Date: October 24, 2005

To: Don Rosenstein, M.D., Chair, IRB, NIMH

Recommended by:
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Protocol Title: PET whole body biodistribution and test retest brain imaging studies using a phosphodiesterase 4 inhibitor \((R)\)-[11C]rolipram

Identifying Words: Dosimetry, pharmacokinetics, compartment analysis, reproducibility

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Robert B. Innis, MD, PhD, NIMH

Estimated Duration of Study: three years

<table>
<thead>
<tr>
<th>Study Subjects</th>
<th>Number</th>
<th>Sex</th>
<th>Age Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy controls</td>
<td>25</td>
<td>M &amp; F</td>
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</tr>
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</table>

Off Site Project: NO
Project uses ionizing radiation: YES
Project uses Durable Power of Attorney: NO
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I. PRECIS

Both basic and clinical studies have indicated that the 3′, 5′-cyclic adenosine monophosphate (cAMP) system plays critical roles in several brain diseases, particularly in mood disorders and drug addiction. cAMP is synthesized from adenosine 5′-triphosphate (ATP) by adenylyl cyclase and metabolized by cyclic nucleotide phosphodiesterases (PDEs). Among components of the cAMP pathway, PDE4 appears to be critical for antidepressant effects. 4-[3-(cyclopentoxyl)-4-methoxyphenyl]-2-pyrrolidone (rolipram) is an inhibitor of PDE4. As a positron emission tomography (PET) brain imaging agent, rolipram has good properties such as high affinity of 1–2 nM and appropriate lipophilicity (Log P) of ~3. A rat study gave an estimation of low radiation absorbed doses of the active enantiomer (R)-[11C]rolipram. A subsequent study on healthy human subjects showed good brain uptake and good image quality. Therefore, R-[11C]rolipram is a promising PET ligand. However, radiation absorbed doses have not been estimated from human whole body imaging studies and a method to measure binding of (R)-[11C]rolipram in human brain has not been established.

The purposes of this protocol are to estimate radiation absorbed doses of (R)-[11C]rolipram by performing whole body imaging studies on healthy human subjects and also to establish an accurate method to measure PDE4 levels in brain by performing test retest brain imaging studies. The results of this overall study are required to apply this PET ligand in various neurological and psychiatric disorders in the future.

II. INTRODUCTION

A. Type of Protocol

Healthy subjects will be studied to estimate radiation absorbed doses of (R)-[11C]rolipram from whole body imaging studies and also to establish an accurate method to measure PDE4 levels by performing test retest brain imaging studies. Both of these studies will be performed with an intravenous injection of up to 20 mCi of (R)-[11C]rolipram and imaging for 2 h.

B. Background

cAMP is a prevalent second messenger that mediates signal transduction of several neurotransmitters including dopamine, epinephrine, histamine, and adenosine. cAMP is synthesized from ATP by adenylyl cyclase and metabolized by PDEs. Thus, PDEs terminate the actions of the second messenger cAMP. At least 11 types of PDE exist in mammals, and PDE4 is selective to cAMP in the brain. PDE4 consists of four independently coded subtypes, PDE4A, B, C, and D (Houslay, 2001).

There is large body of literature indicating that the cAMP pathway plays important roles in psychiatric illnesses, including mood disorders (Duman et al., 1997) and drug addiction (Nestler and Aghajanian, 1997). Among components of the cAMP pathway, PDE4 appears to be critical for antidepressant effects. Repeated antidepressant treatment increased PDE4 (Ye et al., 1997; Takahashi et al., 1999; Zhao et al., 2003), and an inhibitor of PDE4, rolipram, showed antidepressant effects both in animals (Wachtel, 1983; Mizokawa et al., 1988) and humans (Fleischhacker et al., 1992). However, adverse reactions such as emesis and sedation precluded rolipram from clinical applications. Rolipram is almost equipotent at all four PDE4 subtypes. Inhibitors selective to PDE subtypes may have therapeutic effects with minimal adverse reactions (O'Donnell and Zhang, 2004).

