


BROOKHAVEN NATIONAL LABORATORY INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) CONTINUING REVIEW FORM	
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Protocol #:	102
Title:	Radiotracer Development
Principal Investigator:	FOIA (b) (6) Privacy
Institution:	BNL
BNL Contact:	

In accordance with BNL Policy, the IACUC reviews all research protocols involving animals no less than annually.
The above protocol is approved until . In order for the IACUC to approve this protocol for another year, please return the completed, signed form and any attachments to FOIA (b) , FOIA (b)(6) by . The period of review is .

1. PROTOCOL STATUS: Please indicate (X) the status of this project by clicking on the appropriate box.	
Request protocol continuance <input type="checkbox"/> Active – project ongoing <input type="checkbox"/> Not started – anticipated start date:	Request protocol termination <input type="checkbox"/> Inactive – project never started <input checked="" type="checkbox"/> Completed – no further activities will be done

2. RECORD OF ANIMAL USAGE			
Species	Total approved	Used during reporting period	Pain/Distress Category (A, B, C – see below)
Baboons	12	7	B
Rats	100		
Mice	100		

USDA PAIN/DISTRESS CATEGORY LEVEL A: No Pain or Distress: Animals will be euthanized without any treatments or manipulations or irradiation with unrestricted movement and without anesthesia and without anticipated subsequent effects at BNL. LEVEL B: Relieved or Momentary Pain or Distress: Momentary pain or potential pain or distress relieved by pharmacologic, behavioral or other means. e.g., tranquilization/sedation, general or local anesthesia, post-procedural analgesics, behavioral conditioning to restraint or minor pain/stress, medical treatment of disease states LEVEL C: Unrelieved or Sustained Pain or Distress: Any procedure that would cause more than momentary or slight pain or distress. e.g., chronic untreated disease states, pain research

3. LITERATURE SEARCH: For animals used in Level B or C, perform a literature search for alternatives to pain/distress. Please note the Research Library Staff is available to assist with literature searches.

List procedures that may cause pain/distress (e.g. imaging, surgery, injection, behavioral testing, food restriction, etc) and perform a search using the procedures. Procedures that have pain eliminated by the use of anesthetics and/or analgesics are still considered painful even though the animal is not expected to experience any pain/distress.

Date of Search:

Databases Searched:

Years included:

Provide a narrative of Search Results When alternative procedures are discovered, you must identify them and justify why those procedures are not being considered:

4. PERSONNEL

In each box, list all personnel currently working directly with animals and indicate number of years of experience for each procedure for each species.

NAME	SPECIES	MONITORING & HANDLING	NONSURGICAL MANIPULATION	ANESTHESIA, SURGERY	BLOOD COLLECTION	EUTHANASIA

5. PROGRESS REPORT. Please provide a brief but complete, non-scientific description of work done, data collected and conclusions reached, if any, during the past year or a copy of progress reports supplied to DOE, NIH or other funding agency and any publications. If no work has been done, this

should be indicated.

A manuscript on dopamine D2/D3 occupancy by buspirone was written and submitted from publication.

Title: Orally administered buspirone blocks D3 but not D2 receptors in the living non-human primate brain

6. PROBLEMS/ADVERSE EVENTS. Describe any unanticipated adverse events, morbidity or mortality, the cause(s), if known, and how these problems were resolved. If **NONE**, this should be indicated.

none

7. DUPLICATION. Activities involving animals must not unnecessarily duplicate previous experiments. Provide written assurance that the activities of this project remain in compliance with the requirement that there must be no unnecessary duplication.

8. FUTURE PLANS. Please provide a brief non-scientific description of what is to be studied during the coming year (the questions/hypotheses being tested in lay terms). If changes are planned, submit an addendum that outlines planned studies and justification for the proposed changes. *[Please note that if the modifications are significant, you may be required to complete a new application. If you have questions or require assistance in making this determination, please contact the IACUC Office and/or the Attending Veterinarian.]*

Program has been closed

CERTIFICATION OF THE PRINCIPAL INVESTIGATOR I am aware that all research outlined in this protocol must be carried out under an approved Experimental Safety Review (ESR) and that the protocol must contain the same information as that listed in the approved ESR(s). I am aware that it is my responsibility to ensure that all individuals working on this protocol have been listed on the ESR(s), that their training is appropriate and up to date and that they have read and understood their responsibilities on this protocol.

PRINCIPAL INVESTIGATOR

FOIA (b)(6) Privacy

DATE

7-17-13

Your Department Safety Coordinator will be notified of your IACUC approval.

BNL DEPARTMENT CHAIR

DATE

FO

From: FOIA (b)(6)
Sent: Tuesday, July 16, 2013 11:03 AM
To: FOIA (b)(6)
Subject: Re: Protocols

That is correct.

From: FOIA (b)(6) Privacy @bnl.gov>
Date: Tuesday, July 16, 2013 10:19 AM
To: FOIA (b)(6) Privacy "FOIA (b)(6) Privacy" <FOIA (b)(6) @stonybrookmedicine.edu>
Subject: Protocols

I understand that there will be no more primate studies conducted here. Currently there are 3 active protocols listing primates. Please confirm this so I can remove training requirements for primate research. Also please inactivate the protocols. Please contact me if you have FOIA (b)(6) Privacy

FOIA (b)(6)
Privacy
Brookhaven National Laboratory
FOIA (b)
Upton, NY 11973-5000
631 344-FOI phone
631 344- Fax

Protocol: 102

Title: Radiotracer Development

FOIA (b)(6) Privacy

P.I: F O [REDACTED], BNL

Other Investigators: FOIA (b)(6) Privacy [REDACTED]

Animals Approved

Date	Species	Total Number
12/02/10	Baboons	12
	Rats	100
	Mice	30
06/09/11	Mice	100 total

Animals Studied

Date	Species	Number
12/10-10/11	Baboons	5
	Rats	4
	Mice	27
12/11-10/12	Baboons	7

Approvals

Date	Status	Comments
11/04/10	Continuing Review	Effective 12/07/10
12/02/10	Triennial	
05/24/11	Addendum	Administer HDAC
06/09/11	Addendum	Use MT1-MMP and add 70 mice
06/14/11	Addendum	Use HT0712, take CSF sample and add FOIA (b) [REDACTED]
06/17/11	Addendum	(6) Add vehicles which can dissolve drugs for iv administration
11/01/11	Continuing review	Effective 12/07/11
11/06/12	Continuing review	Effective 12/07/12
02/28/13	Addendum	Revise minimum time between scans
04/17/13	Addendum	Use 6-OH-buspirone

BROOKHAVEN NATIONAL LABORATORY INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) ANIMAL USE PROTOCOL	BROOKHAVEN NATIONAL LABORATORY
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The protocol must be submitted in typed form and all applicable items must be answered. Answers must be written in English and in terms understandable to all IACUC members.

PROTOCOL #:	102
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Title:	Radiotracer Development		
Principal Investigator*:	FOIA (b)(6)		
Address:	FOIA (b)(6) Privacy		
Phone:	631-344-FOI		
Fax:	631-344-FOI		
E-mail:	FOIA @bnl.ov		
Key Investigators*:	FOIA (b)(6) Privacy		
<small>* Note - if no investigators are BNL employees, please list a BNL employee contact:</small>			
Funding Source: Submit animal methods section of grant	NIAAA intramural, NIH, CRADA Helicon, SBU CRADA	BNL Account Number:	
Protocol Type (e.g. Research, Teaching, Other):	research		
Home Institution IACUC Approval # and dates			

A. OVERVIEW

A.1 Please provide a brief description of the proposed studies in lay terms.

