Emory IR & IGM Lecture Series
[Course Director: Gail Peters]
Interventional Radiology and Image Guided Medicine
Emory University School of Medicine, Atlanta, GA, Jan 22, 2009

58. Current Treatments of HCC Part II, Emory IR & IGM Lecture Series
[Course Director: Gail Peters]

Interventional Radiology and Image Guided Medicine
Emory University School of Medicine, Atlanta, GA, Jan 29, 2009

59. Senior Diagnostic Radiology Board Review
Department of Radiology
Emory University School of Medicine, Atlanta, GA, Feb 27, 2009

Other Programs:

1. Introduction to TIPS, Intensive care unit staffs, The Johns Hopkins Hospital, Baltimore, MD, December 5, 2001

2. Introduction to Uterine Fibroid Embolization, The Johns Hopkins Hospital, Marburg Pavilion, Baltimore, MD, August 7, 2002

3. New Treatment of Uterine Fibroids, Johns Hopkins Cosmetic Center [Course Director: Karen Scully], Baltimore, MD, Dec. 9, 2004

4. New Treatment of Leg Varicose Vein / Uterine Fibroids, Johns Hopkins Cosmetic Center [Course Director: Karen Scully], Baltimore, MD, Nov. 18, 2004

5. New Treatment of Uterine Fibroids, Johns Hopkins Cosmetic Center [Course Director: Karen Scully], Baltimore, MD, Nov. 4, 2004

6. New Treatment for Leg Varicose Vein, [Course Director: Patrick McElguinn] Johns Hopkins Cosmetic Center, Baltimore, MD, February 18, 2004

7. New Treatment for Leg Varicose Vein, [Course Director: Patrick McElguinn] Johns Hopkins Cosmetic Center, Baltimore, MD, January 21, 2004

8. New Treatment of Leg Varicose Vein / Uterine Fibroids, Johns Hopkins Cosmetic Center [Course Director: Karen Scully], Baltimore, MD, May 12, 2004

9. New Treatment of Leg Varicose Vein / Uterine Fibroids, Johns Hopkins Cosmetic Center [Course Director: Karen Scully], Baltimore, MD, March 17, 2005

10. New Treatment of Leg Varicose Vein / Uterine Fibroids, Johns Hopkins Cosmetic Center [Course Director: Karen Scully], Baltimore, MD, Jan. 20, 2005

11. New Treatment of Leg Varicose Vein / Uterine Fibroids, Johns Hopkins Cosmetic Center [Course Director: Karen Scully], Baltimore, MD, Feb. 16, 2006

SUPERVISORY TEACHING:
Mentoring

Trainees:

Michael Goldberg, medical student at Johns Hopkins
2003-2004
Project: new percutaneous therapies for SMV thrombosis
Current position: University of Pennsylvania Diagnostic Radiology Residency

Carole Fakhry, medical student at Johns Hopkins
2002-2003
Project: new therapies for Takayasu's arteritis
Current position: Johns Hopkins ENT / Otolaryngology Residency

George Kuo, medical student at Johns Hopkins
2003-2004
Project: new percutaneous therapies for PNH
Current position: Johns Hopkins Diagnostic Radiology Residency

Amit Malhotra, medical student at Johns Hopkins
2003-2004
Project: new percutaneous therapies for Chronic Pelvic Pain
Current position: Albert Einstein / Montefeiore Diagnostic Radiology Residency

Ikechi Nwankwo, medical student at Johns Hopkins
2003-2004
Project: new laser therapies for Varicose Vein
Current position: Lennox Hill Diagnostic Radiology Residency

Jawad Khan, medical student from Pakistan
2004-2005
Project: new laser therapies for Varicose Vein
Current position: currently applying for a Diagnostic Radiology Residency

Ajanta Patra, medical student at Johns Hopkins
2004-2005
Project: new percutaneous therapies for Uterine Fibroids and DVT
Current position: Johns Hopkins Diagnostic Radiology Residency

Jason Tsai, medical student at Johns Hopkins
2005-2006
Project: new percutaneous therapies for Uterine Fibroids
Current position: Tuft University Diagnostic Radiology Residency