Rolipram has two enantiomers. The R(-) enantiomer has 20 times greater affinity than the S(+) enantiomer and the racemic rolipram had Kd = 1–2 nM (Schneider et al., 1986). In the brain, the density of the racemic rolipram binding sites is high (20 nM) (Schneider et al., 1986) compared to other proteins that have been imaged in vivo, and the lipophilicity of rolipram appears to be appropriate for brain imaging (Waterhouse, 2003). Considering the importance of PDE4 in diseases, high density of PDE4, and chemical characteristics of (R)-rolipram, this
compound may be a quite promising as a brain imaging agent. In fact, following initial rodent studies (Lourenco et al., 1999; Lourenco et al., 2001), (R)-[11C]rolipram has been successfully applied in non-human primates (Tsukada et al., 2001) and humans (DaSilva et al., 2002; Matthews et al., 2003). PDE4 is activated by phosphorylation with protein kinase A (Conti et al., 1995), and a study using recombinant DNAs has indicated that phosphorylation of PDE4 affects binding affinity of rolipram (Hoffmann et al., 1998). Therefore, in addition to measuring binding density and affinity, (R)-[11C]rolipram PET imaging may provide information on the phosphorylation state of PDE4.

Radiation absorbed doses of (R)-[11C]rolipram has been estimated from rat but not from human data (Lourenco et al., 2001). The whole body absorbed dose was 0.0052 rad/mCi, which is well within the limit. Prior studies of (R)-[11C]rolipram in humans and non-human primates were not quantitative and did not distinguish changes in delivery of radioligand from changes in density of PDE4. Using a small animal PET scanner, Advanced Technology Laboratory Animal Scanner (ATLAS) (Seidel et al., 2003), we have established a method to accurately measure PDE4 levels in living rats (Fujita et al., 2004). In the present protocol, we plan to perform a kinetic whole body imaging study in 10 healthy humans in order to estimate radiation-absorbed doses of (R)-[11C]rolipram. By doing this, we will confirm that radiation-absorbed doses of (R)-[11C]rolipram is within limits, and is a safe radioligand for human use. Then we will establish an accurate method to measure PDE4 levels by performing test retest brain imaging studies and comparing results in two studies in individual subjects.

C. Research question
This protocol seeks to determine whether radiation-absorbed doses of (R)-[11C]rolipram in human subjects is within limits. The protocol also seeks to establish an accurate method to measure PDE4 levels in brain regions.

D. Background of Approach
In the evaluation of a new radioligand, it is routine to perform whole-body biodistribution studies, first, and then perform test retest brain imaging studies to evaluate the accuracy of the measurement. Protocols performing these standard procedures submitted from Molecular Imaging Branch, NIMH apply basically the same procedures with variations mainly in the length of data acquisition based on the characteristics of the PET ligand. The current protocol has been prepared based on an approved protocol “Kinetic studies in whole body and brain of [11C]DASB PET imaging of serotonin transporters” (#03-M-0159, PI: R. B. Innis, MD, PhD).

E. Qualifications of investigators
Drs. Fujita and Innis have more than 10 years experience of using neuroreceptor imaging radioligands. Dr. Innis is a clinical authorized user (CAU) of radioisotopes. Drs. Innis and Ramachandran are credentialed physicians. Ms. Sangare is a credentialed nurse practitioner. The clinical authorized user for this protocol, Peter Herscovitch, MD, has more than 24 years experience of PET imaging.

III. STUDY DESIGN AND METHODS
A. Study design
The protocol is composed of two phases. Part 1 is whole body imaging studies to estimate radiation-absorbed doses of (R)-[11C]rolipram. Part 2 is test retest brain imaging studies to establish and evaluate the accuracy measuring PDE4 levels in the brain. There will be no randomization involved in the study.
B. Overview

In part 1 of the study, radiation absorbed doses of (R)-[\(^{11}\)C]rolipram will be estimated by performing whole body imaging in 10 healthy subjects (~ 5 males and 5 females). On the first visit, the subjects will be screened for eligibility. On the second visit, whole body PET scanning will be performed, followed by routine safety monitoring with laboratory blood and urine tests. The length of time between the initial visit and PET scanning will be within 4 months.