This is an ongoing protocol using primates, rats, and mice to develop new radiotracers for studies of biochemical transformations and the movement of drugs in the brain and peripheral organs. The primate studies are non-invasive and non-terminal and predicated on studying these animals over periods of years to decades. Therefore, for the most part our primate studies require that the animals be returned to their home cages immediately following each study. Radiotracers are labeled with C-11 (half life: 20.4 min), F-18 (half life: 110 min), N-13 (half life: 10 min) and are administered either intravenously or orally via nasogastric tube to primates and either intravenously or orally or intraperitoneally to rodents. With primates their distribution and clearance in different organs is measured with PET. Parameters measured are enzyme activity, receptor and transporter concentration and changes in neurotransmitter concentration. Unlabeled drugs are also used to determine the binding mechanisms of radiotracers. Rodents are used to determine

chemical form in the tissue and involve microPET studies and sacrifice and dissection and tissue analysis. They are also used in behavioral tests such as novel object recognition as needed. In some cases MRI and microMRI are used to define organ anatomy.

B. PERSONNEL AND TRAINING

B.1 In each box, list all personnel working directly with animals and indicate number of years of experience for each procedure for each species. All BNL personnel will be put on the appropriate Occupational Medicine Protocol. Non-BNL employees working with primates will be put on the appropriate Occupational Medicine Protocol.

NAME	SPECIES	MONITORING & HANDLING	NONSURGICAL MANIPULATION	ANESTHESIA, SURGERY	BLOOD COLLECTION	EUTHANASIA
FOIA (b)(6) Privacy	baboon	14	14	14	14	NA
FOIA (b)(6) Privacy	baboon	34	34	34	34	NA
FOIA (b)(6) Privacy	baboon	19	19	19	19	NA
FOIA (b)(6) Privacy	rodents	16	16	16	16	16
FOIA (b)(6)	"	6	6	6	6	6
FOIA (b)(6)	"	6	6	6	6	6
FOIA (b)(6)	"	1	1	1	1	1

Note: Any personnel with less than one year experience in any of the above categories must take the applicable training listed below.

B.2 Indicate which training courses apply to this protocol. Use A to indicate all personnel or put initials of those required to take the training. All courses are located at <http://www.bnl.gov/training>

Required	COURSE TITLE	PROCEDURES COVERED
A	Basic Overview of Laboratory Animal Care and Use	Overview required by all animal users
FOIA (b)(6)	Biomethodology of the Mouse	Restraint, handling, identification, sexing, husbandry, behavior of mice
FOIA (b)(6)	Biomethodology of the Rat	Restraint, handling, identification, sexing, husbandry, behavior of rats
FOIA (b)(6)	Experimental Techniques in Rodents	Injections, blood sampling, oral gavage, euthanasia
FOIA (b)(6)	Post-Procedure Care of Mice and Rats: Reducing Pain and Distress	Analgesia, pain & distress recognition and alleviation, post-operative care
FOIA (b)(6)	Survival Surgery in Rodents	Anesthesia, aseptic surgical techniques
A	Primate Safety	Covers safe handling of non-human primates
A	Controlled Substance Awareness and DEA background Check	Required if any controlled substances will be used
A	Regulated Medical Waste Management	Required if regulated medical waste (animal carcasses, needles, syringes) will be generated as a result of the work

C. PROCEDURES

C.1 Concisely describe all manipulations and experimental procedures, including surgeries, performed on the animals. *Everything done to the live animal at BNL must be detailed here. A short description of experimental procedures done elsewhere should be included. Include the end point of the experiment and timing of euthanasia, if applicable. Flow diagrams or charts are helpful. Materials and methods portion of grant applications or other detailed descriptions may be attached.*

Primates:

Anesthesia SOP: Imaging studies require that primates be anesthetized for periods of time not to exceed 8 hours. *It should be noted that all primate studies will be coordinated with other BNL IACUC approved protocols that use these same animals. We make sure that none of these animals is used more frequently than currently approved as a consequence of their being placed on other, BNL approved, IACUC protocols.* **FOIA (b)(6) Privacy** (a nurse and our study coordinator) is responsible for selecting animals for each primate imaging study. *She speaks directly with the PI's for the individual study.* Scanning the same animal on consecutive days is infrequently required and when it is done, minimal volumes of blood are removed from the animals on the second day. Animals selected for the scanning study are not fed the night prior to scanning, consistent with human studies in which subjects are requested to not eat the night before their scan. None of our human subjects have reported any difficulties complying with this request as a result of pain or discomfort. The morning of the scanning procedure, animals are initially sedated with an intramuscular injection of ketamine hydrochloride (10 mg/kg).

Once sedated, the animal is removed from the cage, placed on a clean stainless steel table, covered, and transported to the prep room located just next to the primate unit. Once in the preparation room, the animal is weighed, and a visual inspection of the animal is made prior to beginning the intubation procedure. The animal is then intubated with a laryngoscope and a disposable pediatric endotracheal tube, which is then held in place with Velcro strips. An ambu bag is attached to the endotracheal tube and is compressed in order to determine tube placement and proper inflation of both lungs. Upon verification of tube placement, the cuff is inflated to aid in tube stability. A disposable core temperature probe is then placed into the esophagus for body temperature monitoring. Once this procedure is completed, the animal is placed into a transfer cage and then into the Chemistry Department van. The animal is transported to the PET facility. Upon entering the scanning room, the animal is removed from the transport cage and is placed on the scanning table. The animal's head is then placed into a specific head holder and the endotracheal tube is connected to the anesthesia machine. The gaseous anesthesia used for PET studies consists of isoflurane (Forane® 1.0 - 4.0%), oxygen (1500 ml/min) and nitrous oxide (800 ml/min). Animals are maintained on gas throughout the length of the study. **Gas cylinders (oxygen and nitrous oxide) are checked to assure that they have sufficient gas for an entire study. The regulator pressure on the oxygen tank must be 30 psi.** Prior to arterial and venous line placement, animals are again inspected to ensure that transport didn't change the endotracheal tube or its position. For the duration of the study, isoflurane levels are routinely maintained at between 1.0 - 1.8%. All PET studies require venous and arterial cannulation. For venous cannulations a QuikCath (21 gauge) is placed into a radial arm vein, typically into the antecubital region. Much less frequently, the venous catheter is placed into a vein in the leg located immediately posterior to the gastrocnemius muscle. Regardless of the site, the venous line is maintained with heparized saline under normal pressure. This venous line is used for radioisotope and pharmacologic drug injections only.

In order to evaluate PET data, arterial blood is drawn from the animal throughout the duration of the study. Arterial cannulation is performed using a QuikCath (21 gauge) most typically along the mesial aspect of the popliteal region of the leg. Much less frequently, arterial cannulation occurs in the lower

aspect of the inguinal region. On rare occasions, radial or ulnar arterial cannulation is performed. Upon establishing the arterial line, a blood sample is drawn for hematocrit determination. The arterial line is maintained with heparinized saline under pressure to slightly exceed normal resting states. The arterial line is then connected to a pediatric pressure transducer for invasive monitoring of heart rate and blood pressure using a SpaceLabs Pediatric Patient Care Monitoring System. During the study, blood is drawn continuously for the first 2 minutes and then at selected times throughout the scanning period. For all baboons used under this application, any given radioisotope injection includes no more than 100 mls of blood sampling. Immediately following arterial cannulation and blood pressure monitoring, chest leads are connected for electrocardiogram (EKG) monitoring, the temperature probe is connected for core temperature monitoring, a respirator monitor is connected for respiration monitoring, and finally, the system is set to alarm should any vitals fall outside a well delineated range specific for each animal. Upon completion of these procedures, a disposable blanket is placed over the animal and connected to an electric heating unit that maintains warm air circulation in order to keep the animals' core temperature to within a specific range. Once this animal preparation is completed, usually within 30 minutes, the animal is placed into the tomograph for the necessary preliminary scans to be completed prior to radioisotope injection. Radioisotopes and specific drugs detailed in this proposal are injected via an intravenous line. Specifically, drugs used in all studies are injected at pre-selected intervals (pretreatment times) in order to maximize the CNS effects. Drugs are typically administered as a bolus but in certain cases, drugs may be administered over a period of minutes to hours as drug safety dictates. Drugs are also sometimes administered via nasogastric tube which is installed after the animal is anesthetized. The nasogastric tube placement is always checked prior to administration of any fluid or drug. This is to prevent aspiration if the tube placement was wrong.

