[11C]Acetate Positron Emission Tomography (PET) in patients with Lymphangioleiomyomatosis (LAM) and Tuberous Sclerosis Complex (TSC).

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Duration of study: 6 months

Number and type of subjects: 8 or 16 adult female subjects diagnosed with an angiomyolipoma

Ionizing radiation: Yes

Project uses IND/IDE: IND no. 146871

Multi-Institutional Project: No

Participating Institutions: Brigham and Women's Hospital, Boston, MA;
Massachusetts General Hospital, Boston, MA

I. Background and Significance

a. Historical Background: Lymphangioleiomyomatosis (LAM) is a rare, multisystem disease of women, consisting of a diffuse proliferation of smooth muscle actin-positive cells (LAM cells), which harbor inactivating mutations in either the *TSC1* or *TSC2* tumor suppressor gene. These inactivating mutations result in constitutive activation of mammalian/mechanistic TOR (target of rapamycin) complex 1 (mTORC1) (2-5), which integrates growth factor and nutrient signaling to stimulate cell growth and metabolism (6-10). Pulmonary LAM is characterized by associated progressive cystic destruction of the lung parenchyma, recurrent pneumothorax, and chylous pleural effusions. Extrapulmonary proliferative lesions of LAM include renal angiomyolipomas and lymphangiomyomas. LAM can occur as a sporadic disorder where LAM cells harbor somatic inactivating mutations of the *TSC1 or TSC2* gene, or in women with Tuberous Sclerosis Complex (TSC). TSC is an autosomal dominant disease characterized by neurologic manifestations and hamartomas of the brain, skin, heart, and kidneys (11). Up to 80% of women with TSC have radiologic evidence of cystic lung degeneration (11, 12).

b. Previous pre-clinical or clinical studies leading up to and supporting the proposed research: Preclinical work was conducted in the laboratory of Dr. Priolo and published in part in Clinical Cancer Research (1). The Priolo lab was able to show that lipogenic pathways can be detected in preclinical models of TSC and LAM in vivo using microPET-based metabolic imaging

c. Rationale behind the proposed research and potential benefits to patients and/or society: Rapamycin is an FKBP12-dependent allosteric inhibitor of mTORC1 approved by the FDA for the treatment of LAM and TSC-associated renal angiomyolipomas. Clinical trials of TSC and LAM have shown that 12 month-treatment with rapamycin induces response of renal angiomyolipomas and stabilization of pulmonary function and clinical benefit is seen after 3 months for both LAM and renal angiomyolipomas (13-15). However, lung function decline and tumor growth resume when treatment is interrupted. In addition, magnitude of clinical response to rapamycin varies across patients. For instance, in the EXIST-2 trial (double-blind, placebo-controlled, phase 3 trial) the response rate was 42%, with the primary efficacy endpoint being the proportion of patients with confirmed angiomyolipoma response of at least a 50% reduction in total volume of target angiomyolipomas relative to baseline (14).

This clinical evidence highlights the critical need for sensitive and specific biomarkers of response to therapy and/or disease progression, including biomarkers of tumor metabolic activity. Currently, elevated levels of vascular endothelial growth factor-D (VEGF-D) in the blood of LAM patients represent the only biomarker with diagnostic role in LAM (16, 17) and potentially a role as a biomarker of therapeutic response to mTORC1 inhibitors (18). However, not all LAM patients have clinically significant blood VEGF-D levels.

Metabolic imaging biomarkers of disease activity are not currently available for TSC/LAM. [^{18}F]fluorodeoxyglucose (FDG)- PET has shown utility to identify malignant neoplasms including malignant perivascular epitheliod cell tumors (PEComas), primary lung cancers, and lymphomas, in patients with TSC and/or LAM. However, TSC and LAM lesions (renal angiomyolipomas, pulmonary LAM, lymphangiomyomas) did not show abnormal FDG

uptake, likely due to aberrant trafficking of glucose transporters (19-21). LAM patients would benefit from a metabolic imaging biomarker in multiple ways. *First*, a sensitive a specific imaging biomarker would help answer outstanding questions regarding personalized dosage and length of treatment for rapamycin and its analogs (rapalogs). *Second*, biomarkers of disease progression and therapeutic response would streamline the design, cost and duration of LAM/TSC clinical trials. *Third*, a metabolic imaging
biomarker and circulating VEGF-D could be used as complementary diagnostics to enhance clinical decision making.
Forth, PET is a technique already widely used in the clinics, therefore there will be no need to generate Intellectual Property or secure additional funding to commercialize any product of our study.

II. Specific aims

The proposed study aims to quantitatively and non-invasively assess metabolic activity of renal angiomyolipomas as an early biomarker of response to rapamycin and rapalogs and to implement modeling of LAM lung metabolic activity in LAM and TSC patients using [^{11}C]acetate positron emission tomography (PET) imaging.
These milestones will be achieved in the following Specific Aim:
Specific Aim 1. Test feasibility of [^{11}C]acetate PET to quantify metabolic activity of LAM or TSC patient lesions before and after treatment with rapamycin or rapalogs**.** We plan to enroll eight women with LAM or TSC who have renal angiomyolipomas and are rapamycin-naive. Our preliminary studies reveal that incorporation of acetate in TSC2-deficient cells is strongly suppressed by rapamycin. In addition, our proof of concept preclinical studies with the acetate derivative fluoroacetate showed rapid uptake of this tracer by TSC2-deficient tumors, including tumors generated with LAM patient renal angiomyolipoma-derived cells, using dynamic PET.