In part 2 of the study, brain imaging study with (R)-[\(^{11}\)C]rolipram will be performed twice to examine reproducibility of the measurement. On the first visit, the subjects will be screened for eligibility. On the following three visits, subjects will have two PET scans of (R)-[\(^{11}\)C]rolipram and an MRI scan. The length of time between the initial visit and the last scan will be within 6 months.

C. Study phases

This protocol consists of two phases, whole body imaging studies and test retest brain imaging studies. A break-down of these phases are shown below. Part 2 will be initiated after completing part 1 and estimating radiation-absorbed doses from human data in part 1.

<table>
<thead>
<tr>
<th>Whole body imaging (part 1)</th>
<th>1st Visit – Screen</th>
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<tr>
<td>Informed consent</td>
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<tr>
<td>Physical Exam</td>
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<td></td>
</tr>
<tr>
<td>Pregnancy test (female ≤ 55)</td>
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<td>×*</td>
</tr>
<tr>
<td>PET whole body imaging</td>
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<td></td>
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<tr>
<td>Blood and urine tests</td>
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Test retest brain imaging study (part 2)

<table>
<thead>
<tr>
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<td>Physical Exam</td>
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<td>Neurological Exam</td>
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<td>Pregnancy test (female ≤ 55)</td>
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<tr>
<td>MRI***</td>
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<tr>
<td>Brain PET</td>
<td>×</td>
<td>×</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood and urine tests</td>
<td>×**</td>
<td>×</td>
<td>×</td>
<td></td>
</tr>
</tbody>
</table>

*A pregnancy test will be done within 24 h of the PET ligand administration.

**If the interval between screening blood and urine tests will be more than 30 days, these tests will be repeated before the PET scan.

***Depending on the availability of PET and MRI scanners, an MRI scan may be scheduled at any point in time for this protocol, either before or after the PET procedures.

D. Sample stratification

We request to study a total of 25 healthy subjects aged 18–65 years. Ten and 15 subjects will be studied in part 1 and 2, respectively. In part 1 (whole body imaging), approximately an equal number of female and male subjects will be studied to take into account possible gender differences in whole body distribution of radioactivity. Because within subject comparison (test retest reproducibility) will be done in part 2, gender does not need to be balanced. All subjects must meet the inclusion and exclusion criteria listed in Section IV – Subject Enrollment.

E. Sample size justification

To take into account inter-subject variability, radiation absorbed doses are usually estimated from approximately 6-8 subjects (Seibyl et al., 1994; van Dyck et al., 1996; Fujita et al., 2002). To also take into account possible gender differences, we propose to study approximately an equal number of male and female subjects in the whole body imaging study. By taking into account possible withdrawal, we request permission to study 10 subjects in part 1.

After estimating radiation-absorbed doses, we plan to study the accuracy of the measurement of PDE4 levels by evaluating identifiability of distribution volumes using arterial input function. To study the reproducibility of the measurement, we also plan to perform a test retest study in the same population by obtaining arterial input function in each study. A sample size of approximately 10 is required in such studies (Abi-Dargham et al., 1995; Seibyl et al., 1996; Varrone et al., 2000; Soares et al., 2001). By taking into account possible withdrawal in the study with two PET scans with arterial blood sampling, we request permission to study 15 subjects in part 2.
F. Data analysis
In whole body imaging studies, organ time-activity curves will be obtained from the dynamic PET images, and used to calculate organ residence times. Residence time of the urinary bladder will be calculated using a dynamic bladder model (Cloutier et al., 1973). The residence times will be used in OLINDA/EXM (http://www.doseinfo-radar.com/OLINDA.html) to obtain radiation-absorbed dose estimates.

Data of test retest brain imaging studies will be analyzed with compartmental nonlinear least squares analyses and non-compartmental linear and multilinear regression analyses using arterial input function. Distribution volume (Bmax/Kd plus radioactivity not specifically bound to PDE4) will be calculated in various brain regions, and it will be compared between test and retest studies of each subject. Because there is no brain region without PDE4, which is large enough to use as a reference region (Perez-Torres et al., 2000), arterial blood is required for the quantification.