Commencing with radioisotope injection, an automated blood sampling machine (Ole Dich) is activated and blood (For all non-human primates used under this application, any given radioisotope injection includes no more than 100 ml of blood sampling.) is continuously drawn for the first 2 minutes. Blood samples are placed into pre-heparinized vials for further analysis. This sampling interval removes approximately 17 ml (for all non-human primates used under this application) over 2 minutes. During the entire scanning procedure, vital signs are automatically recorded and strips of the EKG trace are printed and placed into the experimental records. At the end of the scanning procedure, the venous line is removed and held off for at least 5 minutes. The arterial line is then removed and pressure is continuously applied for at least 10 minutes, with observations made after 5 mins. Once the line has been determined to be closed, the animal is removed from the anesthesia machine. At this point, only oxygen is administered, i.e., both isoflurane and nitrous oxide are shut off. Ketamine is available should the animal require additional sedation during transport. The use of ketamine following a study for this purpose is extremely rare. Generally, within 15 - 20 minutes the animal has a positive eye-lid response and begins to cough. The endotracheal tube is removed and the animal is placed back into the cage, now containing an absorbable and disposable diaper, and is transported back to the BLAF. Once back in her home cage, the animal is frequently checked and must be able to sit up on her own before the last team member leaves for the day.

In some cases for drug studies we may take a CSF sample. This will be done by **FOIA (b)(6) Privacy** neurologist who has experience with CSF sampling.

We sometimes run anatomical MRI scans on all of our baboons at BNL. This will be done at the 4 Tesla MRI scanner in Bldg 560 at Brookhaven. We require MRI scans for anatomical registration with the PET scans. We need to be able to do this for all of our tracers. This anatomical information advances our ability to develop and evaluate new radiotracers to study the brain. We will obtain MRI scans on all of the baboons who are at BNL and who are currently used for PET scans. Baboons will be anesthetized for the MRI scans with ketamine only. It is estimated that each scan will require less than 1 hour.

Rodents: Rodents are used for radiotracer validation either by microPET scanning or for tissue distribution

and dissection and chemical analysis. For the microPET studies the rodents are anesthetized with isoflurane or ketamine (ip). Tail veins are cannulated for radiotracer injection and anesthesia is maintained while they are in the scanner. In some cases we inject the radiotracer ip while the animal is awake and then after a short period (<1 hr) they are anesthetized and scanned. All sacrifices of rodents (decapitation or cervical dislocation) are done under anesthesia.

C.2 Does this work duplicate previous experiments/activities? If yes, justify.

no

D. ANIMAL DESCRIPTION

D.1 Species:	baboons, mice rats
D.2 Strain/Breed:	rats: Sprague Dawley; Wistar; Zucker. Mice, Swiss Webster; baboons, papio Anubis Athymic nude mice (nu/nu), wild type and cancer cell bearing (MCF-7)
D.3 Sex:	females and males
D.4 Age/Weight:	primates, neonates-30 yrs, 5-30 kg, Rats, 1-6 months, 100-500 g), mice are (20-40 g)
D.5 Supplier:	Rats, Taconic farms and Charles River; baboons, BNL; athymic nude mice: Taconic Farms (Germantown, NY, 1-888-822-6642).

*If not a commercial vendor, a recent health report (no older than three months) from the animal facility must be submitted to the BLAF Manager **at least six weeks before** the planned experiment or shipment of animals. Please contact the BLAF Manager at 631 344-FOIA to make arrangements for the receipt of the animals.*

D.6 Justify that the work is appropriate to be done in an animal model.

In order to translate new radiotracers for in vivo imaging applications we must evaluate them in an intact living animal. In some cases we need to obtain brain and peripheral organ tissue samples for chemical analysis of the form of the radioisotope. Rodents are used in the latter case and baboons are used in non terminal studies to obtain a detailed kinetic analysis of the complex brain and other organs. Nude mice are used to investigate tumor-seeking radiotracers.

D.7 Justify species to be used and why a lower phylogenetic species cannot be used.

Baboons

We use primates primarily because of the physical size of their brains in combination with the known resolution of the imaging devices. We use female animals for three reasons. First, primates are a very sexually dimorphic species. For example, males can be as much as 4 –5 times the size of female animals and are therefore, much more difficult to handle and present a health and safety issue to vet service personnel. Furthermore, the size of these animals would require the addition of larger caging and this caging, along with the room needed to hold these cages, is currently unavailable at BNL. Second, female animals provide information relative to hormonal fluctuations that are particularly relevant to our research goals (new directions in breast cancer research are currently being developed). Baboons are also used to obtain measurements for dosimetry calculations prior to translation of a new radiotracer to humans.

Rodents

Radiotracer development studies: We use rodents to examine the biochemical characteristics of the radiotracer (how well it models known systems, how long it lasts in the CNS, where to look in various brain regions of the primate, whether the neuroanatomic localization is appropriate for imaging, etc...) prior to performing primate imaging studies. Nude mice are used to investigate tumor-seeking radiotracers.

D.8 Animal Numbers

D.8.a Total for first three years:	Baboons: 12; Rats, 100, Mice; 50
D.8.b Maximum housed at one time:	Baboons, 12; Rats, 50, Mice, 20

D.9 Justify number of animals. Indicate design of study groups and statistical methods and include power calculations. Include steps taken to minimize the number of animals required.

The number of animals being requested for the proposal year (primates, rats, and mice) was determined using a multiple analysis approach. Specifically, these numbers are based on a 30 year history of our primate and rodent use, on the number of ongoing projects that require imaging and rodent data, on the number of estimated PET and radiochemical synthesis failures, on the number of animals used to obtain statistical significance with a power analysis and a significance level of ($p < 0.05$), on the number of PET, microPET, MRI, and microMRI scanners currently supported at BNL on the number of days available for scanning and finally on the number of people available to perform the studies. For the past 15 years, we have averaged 75 primate PET studies/year with our current colony. The test-retest design is used where the animal serves as her own control.

Generally for our rodent studies, animal numbers are designed to achieve a sample size of 6-10 animals/condition for PET experiments for radiotracer development and validation. Using a standard power analysis, it was determined that sample sizes in this range will provide sufficient power (~80%) to allow statistical analysis of the data using analyses of variance (ANOVAs) followed by a series of post hoc comparisons.

E. PAIN/DISTRESS

E.1 List total number of animals at applicable levels of stress/discomfort

Level A: No pain or distress: Animals will be euthanized without any treatments or manipulations or

irradiation with unrestricted movement and without anesthesia and without anticipated subsequent effects at BNL.

Level B: Relieved or momentary pain or distress: Momentary pain or potential pain or distress relieved by pharmacologic, behavioral or other means, e.g., injection of any substance including anesthetics, post-procedural analgesics, behavioral conditioning, restraint or minor pain/distress and medical treatment of disease states.

Level C: Unrelieved or sustained pain or distress: Any procedure that would cause more than momentary or slight pain or distress, e.g., chronic untreated disease states, pain research

Species	LEVEL A	LEVEL B	LEVEL C
baboons		15	
rats		100	
mice		30	

E.2 For animals used in Level B or C, perform a literature search for alternatives to pain/distress.
Please note the Research Library Staff is available to assist with literature searches.

List procedures that may cause pain/distress (e.g. imaging, surgery, injection, behavioral testing, food restriction, etc) and perform a search using the procedures. *Procedures that have pain eliminated by the use of anesthetics and/or analgesics are still considered painful even though the animal is not expected to experience any pain/distress.*

Date of Search:	Oct. 4, 2011
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Databases Searched:	medline
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Years included:	1967-present
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Provide a narrative of Search Results *When alternative procedures are discovered, you must identify them and justify why those procedures are not being considered:*

I searched baboon, anesthesia, pain. There were no new articles over the time interval since the last search. Below I repeat the results from the 2010 report.