Ben Paxton, medical student at Johns Hopkins
2005-2006
Recipient of a Summer Educational Grant from the Johns Hopkins University School of Medicine
Project: new percutaneous therapies for Varicose Veins and DVT
Current position: Duke University Diagnostic Radiology Residency

Gregory Czuczman, medical student at Johns Hopkins
2005-2006
Recipient of a Summer Educational Grant from the Johns Hopkins University School of Medicine
Project: new percutaneous therapies for Varicose Veins and DVT
Current position: Harvard University / Massachusetts General Hospital Diagnostic Radiology Residency

Mark Young, medical student at Johns Hopkins
2006-2007
Recipient of a Summer Educational Grant from the Johns Hopkins University School of Medicine
Project: new percutaneous therapies for Retrievable IVC filters
Current position: 4th Year Medical Student

Stephen Preece, medical student at Johns Hopkins
2007-2008
Project: percutaneous therapies for DVT in cancer patients
Current position: Duke University Diagnostic Radiology Residency

Juan Baez, medical student at Johns Hopkins
2007-2008
Project: percutaneous therapies for IVC Thrombosis
Current position: Harvard University / Brigham and Women's Hospital Diagnostic Radiology Residency.

Clinical Interventional Radiology Fellows:

David Dubois, M.D.
July 2000 – June 2001; Interventional Radiology Fellow
Current position: Staff radiologist, Virginia

Miguel Gelman, M.D.
July 2000 – June 2001; Interventional Radiology Fellow
Current position: Assistant Professor, University of Missouri

Brian Lawler, M.D.
July 2000 – June 2001; Interventional Radiology Fellow
Current position: Staff radiologist, Kentucky

Daniel Long, M.D.
July 2000 – June 2001; Interventional Radiology Fellow
Current position: Staff radiologist, Ohio

Nitin P. Shirodkar, M.D.
July 2000 – June 2001; Interventional Radiology Fellow
Current position: Assistant Professor, University of Iowa

Shawn Shrawny, M.D.
July 2000 – June 2001; Interventional Radiology Fellow
Current position: Staff radiologist, North Dakoda

Anil Wadhwani, M.D.
July 2001 – June 2002; Interventional Radiology Fellow
Current position: Staff radiologist, California

Shrish Patel, M.D.
July 2001 – June 2002; Interventional Radiology Fellow

Current position: Staff radiologist, Wisconsin

Kelly VanEpps, M.D.
July 2001 – June 2002; Interventional Radiology Fellow
Current position: Staff radiologist, Florida

Brian Johnson, M.D.
July 2001 – June 2002; Interventional Radiology Fellow
Current position: Staff radiologist, Maryland

Elizabeth Ignasio, M.D.
July 2001 – June 2002; Interventional Radiology Fellow
Current position: Associate Professor, George Washington University

Michael Neuwirth, M.D.
July 2001 – December 2002; Interventional Radiology Fellow
Current position: Staff radiologist, Illiois

Clayton K. Trimmer, D.O.
July 2001 – June 2002; Interventional Radiology Fellow
Current position: Associate Professor, University of Texas Southwestern in Dallas

Kenneth H. Cho, M.D.
July 2002 – June 2003; Interventional Radiology Fellow
Current position: Assistant Professor, Walter Reed Medical Center

Christos S. Georgiades, M.D.
July 2002 – June 2003; Interventional Radiology Fellow
Current position: Assistant Professor, Johns Hopkins University School of Medicine

Kelvin K. Hong, M.D.
July 2002 – June 2003; Interventional Radiology Fellow
Current position: Assistant Professor, Johns Hopkins University School of Medicine

Kelvin P. Henseler, M.D.
July 2002 – June 2003; Interventional Radiology Fellow
Current position: Staff radiologist, Minnesota

Craig D. McCormick, M.D.
July 2002 – June 2003; Interventional Radiology Fellow
Current position: Staff radiologist, Virginia

Andrew W. Morton, M.D.
July 2002 – June 2003; Interventional Radiology Fellow
Current position: Staff radiologist, Maryland

Chad W. Brecher, M.D.
July 2003 – June 2004; Interventional Radiology Fellow
Current position: Staff radiologist, Pennsylvania

Gregory C. Bruno, M.D.