G. Justification for the use of placebo, medication washout, or provocative stimuli
This protocol will not involve the use of placebo, medication washout or provocative stimuli.

IV. SUBJECT ENROLLMENT
A. Recruitment - sample composition and characteristics
We will select healthy adult female and male volunteers (age 18–65 years old) in this protocol. We will exclude children or minors because this study involves radiation exposure. The proportion of ethnic minorities (vs. Caucasians) in the total sample will approximately be consistent with the overall U.S. population proportions.

B. Inclusion criteria
All subjects must be healthy and aged 18–65 years.

C. Exclusion criteria
The exclusion criteria are shown below.

Part 1 (whole body imaging studies):
1. Current psychiatric disease, substance abuse or severe systemic disease based on history and physical exam.
2. Laboratory tests with clinically significant abnormalities.
3. More than moderate hypertension (see below for details).
4. Prior participation in other research protocols or clinical care in the last year such that radiation exposure including that from this protocol would exceed a half of the annual limits. Because human dosimetry of (R)-[^11]C]rolipram has been estimated using rhesus monkeys, the total exposure including that from the (R)-[^11]C]rolipram whole body imaging study will be limited to a half of the RSC guidelines.
5. Pregnancy and breast feeding.

Part 2 (test retest brain imaging studies):
1. Current psychiatric disease, substance abuse or severe systemic disease based on history and physical exam.
2. Laboratory tests with clinically significant abnormalities.
3. More than moderate hypertension (see below for details).
4. Prior participation in other research protocols or clinical care in the last year such that radiation exposure would exceed the annual limits. Results of part 1 will be used to calculate total radiation exposure within a year.
5. Pregnancy and breast feeding.
6. Claustrophobia.
7. Presence of ferromagnetic metal in the body or heart pacemaker.
9. A history of brain disease

D. Study initiation and screening methods

We will initiate the study within 1–2 months of final approval. Healthy controls meeting inclusion and exclusion criteria (above) will be recruited from the community and NIH through advertisements in newspaper and newsletter, private physicians and social service agencies. We will obtain informed consent from all healthy controls.

V. PROCEDURES
A. Details of method

1. Evaluation

Except as described below, all subjects will undergo a physical examination to ascertain general good health. All subjects will have an ECG and will be asked to provide blood and urine samples for a battery of laboratory screening tests such as complete blood count including platelet count, chemistries (Na, K, Cl, HCO₃, BUN, Cr, glucose, Ca, PO₄, SGOT, SGPT, LDH, alkaline phosphatase, CPK, bilirubin, total protein, albumin), VDRL, urinalysis, and urine drug screen. All women of child bearing potential will have a blood or a urine pregnancy test.

Subjects will be excluded if they have more than moderate hypertension. Subjects may be on anti-hypertensive medications, however, the initial screening must show no more than moderate hypertension – i.e. <160/95. In addition, the subject must have normal laboratory values (e.g., BUN, creatinine, urinalysis, and ECG) to document lack of end organ damage. On baseline evaluation on the day of the scan (i.e., before injection of tracer), the subject must be asymptomatic (no headache, dizziness, neurological symptoms, or blurred vision) AND have sustained BP < 180/100. After tracer administration, the scan will be discontinued if BP remains greater than 180/100 continuously for more than 5 min. The subject will then be asked to relax. If BP continues to be greater than 180/100 for more than 15–30 min, a cardiology consult will be ordered STAT.

The exception to the general plans above has to do with the timing of the physical exam and laboratory tests. If the subject has been seen at NIH previously, the physical exam and ECG need to have been performed, and in the chart, anytime within the prior year. Furthermore, the laboratory tests (SMA-20, CBC with diff, urinalysis, and thyroid function test) can be performed on the morning of the scan, but must be reviewed and meet criteria, prior to injection of the radiotracer.

2. PET Procedure

The NIMH Radiochemistry Laboratory (Dir., Victor Pike, PhD) will synthesize and perform QC (quality control) for $\text{R}^{[11C]}$rolipram.