From 2010:

There were 4 hits two of which looked promising. I ordered the first one (below) on ILL. The procedures used for the baboon in this paper were almost identical to those that we use here (i.e. im ketamine, intubation, isoflurane, anesthesia). The second reference in Nuclear Medicine and Biology uses ketamine and isoflurane which is the same anesthesia protocol that we use here at BNL.

1. Dormehl IC, Hugo N, Beverley G , *The baboon: an ideal model in biomedical research. Anesth Pain Control Dent.* 1992 Spring;1(2):109-15

2. Alin J. Severance, Ramin V. Parsey, J.S. Dileep Kumar, Mark D. Underwood, Victoria Arango, Vattoly J. Majo, Jaya Prabhakaran, Norman R. Simpson, Ronald L. Van Heertum, J. John Mann. *In vitro* and *in vivo* evaluation of [¹¹C]MPEPy as a potential PET ligand for mGlu₅ receptors *Nuclear Medicine and Biology* 33: Pages 1021-1027, 2006

I also searched **rodents, anesthesia, microPET** in medline in 2011. There were 10 hits, two more than in 2010. The two new articles were not of relevance. To summarize, Matsumura et al., 2003, *Neuroimage* 20(4): 2040 gave a good description of the metabolic and neuronal effects of the different common anesthetics in the context of FDG imaging (which is not of relevance to this protocol). However, this is a good informative article with many references. I conclude from reviewing these papers that isoflurane has no major disadvantages and has the advantage that it mimics the anesthesia that we use in the baboon so for comparison purposes, we still think it is a good choice.

E.3 Indicate how procedures have been refined to reduce the amount of potential pain, distress or morbidity.

We allow at least 4 weeks for recovery after each baboon PET session. We optimize the information from each scan session scanning 2-3 times for one anesthesia, blood sampling session. We always use the animal as her own control in test-retest protocols which increases the power of the study by avoiding the need to consider inter subject variability thereby reducing animal numbers. We use a minimum number of rodents getting both microPET and biochemical information whenever we sacrifice an animal.

For the tumor mice, animals will be monitored twice a week in the first four weeks after injection of tumor cells and will be examined daily including weekends and holidays after the fourth week. The pain and physical inconvenience caused by the tumor growth may occur at the late stage of cancer development. At any time before 16 weeks, mice which are unable to walk, experience of respiratory difficulty or 15% increase or less of body weight (weight will be measured twice a week) due to tumor burden will be euthanized. Serious infections will be signs used to determine indications for euthanasia as well. See Stony Brook University **FOIA (b)(6) Privacy**, Section I, J, K, for surgical pain control and manipulation.

E.4 Describe if animals are subjected to food/water deprivation or prolonged and/or unusual restraint and provide justification. Describe how animal health is monitored during deprivation.

no

E.5 Is death used as a study endpoint wherein animals must die without intervention such as pain relief and/or euthanasia? If yes, explain why an earlier end point is not acceptable.

no

F. ANIMAL CARE

F.1 Please indicate if animals will be housed at BNL in other than in the Brookhaven Laboratory Animal Facility (BLAF). *All singly-housed rodents will be provided with environmental enrichment unless scientifically justified.*

No, although rodents may be kept overnight in the microPET laboratory after scanning to allow decay of the isotope and HP survey if they are to be returned to the BLAF. They will be provided food and water ad libitum

F.2 Describe additional requirements for other than routine animal care (e.g. housing, feeding, hazardous waste bedding disposal) *Investigative staff must be responsible for feeding all animals, weighing the correct amount of food, logging each feeding and adjusting the ration as needed to maintain the animal at the desired weight. If food, equipment and/or other supplies are to be shipped from another institution's animal facility, a recent health report from the facility must be submitted to the BLAF Manager at least six weeks before the planned experiment.*

All care is routine except when investigators feed and water scanned animals for an overnight stay at PET and when PET staff stay with a baboon in BLAF until she recovers from anesthesia after a PET study.

F.3 List the building and room number(s) in which experimental procedures, surgery, and/or postoperative recovery will be performed on live animals (if known).

Initial knockdown and intubation of the baboons is done at BLAF. Arterial catheterization and anesthesia induction and maintenance and radiotracer injection and blood sampling is done in either PET rooms 5 or 6 in bldg 906. Baboons recover from anesthesia in their home cage at BLAF.

For the athymic nude mice, tumor cells will be implanted at Stony Brook University and when they are ready for imaging, the animals will be transported to Brookhaven on the day of the study; mouse carcasses and organs will be disposed of at BNL using approved procedures

G. PROCEDURE SPECIFICS

G.1 List all chemical agents (sedatives, analgesics, anesthetics, paralytics, euthanasia, study drugs, radiotracers) administered to the animals. *For euthanasia involving CO₂, please use 100% CO₂ at a 20% air replacement per minute rate. For ketamine anesthesia, please use intraperitoneal (ip) injections, not intramuscular (im). Ketamine/xylazine may be stored for up to 28 days after mixture.*

Type	Agent	Dose	Route	Frequency	Controlled Substance (Y/N)
stimulant	Cocaine, methamphetamine, methylphenidate, amphetamine	0.0001 – 100.0 mg/kg	Iv or oral or ip	Acute/chronic	Y
opioid	morphine	“	“	acute	Y
hallucinogen	Phencyclidine,	“	“	acute	Y

	ketamine				
sedative	Chloral hydrate	100 – 250 mg/kg, IP (5% solution-rats only)	ip	acute	Y
Aromatase inhibitors	Vorozole and letrozole	0.0001-100 mg/kg	Iv or oral or IP	acute	N
Cytochrome P450 inhibitors	Ketoconazole and others	“	Iv or oral or IP	acute	N
Phosphodiesterase inhibitors	HT0712 and rolipram	“	Iv or oral or IP	Acute and chronic (4-7 days @ 25 mg/day po)	N
Sedative hypnotics	lorazepam	“	“	“	Y
Serotonin reuptake inhibitors	Fluoxetine, citalopram and others	“	“	“	N
Norepinephrine reuptake inhibitors	Nisoxetine, atomoxetine	“	“	“	N
MAO A and B inhibitors	Clorgyline, CX157, deprenyl, harmine	“	“	“	N
Nicotinic/Cholinergics	Nicotine	“	“	“	N
Histone deacetylase inhibitors	suberoylanilide hydroxamic acid (SAHA), valproic acid, butyric acid, phenylacetic acid	“	“	“	N
Histone deacetylase inhibitor *	(benzamide type; H10-21)	0.08-1.0 mg/kg			
NMDA receptor agents	memantine	“	“	“	N
Dopamine receptor antagonists	haloperidol	“	“	“	“
Orexin active compounds		“	“	“	“

¹⁸ F-FDG labeled IS4-5 (¹⁸ F-FDG-IS4-5)		<20 µg	Iv or ip or ic under anesthesia	acute	N
injection vehicles (see attached list)	<p>Some of our drugs are very insoluble in aqueous solution. We need to be able to administer them IV. All of our proposed vehicles are either in the scientific literature, or already approved for human or veterinary use. We would like approval for all means of administration – iv, oral, IM, NG and IP.</p> <p>The maximum volume of each vehicle for iv administration is 5 mL in the baboon, 0.5 mL for the rat and 0.1 mL for the mouse. The rate of iv injection in the baboon will be < 3mL/min. The maximum volume for NG administration is 10 mL for the baboon and 2 mL for the rat and 0.2 mL for the mouse. The maximum volume for IP administration in rats is 1 mL and 0.1 mL for the mouse. The maximum volume for IM administration in rats is 0.5 mL and 0.1 mL for the mouse.</p> <p>Please see Strickley, <i>Pharmaceutical Research</i>, Vol. 21, No. 2, February 2004 and attached word document listing vehicles which have received approval along with supporting information regarding safety and approved use</p>				

** Currently, **FOIA (b)(6) Privacy** (MGH, Boston), a collaborator on this HDAC project, provided H10-21 toxicity data in mice (iv, 0.5 and 5 mg/Kg/day, for 10 days), where any detrimental behavioral changes or apparent toxic effects were observed. Our initial study showed high brain uptake of [¹¹C]H10-21, indicating its suitability as a brain penetrable blocking agent. In addition, there is dosage information for primates and humans on a structurally very similar benzamide HDAC inhibitor (CI-994, 4.4-5.5 mg/kg in monkey, iv ; 6-10 mg/kg in human, oral) in the previous literatures. Here, we are proposing to examine saturability and binding specificity of new PET HDAC tracers in baboon by blocking with C-12 version of H10-21 *in vivo*.