July 2003 – June 2004; Interventional Radiology Fellow
Current position: Staff radiologist, Tennessee

Matthew L. Cohen, M.D.
July 2003 – June 2004; Interventional Radiology Fellow
Current position: Staff radiologist, Virginia

Clinton L. Nichols, M.D.
July 2003 – June 2004; Interventional Radiology Fellow
Current position: Staff radiologist, California

John D. Statler, M.D.
July 2003 – June 2004; Interventional Radiology Fellow
Current position: Staff radiologist, Virginia

Asish Vachhani, M.D.
July 2003 – June 2004; Interventional Radiology Fellow
Current position: Staff radiologist, Virginia

Leo P. Lawler, M.D.
July 2004 – June 2005; Interventional Radiology Fellow
Current position: Staff radiologist, Dublin, Ireland

Peter L. Leuchtmann, M.D.
July 2004 – June 2005; Interventional Radiology Fellow
Current position: Staff radiologist, North Carolina

Mark W. Meyermann, D.O..
July 2004 – June 2005; Interventional Radiology Fellow
Current position: Staff radiologist, Trippler Army Medical Center

Andrew S. Rodgers, M.D.
July 2004 – June 2005; Interventional Radiology Fellow
Current position: Staff radiologist, Maryland

Eric A. Wang, M.D.
July 2004 – June 2005; Interventional Radiology Fellow
Current position: Staff radiologist, North Carolina

Palam Annamalai, M.D.
July 2004 – June 2005; Interventional Radiology Fellow
Current position: Staff radiologist, Texas

Sumit Bhatla, M.D.
July 2005 – June 2006; Interventional Radiology Fellow
Current position: Staff radiologist, Ohio

Robert Liddell, M.D.
July 2005 – June 2006; Interventional Radiology Fellow
Current position: Staff radiologist, Maryland

Henry Lusane, M.D.
July 2005 – June 2006; Interventional Radiology Fellow
Current position: Staff radiologist, Florida

Jonathan Marx, M.D.
July 2005 – June 2006; Interventional Radiology Fellow
Current position: Assistant Professor, Johns Hopkins University School of Medicine

Gerald Wyse, M.D.
July 2005 – June 2006; Interventional Radiology Fellow
Current position: Assistant Professor, Johns Hopkins University School of Medicine

Tamburayi Kamba, M.D.
July 2005 – June 2006; Interventional Radiology Fellow
Current position: Staff radiologist, Oxford, Great Britain

Labib H. Syed, M.D.
July 2006 – June 2007; Interventional Radiology Fellow
Current position: Instructor, Johns Hopkins University School of Medicine

James Reynolds, M.D.
July 2006 – June 2007; Interventional Radiology Fellow
Current position: Staff radiologist, West Virginia

Erik Ray, M.D.
July 2006 – June 2007; Interventional Radiology Fellow
Current position: Staff radiologist, Illinois

Thomas P. Murphy, M.D.
July 2006 – June 2007; Interventional Radiology Fellow
Current position: Staff radiologist, Georgia

Paul Harrod-Kim, M.D.
July 2006 – June 2007; Interventional Radiology Fellow
Current position: Staff radiologist, Maine

Michael D'Angelo, M.D.
July 2006 – June 2007; Interventional Radiology Fellow
Current position: Staff radiologist, New Jersey

Peter Bernstein, M.D.
July 2007 – June 2008; Interventional Radiology Fellow
Current position: Staff radiologist, Nevada

Mandeep Dagli, M.D.
July 2007 – June 2008; Interventional Radiology Fellow
Current position: Assistant Professor, University of Pennsylvania School of Medicine

Conrad Pun, M.D.
July 2007 – June 2008; Interventional Radiology Fellow
Current position: Assistant Professor, University of Wisconsin School of Medicine

David Todd, M.D.
July 2007 – June 2008; Interventional Radiology Fellow
Current position: Staff radiologist, Maryland

Derek Vien, M.D.
July 2007 – June 2008; Interventional Radiology Fellow
Current position: Staff radiologist, California

Clifford Weiss, M.D.
July 2007 – June 2008; Interventional Radiology Fellow
Current position: Assistant Professor, Johns Hopkins University School of Medicine