In the proposed study, dynamic [^{11}C]acetate PET/CT will be used to monitor metabolic activity over time and to extract blood and tissue density components in renal (angiomyolipomas) and lung lesions in LAM or TSC patients. Patients enrolled who are either on treatment with Rapamycin or a rapalog or not will receive 1 scan each and patients who are about to start therapy with rapamycin or rapalogs, will receive 2 scans, one at baseline and one after 3 months of therapy

We expect to achieve the following outcomes:
1. Implement quantitative modeling to detect [^{11}C]acetate uptake in renal angiomyolipoma and pulmonary LAM.
2. Test[11C]acetate PET as a biomarker of rapamycin activity in TSC2-deficient proliferative lesions.

Both outcomes will provide standardized uptake value (SUV) as a measure of metabolic activity of different LAM/TSC lesions in patients.

Our success will be measured as the ability to non-invasively detect and quantify metabolic activity of proliferative lesions in LAM or TSC patients. Importantly, enhanced uptake of [^{11}C]acetate has been reported in 10 patients with renal angiomyolipomas, showing

significantly higher SUV in the tumors compared to normal kidney. SUV was not affected by fat content (1). This published report supports the clinical feasibility of our proposed study.

III. Subject Selection

a. Inclusion/Exclusion Criteria: LAM or TSC patients, aged 18 yrs and over presenting with at least one renal angiomyolipoma (at least 1 cm in each diameter) confirmed by CT, MRI, or ultrasound and have not received any prior treatment with Rapamycin or rapalogs or candidates for initiating treatment with rapalogs or who have been on rapamycin or rapalogs for a minimum of 3 months and maximum of 5 years will be eligible for the study. Patients with LAM and AML who are currently on rapalogs for < 3 months and > 5 year and patients who have participated in other research studies in the past 12 months that have involved radiation exposure, which is more than 50 mSv/year, would not be eligible for this study.

b. Source of subjects and recruitment methods:

Patients are referred to our clinic at the LAM center at Brigham and Women's hospital by local pulmonologists as well as the LAM foundation for their clinical care. All clinic patients found to have an angiomyolipoma and other potential participants referred to us by physicians who care for LAM or TSC patients at various institutions and by the LAM foundation or the Tuberous Sclerosis Alliance could be approached for participation in the study. Care will be taken to allow potential subjects to feel free from tension and subtle coercion. The physician investigators will advise potential subjects that a study is being done, and briefly describe the study to ascertain interest prior to identifying themselves as being involved. Investigators will emphasize that participation is voluntary and that not participating will not jeopardize their future care at Brigham and Women's hospital or any other Partners institution.

The study investigators will also contact providers outside of these institutions who may be caring for patients with LAM or TSC to notify them of the clinical trial design, inclusion and exclusion criteria. This contact will be in the form of a letter to referring physicians. Such physicians will be provided with contact information of key personnel in the trial in order to refer potential subjects for participation.

IV. Subject Enrollment

The primary specialist or heath care provider, usually a physician, who is known to the potential subject and has firsthand knowledge of the patient's medical history must (1) give approval for his/her patient to be contacted for research purposes (2) initially introduce the study to the patient and (3) obtain the patient's permission to be contacted by study staff. A nurse or study coordinator will review the informed consent with the subject to avoid the possibility of coercion or bias since subjects will be recruited from Investigator's own practice. Subjects will be reminded that refusal to participate in this trial will not change the quality of care that she will receive at BWH. Study participation is voluntary and the subject will be advised that she can withdraw at any time.

The subject will be given the opportunity to take the consent home to consider participation. The subject will be asked to read the informed consent form prior to the physician or study coordinator asking the subject any questions concerning their health. Written, informed consent will be obtained after one of the investigators has reviewed the protocol verbally in detail with the subject. The physician will inform the subject that she

has the alternative not to participate in the study. Subjects will receive a signed copy of the consent form for their records. After all questions are answered, and only after the consent form is signed by the patient and one of the MDs listed on the application will study screening commence. Subjects unable to give consent will not be approached.

In cases where the subject is unable to travel to the MGB site for the consent visit, the investigator would call the subject on the phone or over video where details of the study will be discussed. All questions will be answered and the consent form would be sent to the subject electronically along with contact information for the study team. The subject would then review the consent and there would be an additional call to answer if any remaining questions. Once, all questions are answered, the subject would sign and date (including time) the consent form agreeing to their participation in the research and return the signed (handwritten or digital) and dated consent form electronically. The investigator would sign and date (including time) the consent form signed and dated by subject. MGB IRB requirements for digital signatures will be followed when the subjects would prefer to use digital signatures while signing the consent form.