G.1.a List the name(s) of the individual(s) administering the above agents:
FOIA (b)(6) Privacy
G.1.b Indicate building and room numbers where agents are stored and security procedures for controlled substance(s):
All controlled substances are kept in double-lock boxes in the HOT Laboratory in 901 or in the exam room in 906 or the microPET lab in 906.
G.1.c If paralytic agents are used in conjunction with surgical manipulations, indicate the means by which absence of pain is monitored and/or determined, and who is responsible:
Not applicable
G.2 Is surgery involved? If yes, indicate whether surgery is survival or non-survival.
no

G.2.a Describe monitoring and supportive care provided during surgery (*who, what and how will this be done?*):

G.2.b Describe indications for analgesic therapy to be administered before, during, and/or following surgery:

G.2.c Describe post-operative and/or anesthetic monitoring and supportive care (*who, what and how often*): **Please use Surgery and Recovery Record**

Also see primate procedure. Once back in her home cage, the animal is frequently checked and must be able to sit up on her own before the last team member leaves for the day.

G.2.d Who will maintain surgical and post-operative records and where will they be maintained? **Please note: Records must be accessible for inspection**

FOIA (b)(6) and FOIA (b)(6) maintain these records in the drawer of the cart in room 6 of Bldg 906 (PET Lab).

G.3 Is anesthesia involved?

yes

G.3.a Describe monitoring and supportive care provided during anesthesia (*who, what, and how will this be done?*): **Please use Surgery and Recovery Record**

See C1

G.3.b Who will maintain anesthetic records and where will they maintained? **Please note: Records must be accessible for inspection**

FOIA (b)(6) and FOIA (b)(6); records are kept in the PET lab

G.4 Are animals to be used in more than one major surgical procedure from which they are allowed to recover? *If yes, please describe and justify.*

no

G.5 By what method and by whom will animals be euthanized and how will death be confirmed? If a chemical agent is used, please list in Section G.1. *For euthanasia involving CO₂, please use 100% CO₂ at a 20% air replacement per minute rate. Justification must be provided for any physical method, such as decapitation or cervical dislocation, without anesthesia.*

Rodents are typically euthanized by decapitation or cervical dislocation with anesthesia.

Must scientifically justify decapitation/cervical dislocation without anesthesia.

G.6 List criteria for intervention and/or removal of animals from study or early euthanasia.

•Examples are severe ataxia; rapidly increased heartrate or respiratory rates; oral, nasal or vaginal discharge

such as pus or blood; wound dehiscence; marked swelling, tumor(s) greater than 2 cm or ulcerating, ulcer greater than 10% of body surface area, inability to eat or drink, loss of weight, great discoloration in an appendage or surgical area; immobility.

- Unless otherwise noted 100% CO₂ at a 20% air replacement per minute rate will be used for early euthanasia for rodents.

In addition, to those listed above (which we will routinely employ as criteria for intervention and/or removal of animals from study) we will include changes in vital signs during PET scanning and changes in respiration during microPET scanning.

H. SPECIAL CONSIDERATIONS

H.1 Check hazardous materials being used in this study.

<input type="checkbox"/> Human cells or fluid	<input type="checkbox"/> Microorganism	<input type="checkbox"/> Chemicals including fixatives	<input type="checkbox"/> Recombinant DNA
<input type="checkbox"/> Nanoparticles	<input checked="" type="checkbox"/> Radioactivity	<input type="checkbox"/> Other (list)	<input type="checkbox"/>

For each agent listed above, please ensure that it is covered under an approved ESR

H.2 Indicate if animals will be shipped from BNL. If yes, indicate that BNL's preferred shipping procedures will be followed. If other arrangements are necessary, please describe.

no

H.3 If not shipped from an approved vendor, detail how animals will be transported to BNL.

I. INVESTIGATOR ASSURANCE

I affirm to the best of my knowledge that all the above information is complete and accurate and agree to accept responsibility for this project in accordance with applicable Federal and State of New York regulations, USDA guidelines, and established BLAF policies and procedures. No changes will be made without prior approval from the IACUC.

In order to reduce risk to all personnel and laboratory animals, I agree to:

- a. Follow BNL procedures for aspects of the animal care and use such as preoperative care, anesthesia, surgical technique, postoperative care, sampling techniques, euthanasia, and disposal of contaminated carcasses and waste.
- b. Ensure that my instructions to laboratory personnel are implemented.
- c. Ensure that all project personnel comply with the required Occupational Health Program before handling animals.
- d. Instruct all personnel in my laboratory that they should inform me if they believe that the treatment of any research animal is inappropriate. If the situation is not resolved, the employee should contact the Attending Veterinarian, or the IACUC Chair and/or Institutional Official.

I am aware that all research outlined under this protocol must be carried out under approved Experimental Safety Review(s) (ESR). I am aware that it is my responsibility to ensure that all individuals working on this protocol have been listed on an appropriate ESR and that their training is up to date. I am aware that work cannot proceed without an approved ESR.

PRINCIPAL INVESTIGATOR		DATE	
<i>Your Department Safety Coordinator will be notified of your IACUC approval.</i>			

J. APPROVALS

I attest that the following issues have been appropriately addressed: Scientific merit of project; Appropriateness of conducting the project at BNL; Adequacy of funding for the project; Appropriateness of the expertise and experience of the PI and project personnel; Appropriateness of training for the PI and project personnel, and; Adequacy of department resources to support this protocol.

BNL DEPARTMENT CHAIR		DATE	
PHARMACIST (or designee)		DATE	
<i>Required for Schedule I controlled substances</i>			

Potential Injection vehicles for insoluble drugs:

Intralipid is a brand name for the first safe fat emulsion for human use, approved in 1962 in Europe and invented by Professor Arvid Wretling, Sweden. It was approved in the United States in 1972. It is used as a component of parenteral nutrition for patients who are unable to get nutrition via an oral diet. It is an emulsion of soy bean oil, egg phospholipids and glycerin. It is available in a 10%, 20% and 30% concentration. The 30% concentration is not

approved for direct intravenous infusion, but should be mixed with amino acids and dextrose as part of a total nutrient admixture. Commercially available from Baxter as Intralipid 20 – a 20% solution approved for IV injection. (from Wikipedia)

2- Pyrol (2-pyrrolidone) 2-PYROL® is completely miscible with water, ethanol, ethyl ether, ethyl acetate, and carbon disulfide. It has good chemical stability and solubilizes drugs for injectable liquid formulations. Commercially available from International Specialty Products

PHARMASOLVE® is N-methyl-2-pyrrolidone cGMP grade. It is completely miscible with water, and most organic solvents, including alcohols, ketones, aromatic and chlorinated Hydrocarbons; exceedingly resistant to hydrolysis at pH 1.5 to 11.0. It improves drug solubility for wide range of water insoluble drugs in parenteral and topical formulations. It is commercially available from International Specialty Products

Captisol® is a patent protected, uniquely modified cyclodextrin, whose chemical structure was rationally designed to maximize safety and optimize complexation to improve the solubility. It is a polyanionic β -cyclodextrin derivative with a sodium sulfonate salt separated from the lipophilic cavity by a butyl ether spacer group, or sulfobutylether (SBE). The selection of Captisol® as the cyclodextrin with the most desirable safety profile and drug carrier properties was based upon evaluations of the mono, tetra and hepta-substituted preparations. Captisol® is the trade name for CyDex's modified β -cyclodextrin preparation. Captisol® is safe when administered parenterally and does not exhibit the nephrotoxicity associated with beta-cyclodextrin.