Brandt Wible, M.D.
July 2007 – June 2008; Interventional Radiology Fellow
Current position: Assistant Professor, University of Missouri, Kansas City, School of Medicine

Vinnit Khanna, M.D.
July 2008 – December 2008; Interventional Radiology Fellow
Current position: Resident, Alleghany Hospital, Pittsburgh, PA

Research Fellows:

Renumathy Dhanasekaran, M.D.
September 2008 – June 2009; Post-Doc Research Felllow

Advisory Committees

1. Invited Faculty, Caval Filter Complications, Cordis TrapEase IVC Filter Advisory Committee Meeting, Warren, NJ, October 16, 2000

2. Invited Faculty, Uterine Fibroid Ablation, Sponsor: TxSonics/Insightec, American College of Obstetrics and Gynecology Annual Meeting, Chicago, IL, April 29, 2001

3. Invited Faculty, Focused Ultrasound Uterine Fibroid Ablation Advisory Committee Meeting Sponsor: TxSonics/Insightec, London, UK, January 7-8, 2002

4. Invited Faculty, MRI in MR Guided Focused Ultrasound Surgery of Uterine Fibroid Advisory Committee Meeting, Sponsor: TxSonics/Insightec, London, UK, July 24-25, 2003

5. Invited Faculty, State of the Art Thrombolysis Advisory Committee Meeting, Sponsor, Abbot, Carefree, AZ, February 7-9, 2003

LECTURESHIPS, SEMINAR INVITATIONS, AND VISITING PROFESSORSHIPS

INVITED LECTURES (GRAND ROUNDS, NATIONAL AND INTERNATIONAL LECTURES)

1. National/International

1. Senior Diagnostic Radiology Board Review, Grand Round
   Department of Radiology, University of Maryland, Baltimore, MD, April 25, 2000

2. Senior Diagnostic Radiology Board Review, Grand Round
   Department of Radiology, University of Texas, Houston, TX, March 25, 2000

3. State-of-the-Art Vena Caval Filters
   Practicums in Interventional Radiology at Johns Hopkins
   [Course Director: Anthony Venbrux], the Johns Hopkins Medical Institutions,
   Baltimore, MD, September 30, 2000

4. State-of-the-Art Vena Caval Filters
   Practicums in Interventional Radiology at Johns Hopkins
   [Course Director: Anthony Venbrux], The Johns Hopkins Medical Institutions,
   Baltimore, MD, May 4, 2001

5. State-of-the-Art Renal Artery Intervention
   Practicums in Interventional Radiology at Johns Hopkins
   [Course Director: Anthony Venbrux], The Johns Hopkins Medical Institutions
   Baltimore, MD, May 4, 2001

6. Complications of TIPS
   Seventh Annual Johns Hopkins Hepato-Biliary Update [Program Director: Paul Thulavath],
   Department of Medicine and Surgery, Johns Hopkins Medicine, Ocean City, MD
   September 16, 2001

7. Invited Key Note Speaker, Minimally Invasive Surgery in 21th Century
   (Sponsor: US Embassy), Nassau, Bahamas, September 5, 2002

8. Robert Cooley Visiting Professorship, A New Advancement in Uterine Fibroids
   Treatment [Program Director: Charles Swischuck], University of Texas Medical Branch,
   Galveston, TX, October 22, 2002

9. Interventional Radiology in the 21st Century, Costa Rica
   Annual Medical Association Meeting, Novermber 27, 2002

10. Percutaneous Management of Uterine Fibroids, Johns Hopkins Reproductive
    Endocrinology Grand Round [Course Director: Jairo Garcia], Department of Gynecology and
    Obstetrics, Division of Reproductive Endocrinology, The Johns Hopkins Medical Institutions,
    Baltimore, MD, February 27, 2003

11. Interventional Radiology: Surgeries for a New Millenium., Johns Hopkins
    International, The Johns Hopkins Medical Institutions, Baltimore, MD, April 2, 2003

12. State of the Art Catheter Directed Thrombolysis in DVT, Johns Hopkins Hematology Grand Round, Department of Hematology/Oncology, The Johns Hopkins Medical Institutions, Baltimore, MD, April 23, 2003