All women 55 years old or younger and of child bearing potential will have a blood or a urine pregnancy test again within 24 h of each PET tracer injection.

PET dynamic whole body scanning in part 1 will be performed using the GE Advance in the PET Department. Prior to radioligand injection, a transmission scan at each body level will be obtained with a $^{68}$Ge rotating pin source to permit measured attenuation correction. The
radiation-absorbed dose from a transmission scan was estimated to be less than 0.05 rad to each organ (based on measurement by M. Daube-Witherspoon, Ph.D., memo of Nov 29, 1994). After intravenous bolus administration of up to 20 mCi \((R)-[1^1C]rolipram\), a dynamic scan series will be obtained by serial imaging of the body in contiguous segments of 15 cm (the axial field-of-view of the GE Advance scanner) from the head to the upper thigh with increasing length duration over time. Scanning will be performed continuously for 120 min. To confirm the absence of the pharmacological effects of the PET ligand, vital signs including a single lead ECG will be recorded within 3 hours before tracer injection, and again at about 30 and 90 min after radioligand injection. During the PET scan, subjects will also be monitored by pulse oximetry. In addition, after completion of the PET scan, the screening laboratory tests (excluding pregnancy test) described above will be repeated.

PET dynamic brain scanning in part 2 will be performed using the GE Advance or HRRT in the PET Department. Two PET scans will be performed in the same way. Subjects will be placed on the scanner bed with his/her head held firmly in place with a thermoplastic mask fixed to the bed. One antecubital venous and one radial arterial catheters will be placed. One venous catheter is for radioligand injection and the arterial catheter are for blood sampling. One additional antecubital venous catheter may be placed for blood sampling. Just prior to the PET scanning, a transmission scan will be performed with a \(^{68}\text{Ge}\) rotating pin source to provide a measured attenuation correction. The radiation-absorbed dose from a transmission scan was estimated to be 0.05 rad to the red marrow, lens of eyes, thyroid, and the brain (based on measurement by M. Daube-Witherspoon, Ph.D., memo of Nov 29, 1994). The radioligand (20 mCi of \((R)-[1^1C]rolipram\)) will be injected intravenously as a bolus injection. PET images will be acquired in the three-dimensional mode with increasing length of frame for a total duration of 2 h. To measure input function of the radioligand, blood samples will be obtained frequently from the arterial line. Several venous samples may also be obtained at several time points to estimate arterial input function using venous blood data. Blood sampling volume in each study will be no more than 200 mL and the total sampling volume in two studies will be no more than 400 mL. Vital signs will be monitored in the same way as the whole body imaging study. In addition, after completion of the PET scan, the screening laboratory tests (excluding pregnancy test) described above will be repeated.

3. MRI procedure

Subjects participating in part 2 will have an MRI scan for anatomical localization by coregistering onto PET image. MRI scanning will be done on a 1.5 Tesla scanner located at the NIH Clinical Center. Transaxial and coronal scans will be acquired in a spoiled GRASS (SPGR) gradient echo pulse sequence. MRI will take up to 1 h.

If subjects become anxious during a scan, diazepam (Valium® 2–4 mg) or lorazepam (Ativan® 0.5–1mg) may be administered orally. If these medications are given, there will be at least a one week interval between MRI and PET scans.

B. Details of assessment by study phase

This protocol is composed of two parts; whole body imaging and brain test retest studies. In part 1, radiation-absorbed doses will be estimated from human data, and then a method to measure brain PDE4 levels will be established in part 2.

C. Details of secondary procedures

There are no secondary procedures in this protocol.
D. Relationship to other studies proposed
This protocol is based on a template protocol for testing new brain imaging radioligand, “Kinetic studies in whole body and brain of [11C]DASB PET imaging of serotonin transporters” (#03-M-0159, PI: R. B. Innis, MD, PhD) which has been approved.

VI. PROVISION OF CARE TO RESEARCH SUBJECTS
A. Concomitant clinical care
None

B. After care
After participation in this study, subjects will not receive after care in this protocol.

C. Reasons for discontinuation from study
Scanning procedures will be stopped for any subject who asks to stop for any reason at any time. Subjects will be asked if they wish to continue the rest of the study. Subjects have the right to withdraw from this study at any time for any reason.