Cremophor EL is the registered trademark of BASF Corp. for its version of polyethoxylated castor oil. It is prepared by reacting 35 moles of ethylene oxide with each mole of castor oil. The resulting product is a mixture (CAS number 61791-12-6); the major component is the material in which the hydroxyl groups of the castor oil triglyceride have ethoxylated with ethylene oxide to form polyethylene glycol ethers. Minor components are the polyethyelene glycol esters of ricinoleic acid, polyethyelene glycols and polyethyelene glycol ethers of glycerol.^[1] Cremophor EL is a synthetic, nonionic surfactant. Its utility comes from its ability to stabilize emulsions of nonpolar materials in aqueous systems.

Propylene Glycol: From Wikipedia, the free encyclopedia. Propylene glycol is used as a solvent in many pharmaceuticals, including oral, injectable and topical formulations. Notably, diazepam, which is insoluble in water, uses propylene glycol as its solvent in its clinical, injectable form. The acute oral toxicity of propylene glycol is very low, and large quantities are required to cause perceptible health damage in humans; propylene glycol is metabolized in the human body into pyruvic acid (a normal part of the glucose-metabolism process, readily converted to energy), acetic acid (handled by ethanol-metabolism), lactic acid (a normal acid generally abundant during digestion),^[9] and propionaldehyde. Serious toxicity generally occurs only at plasma concentrations over 1 g/L, which requires extremely high intake over a relatively short period of time.

FOIA (b)(6) Privacy

BROOKHAVEN
NATIONAL LABORATORY

FOIA
P.O. Box 5000
Upton, NY 11973-5000
Phone 631 344-FO
Fax 631 344-FO
FOI@bnl.gov

managed by Brookhaven Science Associates
for the U.S. Department of Energy

Memo

* * *

DATE: April 17, 2013

FOIA (b)
(6)
Privacy

Digitally signed by FOIA

TO:

F
O

(b)(6)

Date: 2013.04.17 09:06:44
-04'00'

FROM: FOIA (b) , Institutional Animal Care and Use Committee

SUBJECT: IACUC Protocol 102 "PET Investigations of Central Nervous System Physiology"

As of 04/17/13, the addendum to use 6-OH-buspirone under the above protocol was approved.

This protocol is approved until 12/06/13. This approval is given only for the protocol submitted; any changes must be approved by the IACUC prior to being implemented.

You should be aware that all research outlined in this protocol must be carried out under approved Experimental Safety Review(s) (ESR) and that this application must contain the same information as that listed in the approved ESR(s). You must be aware that it is your responsibility to ensure that all individuals working on this protocol have been listed on an appropriate ESR and that their training is up to date.

FOIA

cc: FOIA (b)

FOIA (b)

DESIGNATED MEMBER REVIEW

Title: PET Investigations of Central Nervous System Physiology

Addendum: Use 6-OH-buspirone

The IACUC Chair, in consultation with the Attending Veterinarian, has performed a designated member review and approved the above protocol addendum.

FOIA (b)(6) Privacy

FOIA

(b)(6)

Priva

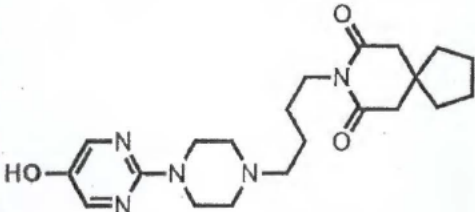
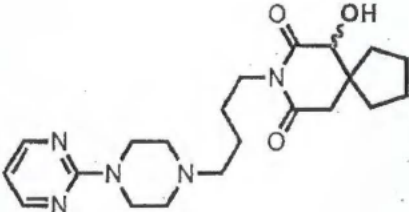
Chair

4/16/13

Date of approval

**BROOKHAVEN NATIONAL LABORATORY
INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC)
ADDENDUM**

Protocol #: 102

Title of Application:	Radiotracer development
Principal Investigator:	FOIA (b)(6) P i
A. Description of Proposed Addendum: baboon pretreatment: 6-OH-buspirone (iv), buspirone (oral)	
The addition of 6-OH-buspirone or 5-OH- buspirone as a pretreatment drug in the baboon (IV administration)	
<div style="display: flex; justify-content: space-around; align-items: center;"> <div style="text-align: center;">  <p>A</p> </div> <div style="text-align: center;">  <p>B</p> </div> </div>	
<p>Please see attached paper: DRUG METABOLISM AND DISPOSITION, Vol 35(8), 1387-92 (5 mg/Kg intraarterial administration in rat)</p> <p>We wish to add the reported baboon equivalent dose of 5 or 6-OH-buspirone (1.45 mg/kg for baboon) use. Buspirone showed very low bioavailability (4%, attached file). The two major metabolites (A and B) is present in human after oral administration. These compounds are detected in human in blood stream (1-40 times higher concentration) after buspirone administration and are being considered for development for human use since they are potentially active ingredients for buspirone efficacy as an anxiolytic.</p> <p><i>Please note: If Schedule I controlled substances are being added, this protocol must be reviewed and approved by the BNL Pharmacist to ensure that the substances are included in BNL's DEA license.</i></p>	
B. Justification and Rationale for Addendum:	
Buspirone administration has been reported to be effective for cocaine cessation in non-human primate. We would like to measure its major metabolites, 6-OH-buspirone and 5-OH-buspirone occupancy on dopamine D2/D3 receptor.	
C. Relevance to Original Protocol:	
We will follow original protocol, except for having approval for new metabolite iv administration.	
D. Species, Strain, Number of Animals Requested and Vendor under addendum (if changed):	
No change	
E. Justification for Number of Animals in D (include power calculations, where applicable) (if changed):	
No change	
F. Method(s) of Anesthesia and/or Euthanasia (if changed):	
No change	
G. Will the addendum change the pain or distress or distress category? If yes, please complete the following:	
NO	
Date of Search: Database(s) Searched: Keywords Searched: Years Included in Search: Narrative of Search Results:	
The Research Library Staff is available to assist in literature searches	

I am aware that all research outlined in this addendum must be carried out under approved Experimental Safety Review(s) (ESR) and that this addendum must contain the same information as that listed in the approved ESR(s). I am aware that it is my responsibility to ensure that all individuals working on this protocol have been listed on an appropriate ESR and that their training is up to date.