13. New Developments in Thrombolysis, Grand Round, Mercy Hospital, Sioux City, IA, May 8, 2003

14. Interventional Radiology: Surgeries for a New Millenium., Turkey Medical Representatives, Sponsor: Johns Hopkins International Service, The Johns Hopkins Medical Institutions, Baltimore, MD, May 27, 2003

15. Catheter Directed Thrombolysis in Pediatric Patients with DVT, Johns Hopkins Pediatric Grand Round, Department of Pediatrics, The Johns Hopkins Medical Institutions, Baltimore, MD, June 6, 2003

16. Featured Lecture: Interventional Radiology in the Next Century, The 20th Annual Korean Medical Association Annual Scientific Meeting [Course Director: James Suh], Ocean City, MD, August 1-2, 2003

17. New Developments in Thrombolysis, Invited Speaker, Summit Club, Fort Wayne, IN, September 18, 2003

18. Catheter Directed Thrombolysis in Pediatric Patients with DVT, Grand Round, The East Baltimore Medical Center, The Johns Hopkins Medical Institutions, Baltimore, MD, September, 2003

19. Controversies in Endovascular Management of GI Bleeding, The 29th Topics in Gastroenterology and Liver Disease Medical and Surgical Aspects [Course Director: William Ravich], Baltimore, MD, September 23, 2003

20. New Developments in Thrombolytic Therapy, Invited Speaker, Lincoln, NE, September 26, 2003

21. Update on Percutaneous Varicose Vein Treatment, The Johns Hopkins Practicum in Embolotherapy [Course Director: Hyun S. Kim & Jeff Geschwind], Baltimore, MD, October 30, 2003

22. Uterine Artery Embolization: Is It Now "Gold Standard" for Treating Symptomatic Uterine Fibroid?, The Johns Hopkins Practicum in Embolotherapy [Course Director: Hyun S. Kim & Jeff Geschwind], Baltimore, MD, October 31, 2003

23. How to Manage Patients with Chronic Pelvic Pain?, The Johns Hopkins Practicum in Embolotherapy [Course Director: Hyun S. Kim & Jeff Geschwind], Baltimore, MD, October 31, 2003

24. Failure of UAE?, The Johns Hopkins Practicum in Embolotherapy [Course Director: Hyun S. Kim & Jeff Geschwind], Baltimore, MD, October 31, 2003

25. New Treatment of Uterine Fibroid, Johns Hopkins Woman's Journey, Baltimore, MD, November 8, 2003

26. New Developments in Thrombolytic Therapy, Invited Speaker, Pikesville, MD, November 11, 2003

27. New Developments in Thrombolysis, Invited Speaker, Huntsville, AL, December 10, 2003

28. Advanced Treatment in Interventional Radiology, Embassy of Chilie, Washington, DC, February 12, 2004

29. Recent Advancement of Uterine Fibroid Treatment, Michigan Angio Club, Detroit, MI, February 17, 2004

30. New Developments in Thrombolysis, Invited Speaker, Pikesville, MD, March 2, 2004

31. State of the Art Catheter Directed Thrombolysis in DVT, Johns Hopkins Gynecology, Obstetrics and Reproductive Sciences Grand Round, [Course Director: Harold Fox], Department of Gynecology, Obstetrics and Reproductive Sciences, The Johns Hopkins Medical Institutions, Baltimore, MD, March 18, 2004

32. Moderator, Legs for Life Workshop at the 29th Annual Scientific Meeting of the Society of Interventional Radiology, Phoenix, AZ, March 30, 2004

33. New Developments in Advanced Uterine Fibroid Treatment, Invited Speaker, Cumberland, MD, May 13, 2004

34. Vascular and Interventional Radiology in the 21st Century, King Edward VII Hospital Grand Round, Paget, Bermuda, May 18, 2004

35. Minimally-invasive and Non-invasive Treatment of Uterine Fibroids, Seoul National University Hospital Radiology Grand Round, Seoul, Korea, May 27, 2004

36. Vascular and Interventional Radiology in the 21st Century, Korea President's Organization Seminar, Invited Speaker, Seoul, Korea, May 27, 2004