D. Toxicity criteria
There is no expected toxicity in this study.

VII. HUMAN SUBJECT RISKS AND PROTECTIONS
A. Consent and assent procedures
Each subject will receive an oral and written explanation of the purposes and potential risks of participation in this protocol. Specifically, they will be told that (a) the information derived may eventually lead to better understanding of brain chemistry and behavior; (b) PET imaging as used in this study is a research tool, hence no diagnostic interpretation will be given; (c) a confidential code number will be used to ensure that information cannot be linked or traced to any person or family; (d) data will be treated to group statistical analyses only; and (e) subjects will be given ample opportunity to ask questions of the investigators.

For women of child bearing potential, a pregnancy test will be conducted within one day of the PET scan. Finally, when the laboratory tests and medical examination show significant abnormalities, appropriate referrals will be made to address their health problems. Consent will be obtained by the Principal Investigator or one of the Associate Investigators.

B. Risks of study participation and minimization of risks
Potential risks from this study include those associated with: 1) medical examinations including laboratory testing that may reveal previously undiagnosed medical disorders, 2) radiation exposure from the PET and transmission scans, 3) PET scanning, and 4) placement of arterial and venous line and blood sampling, 5) blood sampling and 6) MRI.

1. Medical Examination and Laboratory Testing
The potential risks of a medical examination are small but do include the detection of an otherwise undiagnosed disorder. We will first explain and familiarize the subjects with the laboratory testing to minimize discomfort, if any, during testing. In the present protocol, all healthy normal volunteers are expected to undergo recruitment and assessment procedures without any difficulties. However, if, in the opinion of the study staff, PI, or subject, the study participation is adversely affecting the subject's emotional and or physical well-being, the individual circumstances will be reviewed to determine what additional steps should be taken, such as termination of the study and making appropriate referrals to address their underlying
health problems. If the subject desires not to proceed further with testing, we will end these sessions at any time point. Blood tests may lead to the formation of a small subcutaneous hematoma caused by blood leaking from a punctured blood vessel. This hematoma causes only minor discomfort. It is not dangerous and requires no treatment other than reassuring the patient. There is also a small risk of infection at the site of the needle puncture, which can be readily treated with antibiotic therapy. Approximately 25 mL of blood will be withdrawn.

2. Radiation Exposure Risks

Radiation exposure in this protocol will be from \((R)\)\[^{11}\text{C}\]rolipram and \(^{68}\text{Ge}\) transmission scans. The radiation-absorbed dose from a transmission scan is based on the measurement by M. Daube-Witherspoon, Ph.D., (memo of Nov 29, 1994). Radiation dose estimates for \((R)\)\[^{11}\text{C}\]rolipram are based upon whole body imaging on rhesus monkeys performed by Molecular Imaging Branch, NIMH. Detailed results of this dosimetry study are included in the attached NIH 88-23(a). Effective dose in part 1 and 2 are 0.72 and 1.36 rem, respectively, which are within NIH RSC guidelines.

All subjects will be asked about any prior research participation involving radiation exposure so that the total exposure, in combination with the present study, will not exceed an effective dose of \textbf{2.5 rem per 12 months} as described in section IV.C. Part 2 will be initiated after completing part 1 and estimating radiation-absorbed doses from human data in part 1.

3. PET Scanning

PET scanning, which detects injected radioactivity within the body, is associated with no known physical hazards to the subject lying on the table. We routinely use a series of procedures to minimize the risk for discomfort during scanning sessions. Namely, the procedures are conducted in the presence of trained health professionals to whom subjects will have ready access, should they experience any problems. Subjects can communicate with the trained health professionals whilst in the scanner and can withdraw from the study at any time if they wish to do so.

Occasionally subjects become anxious during the scan. In that case, subjects can request the operator of the PET to stop the scan.