V. Study Procedures

Patients who are eligible would be consented to the study by a physician investigator at Partners. Each subject would then be scheduled and would undergo 2 PET scans over a period of 4 months at the Gordon Center for Medical Imaging at Massachusetts General Hospital as part of the study.

Patients would have up to 3 study visits- the first visit would be for consent (lasting about 1 hour) and 2nd and the 3rd visits would be for the PET/CT (lasting about 3 hours each). The PET/CT appointments may need to be rescheduled depending on the patient's convenience and the availability of time slots.

On the day of the PET scan, if the subject is premenopausal, we would be conducting a STAT quantitative serum hCG test before the scan. Then, a low dose x-ray CT scan will be performed for anatomical localization and for attenuation correction of PET images. An intravenous (IV) catheter would be placed on one arm for the radiotracer (contrast) infusion. An intraarterial catheter would be placed on the arm opposite of the IV line for blood draws that would occur at first every 15 seconds and gradually reduce to 10 minute intervals by the end of the scan. The total volume of blood would be less than 150 ml (10 tablespoons). The PET scan would take about 20 to 60 minutes.

Drug to be use: C-11 Acetate is the tracer used in this study.

Data to be collected: PET and CT images as well as concentration of the radiotracer metabolites in the blood of the patients will be collected

Since [^{11}C]acetate is not a proven early biomarker of rapamycin response, the PET scan data obtained in this study will not be used to adjust the dose of rapamycin that a study participant is given.

Study staff may need to access patient's medical records in Epic to locate the lesion and know the pulmonary function before and/or after the study scan appointment as well as to compare the PET/CT images obtained for the study to other imaging tests obtained for clinical purposes.

VI. Biostatistical Analysis:

We will enroll 8 patients. Assuming a standard deviation of 16% (based on our preclinical in vivo imaging data) for the SUV change between baseline and post-rapamycin/ post-rapalog treatment, a group of 8 patients will allow us to reach 80% power to detect at least a decrease of 7% in [11C]acetate uptake by PET imaging (compared to 11% increase without treatment), using a two-sided one sample t-test at alpha=0.05 level. In fact, we expect to find a greater decrease than 7% in the proposed study, and we will have higher power to detect this greater decrease.

Alternative statistical approach. Assuming a standard deviation of 0.53 (based on prior study (1)) for both a rapamycin/rapalog-naïve and a rapamycin/rapalog-treated group, n= 6 patients per group will allow us to reach 80% power to detect a difference of at least 25% in SUVmax between the two groups using a two-sided two sample t-test at alpha=0.05 level. This statistical approach will allow us to analyze imaging data obtained from two independent groups of patients receiving a single PET scan rather than one group of patients receiving two PET scans each (baseline and after treatment).

VII. Risks and Discomforts

The combined radiation exposure from the PET/CT scan in this study will be not more than 9.4 mSv (4.7 mSv per scan). This amount of radiation is equivalent to 3.75 years of normal background radiation (3.1 mSv exposure = 1 yr background). This level of exposure is considered small and there is no evidence that it represents a major health risk.

Placement of the i.v. catheter may be associated with minor discomfort along with some bruising or swelling at the insertion site. Placement of the intra-arteria catheter could lead to swelling and redness at the sites of line placement, as well as temporary loss of pulse at the wrist. This area may have a bruise or feel uncomfortable for 2-3 days after the catheter is removed.

Inserting an arterial line (A-line) can hurt more than having a regular i.v. or having blood drawn with a needle. The A-line will be placed with local anesthesia (i.e., lidocaine), which may cause an allergic reaction. Even if the wrist area is first numbed, the insertion may still hurt. Once the A-line is in place, it usually does not hurt. Even after the catheter is removed, the site of insertion may feel tender or may have a bruise for 2 to 3 days.

The maximum volume of blood drawn at any scan would be 150cc, which is significantly less than the volume drawn for a blood donation (i.e., ~470cc).

It is possible that incidental abnormal findings may be discovered during a subject's participation in this study. Discovery of incidental findings may prompt study anxiety and follow-up testing.

VIII. Potential Benefits:

Individual subjects enrolled in the study would not benefit directly from the study. In the future, from information obtained in this study, LAM and TSC patients would benefit from a metabolic imaging biomarker in multiple ways. First, a sensitive and specific imaging biomarker would help answer outstanding questions regarding personalized dosage and length of treatment for rapamycin and its analogs (rapalogs). Second, biomarkers of disease progression and therapeutic response would streamline the design, cost and duration of LAM/TSC clinical trials. Third, a metabolic imaging biomarker and circulating VEGF-D could be used as complementary diagnostics to enhance clinical decision making.

IX. Monitoring and Quality Assurance

This study will not be monitored by an independent DSMB.

All unanticipated problems including adverse events will be reported to the Partners Human Research Committee (PHRC) in accordance with the accepted guidelines. A 24-hour/7-day telephone number will be provided for contacting the licensed physician investigator for this purpose.

The research staff will monitor all subjects during their study involvement for evidence of any adverse events.

X. References

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