37. Vascular and Interventional Radiology in the 21st Century, CancerAide Seminar, Invited Speaker, Seoul, Korea, May 28, 2004

38. Bile Duct Injury and Benign Strictures, IHPBA (International Hepato-Pancreato-Biliary Association) 6th World Congress, Washington DC, June 4, 2004

39. Update on TIPS (covered stents/Ascites/transplant), IHPBA (International Hepato-Pancreato-Biliary Association) 6th World Congress, Washington DC, June 4, 2004

40. State of the Art Catheter Directed Thrombolysis in DVT, Johns Hopkins Oncology Grand Round, [Course Director: Louis Diehl], Department of Oncology, The Johns Hopkins Medical Institutions, Baltimore, MD, June 18, 2004

41. New Advancements in Deep Venous Thrombosis Treatment, 25th Korean American Medical Association Annual Scientific Meeting, [Course Director: Hyun S. Kim], Cambridge, MD, August 8, 2004

42. Clinical Experience of Focused Ultrasound, Advanced MR Seminar 2004, Melbourne, Australia, August 30, 2004

43. Clinical Experience of Focused Ultrasound, Advanced MR Seminar 2004, Tokyo, Japan, September 1, 2004

44. Clinical Experience of Focused Ultrasound, Advanced MR Seminar 2004, Beijing, China, September 3, 2004

45. Clinical Experience of Focused Ultrasound, Advanced MR Seminar 2004, Hong Kong, September 4, 2004

46. Controversies in TIPS, The 30th Topics in Gastroenterology and Liver Disease Medical and Surgical Aspects [Course Director: William Ravich], Baltimore, MD, October 6, 2004

47. Clinical Experience of Focused Ultrasound, Grand Round, University of Toronto Hospitals, Toronto, Canada, January 12, 2005

48. New Treatment of Uterine Fibroids, 4th International Interventional Radiology Training [Course Director: H.M. Park], Seoul National University Hospital, Seoul, Korea, January 18, 2005

49. New Treatment of Varicose Veins, 4th International Interventional Radiology Training [Course Director: H.M. Park], Seoul National University Hospital, Seoul, Korea, January 18, 2005

50. Femoral PTA/Stents, Update, 4th International Interventional Radiology Training [Course Director: H.M. Park], Seoul National University Hospital, Seoul, Korea, January 18, 2005

51. Iliac PTA/Stents, 4th International Interventional Radiology Training [Course Director: H.M. Park], Seoul National University Hospital, Seoul, Korea, January 18, 2005

52. Clinical Experience of Focused Ultrasound, Advanced MR Seminar 2005, Seoul, Korea, March 11, 2005

53. Clinical Experience of Focused Ultrasound, Advanced MR Seminar 2005, Beijing, China, March 12, 2005

54. Clinical Experience of Focused Ultrasound, Advanced MR Seminar 2005, Shanghai, China, March 13, 2005

55. Endovenous Laser Treatment for Varicose Vein, Johns Hopkins Dermatology Grand Round, Department of Dermatology, the Johns Hopkins Medical Institutions, Baltimore, MD, June 1, 2005

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American Medical Association Annual Scientific Meeting, [Course Director: Hyun S. Kim], Williamsburg, VA, August 7, 2005

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Interventional Radiology Course [Course Director: H.M. Park], Seoul National University Hospital, Seoul, Korea, February 6, 2006

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The Russell H. Morgan Department of Pediatrics,
Johns Hopkins Medical Institutions, Baltimore, MD, August 21, 2008

72. Clinical HIFU, update, Plenary Session at the 7th International MRI Symposium, September 12 2008, Baltimore, MD

73. HIFU at the MRgFUS 2008 International MRSymposium, October 2, 2008, Washington, DC

73. Uterine Fibroid Embolization at the 12rd Asian Oceanian Congress of Radiology, October 27, 2008, Seoul, Korea

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76. HCC Treatments, Current and Future, Emory University School of Medicine Gastrointestinal Grand Round, [Course Director: Dr. Vincent Yang], Department of Medicine, Emory University School of Medicine, Atlanta, GA, January 12, 2009