4. Arterial/Venous line Placement

Arterial catheterization has been shown to be a generally safe and reliable method to obtain arterial blood samples (Lockwood, 1985). Placement of a radial arterial catheter may cause bruising or infection. There is also a risk of occlusion and microemboli. In the past, over 3,000 arterial catheters have been placed in the PET department. Of these, two complications requiring physician’s care were reported. In the first case, a small radial artery aneurysm developed several months later, which was successfully repaired surgically. In the second case, a radial artery thrombosis developed 28 days later, which was also successfully repaired surgically. The arterial line will be placed by a member of the anesthesiology staff after confirming normal double circulation (both radial and ulnar arteries). If there is a medical problem relating to placing an arterial catheter, we will make sure that necessary treatment will be provided at NIH.

Venous catheter insertion, which is less invasive than arterial catheterization, can also be associated with bruising, infection, or clot formation. Using proper placement techniques will minimize these risks.

5. Blood Sampling

Subjects participating in a whole body imaging will have blood sampling of no more than 50 mL during the entire course of the study (approximately 25 mL in each of screening and at the end of the scan).
Subjects participating in the test retest brain PET imaging will have no more than 500 mL blood sampling including that for lab tests. Careful screening of health status and CBC will be done prior to the enrollment in the study. Subjects will be asked not to donate blood for a period of eight weeks after the participation is completed.

6. MRI

MRI is not associated with any known deleterious biological effects. 1.5 Tesla MRI is also widely used as a clinical imaging tool. Subjects will be screened and excluded for the presence of any metallic prostheses both at the time of recruitment and just prior to MR imaging. Subjects will wear ear-plugs to minimize exposure to excessively loud noises. Occasionally subjects become anxious during the scan. In that case, subjects can request the operator of the MRI to stop the scan. Valium® 2-4 mg or Ativan® 0.5-1 mg may be given per oral before MRI upon a request by subjects.

Claustrophobic subjects find it difficult be scanned on MRI and subjects with this condition will be excluded at the time of recruitment.

C. Benefits of study participation

There is no direct benefit to subjects participating in this protocol.

D. Investigator conflicts of interest

There are no investigator conflicts of interest in this protocol.

E. Privacy and confidentiality provisions

Every necessary step will be taken to prevent identification of study participants and other violations of subject confidentiality. Information will be stored using a confidential case number, and no identifiers (name, address, phone number, etc.) will be used that could allow direct linking of database information to individual subjects. Where temporary linking of information with identifiers is needed, such identifiers will be temporarily attached to the data, and will be removed after information has been encoded. Secured e-mail will be used for all electronic communications of subject information between investigators.

F. Adverse event reporting

The PI will report immediately all serious adverse events to the NIMH Clinical Director verbally and the NIMH IRB and NIH RSC verbally and in writing within the guidelines set by the NIH Standards for intramural clinical research.

G. Data and safety monitoring processes

Demographic and clinical data will be archived in EXCEL on a PC server. Imaging and blood data will be offloaded from the scanner/blood sampling device to a PC or a SUN workstation after each imaging session has been completed. Clinical Safety Monitoring data will be archived together with other data. Laboratory test results will be stored on the CRIS.

H. Subject compensation

Reimbursement is based on NIH standards for time devoted to the research project. Subjects will be paid for each portion of the study they have completed whether or not they opt for early withdrawal from participation. (Please refer to Appendix I for breakdown of payment schedule.)
VIII. PHARMACEUTICAL, BIOLOGIC AND/OR DEVICE INFORMATION

A. Source
The NIMH Radiochemistry Laboratory will synthesize and perform QC (quality control) on the tracer \((R)-[^{11}\text{C}]\text{rolipram}\). As for other IND agents synthesized at the CC PET Department, the FDA grants authority for such synthesis and QC. Furthermore, the FDA may inspect the process at any time.

B. Relevant pharmacology
Rolipram is a reversible inhibitor of PDE4. Because of the tracer doses, no pharmacological effects are expected with \((R)-[^{11}\text{C}]\text{rolipram}\).

C. Toxicity
No effects, side effects or toxicity is expected from this radioligand, since it is administered at tracer doses.