Principal Investigator's Signature: _____

Date: 4-17-13

FOIA (b)(6)

FOIA (b)(6) Privacy

Date: 4/17/13

Pharmacist (or designee): _____

Date: _____

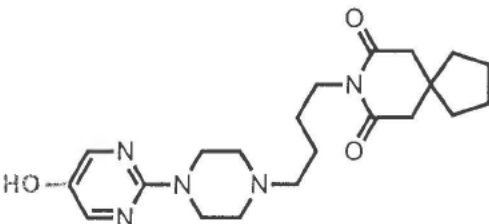
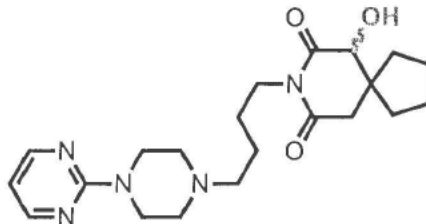
(Required for Schedule I controlled substances)

Approved Experimental Review Number or

RCD Signature: _____ Date: _____

**BROOKHAVEN NATIONAL LABORATORY
INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC)
ADDENDUM**

Protocol #: 102

Title of Application:	Radiotracer development
Principal Investigator:	FOIA (b)(6)
A. Description of Proposed Addendum: baboon pretreatment: 6-OH-buspirone (iv), buspirone (oral)	
The addition of 6-OH-buspirone or 5-OH- buspirone as a pretreatment drug in the baboon (IV administration)	
<div style="display: flex; justify-content: space-around; align-items: center;"> <div style="text-align: center;">  <p>A</p> </div> <div style="text-align: center;">  <p>B</p> </div> </div>	
<p>Please see attached paper: DRUG METABOLISM AND DISPOSITION, Vol 35(8), 1387-92 (5 mg/Kg intraarterial administration in rat)</p> <p>We wish to add the reported baboon equivalent dose of 5 or 6-OH-buspirone (1.45 mg/kg for baboon) use. Buspirone showed very low bioavailability (4%, attached file). The two major metabolites (A and B) is present in human after oral administration. These compounds are detected in human in blood stream (1-40 times higher concentration) after buspirone administration and are being considered for development for human use since they are potentially active ingredients for buspirone efficacy as an anxiolytic.</p> <p><i>Please note: If Schedule I controlled substances are being added, this protocol must be reviewed and approved by the BNL Pharmacist to ensure that the substances are included in BNL's DEA license.</i></p>	
B. Justification and Rationale for Addendum:	
Buspirone administration has been reported to be effective for cocaine cessation in non-human primate. We would like to measure its major metabolites, 6-OH-buspirone and 5-OH-buspirone occupancy on dopamine D2/D3 receptor.	
C. Relevance to Original Protocol:	
We will follow original protocol, except for having approval for new metabolite iv administration.	
D. Species, Strain, Number of Animals Requested and Vendor under addendum (if changed):	
No change	
E. Justification for Number of Animals in D (include power calculations, where applicable) (if changed):	
No change	
F. Method(s) of Anesthesia and/or Euthanasia (if changed):	
No change	
G. Will the addendum change the pain or distress or distress category? If yes, please complete the following:	
NO	
Date of Search: Database(s) Searched: Keywords Searched: Years Included in Search: Narrative of Search Results: The Research Library Staff is available to assist in literature searches	

I am aware that all research outlined in this addendum must be carried out under approved Experimental Safety Review(s) (ESR) and that this addendum must contain the same information as that listed in the approved ESR(s). I am aware that it is my responsibility to ensure that all individuals working on this protocol have been listed on an appropriate ESR and that their training is up to date.

FOIA (b)(6) Privacy

Principal Investigator's Signature: _____

Date: 4-17-13

FOIA (b)(6) Privacy

Date: _____

Pharmacist (or designee): _____

Date: _____

(Required for Schedule I controlled substances)

Approved Experimental Review Number or

RCD Signature: _____ Date: _____

FOIA (b)(6)

P 1

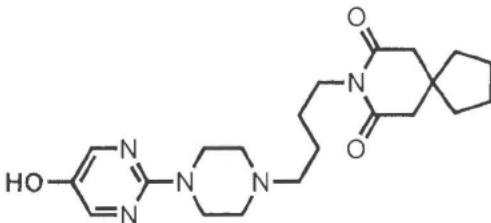
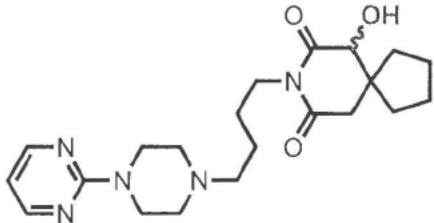
From: FOIA (b)(6)
Sent: Monday, April 15, 2013 8:59 AM
To: FOIA (b)(6) Privacy

Subject: IACUC Protocol 102
Attachments: 6OH buspirone as active metab 2007.pdf; buspironebioavailability.pdf; buspironemetabolites.pdf

Importance: High

Please review the addendum below. The IACUC Chair and Vet have reviewed and will approve unless any IACUC member requests the addendum be reviewed by the full board. Please let me know by Tuesday 4/16/13 at noon if this addendum may be approved by DMR.

Protocol #: 102

Title of Application:	Radiotracer development
Principal Investigator:	FOIA (b)(6)
A. Description of Proposed Addendum: baboon pretreatment: 6-OH-buspirone (iv), buspirone (oral)	
The addition of 6-OH-buspirone or 5-OH-buspirone as a pretreatment drug in the baboon (IV administration)	
<div style="display: flex; justify-content: space-around; align-items: center;"><div style="text-align: center;"> A</div><div style="text-align: center;"> B</div></div>	
<p>Please see attached paper: DRUG METABOLISM AND DISPOSITION, Vol 35(8), 1387-92 (5 mg/Kg intraarterial administration in rat)</p> <p>We wish to add the reported baboon equivalent dose of 5 or 6-OH-buspirone (1.45 mg/kg for baboon) use. Buspirone showed very low bioavailability (4%, attached file). The two major metabolites (A and B) is present in human after oral administration. These compounds are detected in human in blood stream (1-40 times higher concentration) after buspirone administration and are being considered for development for human use since they are potentially active ingredients for buspiron efficacy as an anxiolytic.</p> <p><i>Please note: If Schedule I controlled substances are being added, this protocol must be reviewed and approved by the BNL Pharmacist to ensure that the substances are included in BNL's DEA license.</i></p>	
B. Justification and Rationale for Addendum:	
Buspirone administration has been reported to be effective for cocaine cessation in non-human primate. We would like to measure its major metabolites, 6-OH-buspirone and 5-OH-buspirone occupancy on dopamine D2/D3 receptor.	
C. Relevance to Original Protocol:	
We will follow original protocol, except for having approval for new metabolite iv administration.	
D. Species, Strain, Number of Animals Requested and Vendor under addendum (if changed):	
No change	
E. Justification for Number of Animals in D (include power calculations, where applicable) (if changed):	
No change	

F. Method(s) of Anesthesia and/or Euthanasia (if changed):
No change
G. Will the addendum change the pain or distress or distress category? If yes, please complete the following:
NO

FOIA (b)(6)

FOIA (b)(6) Privacy

Brookhaven National Laboratory

FOIA (b)

Upton, NY 11973-5000

631 344-FOI phone

631 344-FOIA fax

FOIA (b)(6) Privacy

From: FOIA (b)(6)
Sent: Tuesday, March 12, 2013 9:48 AM
To: FOIA (b)(6) ; FOIA (b)(6) ; FOIA (b)(6)
Cc: FOIA (b)(6) Privacy
Subject: IACUC Protocol 102

Importance: High

Below is a modification to the 2/28/13 IACUC approval to reduce the recovery period from 4 to 2 weeks for studies that do not require a blood draw:

Any proposal to use an animal more frequently than 4 week intervals must be discussed with and approved by the Attending Veterinarian prior to the study.

Please notify all applicable personnel.

FOIA (b)(6)
FOIA (b)(6) Privacy
Brookhaven National Laboratory
Bldg. FO
Upton, NY 11973-5000
631 344-FOI phone
631 344-FOI fax

FOIA (b)(6) Privacy

BROOKHAVEN
NATIONAL LABORATORY

FOIA
P.O. Box 5000
Upton, NY 11973-5000
Phone 631 344-
Fax 631 344-
FOI@bnl.gov

managed by Brookhaven Science Associates
for the U.S. Department of Energy

Memo

* * *

DATE: February 28, 2013

TO: FOIA (b)

FOIA
(b)(6)
Privacy

Digitally signed by FOIA
(b)(6)
Date: 2013.02.28 09:28:04
-05'00'

FROM: FOIA (b)(6), Institutional Animal Care and Use Committee

SUBJECT: IACUC Protocol 102 "PET Investigations of Central Nervous System Physiology"

As of 02/28/13, the addendum to revise minimum time between scans under the above protocol was approved.