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ATTACHMENT 3

Cardinal Health LOA and DMF

Cardinal Health
Quality and Regulatory Department
7000 Cardinal Place
Dublin, OH 43017
tel 614.757.5000
fax 614.652.4688

www.cardinal.com

CardinalHealth

August 17, 2010

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
Drug Master File Staff
5901-B Ammendale Road
Beltsville, MD 20705

Re: Letter of Authorization for Type II DMF 23002
Fluoromisonidazole F 18 Injection Drug Substance
Holder: Cardinal Health 414, LLC
Manufacturer: Cardinal Health 414, LLC

Sir/Madam:

We hereby authorize FDA to review the aforementioned specific information in DMF 23002, dated 6/16/2009 for Fluoromisonidazole F18 Injection drug substance with respect all new, existing and / or supplemental IND applications filed by Emory University Hospital Department of Radiology:

Emory University Hospital Department of Radiology
Room E152, 1364 Clifton Road
Atlanta, GA 30322

Contact: David M Schuster, MD
Director, Division of Nuclear Medicine and Molecular Imaging
Department of Radiology
Emory University Hospital, Room E152
1364 Clifton Road
Atlanta, GA 30322
Phone: 404-712-4859
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dschust@emory.edu

We request that all information in this file be treated as confidential to the extent possible in accordance with 21 CFR 314.430 and 21 CFR 20.61 and that no information from this file be provided to any unauthorized persons without our written consent.

Cardinal Health agrees that DMF 23002 is current, they will comply with the statements made within it, and the drug substance will be made in compliance with Current Good Manufacturing Practices.

Should you have any questions, please contact us at 614-757-4547.

Sincerely,

Nancy J. Taylor
VP, Quality & Regulatory Affairs
Nuclear Pharmaceutical Manufacturing
Cardinal Health
7200 Cardinal Place
Dublin, OH 43017

FMiso Specifications as Manufactured by Cardinal Health

DMF #23002

Fluoromisonidazole F 18 Injection prepared by Cardinal Health PET Manufacturing Facilities meet the following Quality Control specifications:

Test Description	Specification	
Activity Concentration	**≤ 30 mCi/mL**	
Residual Solvent (Gas Chromatography)	**Acetonitrile < 400 ppm**	
Radionuclidic ID (Half-Life Test)	**105-115 minutes**	
Bacterial Endotoxin	**< 175 EU per dose**	
pH	**5-7**	
Chemical Purity (TLC Analysis by TBA Color-spot Test)	**< 0.275 mg/mL TBA**	
Chemical & Radiochemical Purity (HPLC)	**Radiochemical Purity:**	**>95% Chemical Purity (by UV @327 (pref), 280, or 254 nm)** **FMISO < 15 µg/dose Other < 35 µg/dose**
	Specific Impurities:	**~4.0 min ≤ 3 µg/mL** **~6.0 min ≤ 4 µg/mL**
Chemical Purity (Particulates)	**Clear, Colorless, No particulates**	
Radionuclidic Purity (MCA)	**Peak correlates to 511 keV**	

PET Manufacturing Services
Quality and Regulatory
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ATTACHMENT 4

NCI LOA

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
National Cancer Institute
Bethesda, Maryland 20892

19 August 2010

Rafael Dwayne Rieves, M.D.
Director, Division of Medical Imaging and Hematology Products
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Re: IND Reference Letter of IND#76,042 [^{18}F]FMISO

Dear Dr. Rieves:

This letter is to authorize reference to NCI IND 76,042 for [F-18] FMISO, [18F]-fluoromisonidazole. Specifically we are allowing the individual or entity named below to reference the pharmacology and toxicology and Previous Human Experience sections of the IND. The IND has a letter of Authorization to the DMF from Cardinal Health and the sponsor can either obtain the agent from them or submit their own CMC section. The remaining sections of an IND submission will be the responsibility of the sponsor to provide in their submission.

Permission to reference IND 76,042 is granted to:

David M Schuster, MD
Director, Division of Nuclear Medicine and Molecular Imaging
Department of Radiology
Emory University Hospital, Room E152
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404-712-4859
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If you have any questions or require additional information, please do not hesitate to contact me.

Sincerely Yours,

Paula M. Jacobs

Paula M. Jacobs, Ph.D.
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