D. Formulation and preparation
\((R)-[^{11}\text{C}]\text{rolipram}\) will be synthesized at the radiochemistry lab of MIB/NIMH by \(^{11}\text{C}\text{-methylation of } (R)-\text{desmethyl-rolipram and will be formulated in normal saline (Fujita et al., submitted)}\).

E. Stability and storage
\((R)-[^{11}\text{C}]\text{rolipram}\) will be administered within 60 minutes after synthesis of the radioligand. The radioligand is stable during this period.

F. Incompatibilities
\((R)-[^{11}\text{C}]\text{rolipram}\) will be administered at a tracer dose and no other medication will be involved in this protocol. Therefore, we do not expect pharmacological effects or interactions with concomitant medication the subject is taking.

G. Administration procedures
The radioligand is administered via an indwelling intravenous catheter over \(\sim 1\) min.
IX: REFERENCES


X. APPENDIX: REIMBURSEMENT SCHEDULE

Whole body imaging:

<table>
<thead>
<tr>
<th></th>
<th>Inconvenience Units</th>
<th>Pay for inconvenience (1)</th>
<th>Time (h)</th>
<th>Pay for time (2)</th>
<th>Total Pay (1 + 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Visit 1 (Outpatient)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History taking, physical exams, blood test, and urinalysis</td>
<td>2</td>
<td>$20</td>
<td>2</td>
<td>$30</td>
<td>$50</td>
</tr>
<tr>
<td><strong>Visit 2 (outpatient)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PET scanning</td>
<td>10</td>
<td>$100</td>
<td>4</td>
<td>$50</td>
<td>$150</td>
</tr>
<tr>
<td>Antecubital venous catheters</td>
<td>3</td>
<td>$30</td>
<td></td>
<td></td>
<td>$30</td>
</tr>
<tr>
<td>Pregnancy test</td>
<td>1</td>
<td>$10</td>
<td></td>
<td></td>
<td>$10</td>
</tr>
<tr>
<td>Movement restriction</td>
<td>1</td>
<td>$10</td>
<td></td>
<td></td>
<td>$10</td>
</tr>
<tr>
<td>Blood test and urinalysis</td>
<td>2</td>
<td>$20</td>
<td></td>
<td></td>
<td>$20</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td><strong>$260 - 270</strong></td>
</tr>
</tbody>
</table>
## Test retest brain imaging:

<table>
<thead>
<tr>
<th>Visit 1 (Outpatient)</th>
<th>Inconvenience Units</th>
<th>Pay for inconvenience (1)</th>
<th>Time (h)</th>
<th>Pay for time (2)</th>
<th>Total Pay (1 + 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>History taking, physical exams, blood test, and urinalysis</td>
<td>2</td>
<td>$20</td>
<td>2</td>
<td>$30</td>
<td>$50</td>
</tr>
</tbody>
</table>

| Visit 2 to NIH (outpatient) |  |
|-----------------------------|-----------------|----------|----------|----------------|------------------|
| MRI                         | 6               | $60      | 1        | $20            | $80              |

| Visit 3 (outpatient) |  |
|----------------------|-----------------|----------|----------|----------------|------------------|
| PET scanning         | 10              | $100     | 4        | $50            | $150             |
| Arterial catheter    | 6               | $60      |          |                | $60              |
| Antecubital venous catheters | 3      | $30      |          |                | $30              |
| Pregnancy test       | 1               | $10      |          |                | $10              |
| Movement restriction | 1               | $10      |          |                | $10              |
| Blood test and urinalysis | 2            | $20      |          |                | $20              |

| Visit 4 (outpatient) |  |
|----------------------|-----------------|----------|----------|----------------|------------------|
| PET scanning         | 10              | $100     | 4        | $50            | $150             |
| Arterial catheter    | 6               | $60      |          |                | $60              |
| Antecubital venous catheters | 3      | $30      |          |                | $30              |
| Pregnancy test       | 1               | $10      |          |                | $10              |
| Movement restriction | 1               | $10      |          |                | $10              |
| Blood test and urinalysis | 2            | $20      |          |                | $20              |

**Total** | **$670 - 690**