This protocol is approved until 12/06/13. This approval is given only for the protocol submitted; any changes must be approved by the IACUC prior to being implemented.

You should be aware that all research outlined in this protocol must be carried out under approved Experimental Safety Review(s) (ESR) and that this application must contain the same information as that listed in the approved ESR(s). You must be aware that it is your responsibility to ensure that all individuals working on this protocol have been listed on an appropriate ESR and that their training is up to date.

FOIA
cc: FOIA (b)
FOIA (b)

7/18/13

DESIGNATED MEMBER REVIEW

Title: PET Investigations of Central Nervous System Physiology

Addendum: Revise minimum time between scans

The IACUC Chair, in consultation with the Attending Veterinarian, has performed a designated member review and approved the above protocol addendum.

FOIA (b)(6) Privacy

FOIA (b)(6)

2/28/13

Date of approval

From: FOIA (b)(6)
 Sent: Tuesday, February 26, 2013 3:03 PM
 To: FOIA (b)(6) Privacy

T

Subject: FOIA
 IACUC Protocol 102

Please review the addendum below and let me know by Thursday 2/28/13 at noon whether it can be reviewed and approved by the IACUC Chair and Vet. Thanks.

Protocol #: 102

Title of Application:	Radiotracer Development
Principal Investigator:	FOIA (b)(6)
A. Description of Proposed Addendum:	
<p>We would like to reduce the recovery period that baboons wait between PET imaging studies from 4 weeks to 2 weeks for studies that do not require a blood draw for plasma radioactivity measurements.</p> <p><i>Please note: If Schedule I controlled substances are being added, this protocol must be reviewed and approved by the BNL Pharmacist to ensure that the substances are included in BNL's DEA license.</i></p>	
B. Justification and Rationale for Addendum:	
<p>When blood is not taken for tracer plasma radioactivity concentration measurements recovery from anemia becomes largely unnecessary. There would still be a minimum two week period required to recover from anesthesia and trauma associated from technical operations such as intubation and venous and arterial cannulation.</p>	
C. Relevance to Original Protocol:	
<p>Change in the frequency of use of baboon undergoing PET imaging studies.</p>	
D. Species, Strain, Number of Animals Requested and Vendor under addendum (if changed): N/A	
E. Justification for Number of Animals in D (include power calculations, where applicable) (if changed): N/A	
F. Method(s) of Anesthesia and/or Euthanasia (if changed): N/A	
G. Will the addendum change the pain or distress or distress category? If yes, please complete the following:	
<p>The pain or distress category will not change.</p>	

FOIA (b)(6)

Privacy

Brookhaven National Laboratory

FOIA (b)

Upton, NY 11973-5000

631 344-FOI phone

**BROOKHAVEN NATIONAL LABORATORY
INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC)
ADDENDUM**

Protocol #: 102

Title of Application:	Radiotracer Development
Principal Investigator:	FOIA (b)(6) P i
A. Description of Proposed Addendum:	
<p>We would like to reduce the recovery period that baboons wait between PET imaging studies from 4 weeks to 2 weeks for studies that do not require a blood draw for plasma radioactivity measurements.</p> <p><i>Please note: If Schedule I controlled substances are being added, this protocol must be reviewed and approved by the BNL Pharmacist to ensure that the substances are included in BNL's DEA license.</i></p>	
B. Justification and Rationale for Addendum:	
<p>When blood is not taken for tracer plasma radioactivity concentration measurements recovery from anemia becomes largely unnecessary. There would still be a minimum two week period required to recover from anesthesia and trauma associated from technical operations such as intubation and venous and arterial cannulation.</p>	
C. Relevance to Original Protocol:	
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D. Species, Strain, Number of Animals Requested and Vendor under addendum (if changed): N/A	
E. Justification for Number of Animals in D (include power calculations, where applicable) (if changed): N/A	
F. Method(s) of Anesthesia and/or Euthanasia (if changed): N/A	
G. Will the addendum change the pain or distress or distress category? If yes, please complete the following:	
<p>The pain or distress category will not change.</p> <p>Date of Search: Database(s) Searched: Keywords Searched: Years Included in Search: Narrative of Search Results:</p> <p>The Research Library Staff is available to assist in literature searches</p>	

I am aware that all research outlined in this addendum must be carried out under approved Experimental Safety Review(s) (ESR) and that this addendum must contain the same information as that listed in the approved ESR(s). I am aware that it is my responsibility to ensure that all individuals working on this protocol have been listed on an appropriate ESR and that their training is up to date.

Principal Investigator's Signat

Date: 2/28/13

Department Chair's Signature: _____ Date: _____

Pharmacist (or designee): _____ Date: _____
(Required for Schedule I controlled substances)

Approved Experimental Review Number or
RCD Signature: _____ Date: _____

FOIA (b)(6)
From: FOIA (b)(6)
Sent: Tuesday, February 26, 2013 11:10 AM
To: FOIA (b)(6)
Subject: Fwd: question about a baboon study for Thursday

Sent from my iPhone

Begin forwarded message:

From: FOIA (b)(6) Privacy @stonybrook.edu>
Date: February 26, 2013, 10:58:10 AM EST
To: "FOIA (b)(6) Privacy @bnl.gov>
Cc: FOIA (b)(6) Privacy @notes.cc.sunysb.edu>, FOIA (b)(6) Privacy @bnl.gov>, FOIA (b)(6) Privacy @bnl.gov>
Subject: Re: question about a baboon study for Thursday

Hi FOIA (b)(6),
I don't have a problem with what you propose and I would be happy to work with you to update the 'use' guidelines.

FOIA (b)(6)

On Tue, Feb 26, 2013 at 10:49 AM, FOIA (b)(6) Privacy @bnl.gov> wrote:
Dear FOIA (b)(6),

I am writing to find out if we can we scan the same baboon with only a 2 week interval between scans if the protocol does not involve blood sampling?

Our current practice is to allow a 4 week interval between scans for which we do blood sampling.

We are trying to schedule baboon Brooke for Thursday February 28. She was last scanned 3 weeks ago on February 8 (without arterial blood sampling). We also do not need to do arterial blood sampling for the Thursday scan.

We attach a article describing weekly PET scans for your information. However, we want to adhere to the best practices for these animals but also considering our scientific needs.

Thanks FOIA (b)(6)

FOIA (b)(6)

PS. With your help I would like to add some general guidelines to IACUC #102 so that we don't have to keep asking you.

On 2/25/13 10:49 AM, "FOIA (b)(6) Privacy [REDACTED]@bnl.gov" wrote:

>Dear FOI [REDACTED] and FOIA [REDACTED],

>

>I am sending one paper (we are using the same tracer and similar strategy
>for our experiment).

>We are also using the same anesthesia protocol (I highlighted it).

>I hope that this paper help your discussion.

>

>I am in trouble to setting up my baboon studies.

>I wish that I can get your decision soon.

>

>Thank you very much for your consideration in advance.

>

>Best,

>

>FOIA [REDACTED]

>(b)(6)

FOIA (b)(6)

P i

From: FOIA (b)(6)
Sent: Tuesday, February 26, 2013 12:46 PM
To: FOIA (b)(6)
Cc: FOIA (b)(6); FOIA (b)(6)
Subject: RE: Addendum to 102

I will process the addendum. In the meantime, the IACUC Chair and Vet have approved your request to use Brooke tomorrow.

FOIA

From: FOIA (b)(6)
Sent: Tuesday, February 26, 2013 12:12 PM
To: FOIA (b)(6)
Cc: FOIA (b)(6); FOIA (b)(6)
Subject: Addendum to 102

FOIA ,

Please read and approve or change.

FOIA ,

Let us know what else you need and if FOIA (b) and F approve using an animal with 3 week recovery period (no blood) tomorrow.

Thanks.

FOI