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CONTRACTING ORGANIZATION: Columbia University, New York, NY

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14. ABSTRACT

Given the multi-organ manifestation of TS lesions, and the mesenchymal lineage of tumors recovered from TS patients, it has been postulated that TS is a neurocristopathy in which tumorigenesis is initiated by neural crest cells, but direct supporting experimental evidence has not been produced. We hypothesize that by tracking neurocristogenesis in a $TSC2^{+/-}$ mouse model, we will delineate the molecular mechanisms underlying temporal ontogenesis and progression of benign neoplasms characterizing TS and LAM. Furthermore, we hypothesize that HMGA2 misexpression defines tumorigenesis in TS and LAM caused by differentiating neural crest progenitor cells. This will subsequently lead to novel therapeutic approaches to the disease. ***Aim 1:*** *To delineate the biochemical signaling that determines the temporal sequence of neural crest cell-induced initiation and progression of tumors using a $TSC2^{+/-}$ mouse model*. **Aim 2:** *To determine the role of HMGA2 in tumor pathogenicity driven by TSC2-haploinsufficient iPSC-derived neural crest precursors.*

15. SUBJECT TERMS
None listed.

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TABLE OF CONTENTS

	Page
1. Introduction	4
2. Keywords	4
3. Accomplishments	5
4. Impact	6
5. Changes/Problems	7
6. Products	8
7. Participants & Other Collaborating Organizations	8
8. Special Reporting Requirements	9
9. Appendices	9

INTRODUCTION:

Lymphangioleiomyomatosis (LAM) is a rare disease almost exclusively in women that involves the lungs either as part of Tuberous Sclerosis Complex (TSC) or in sporadic form. LAM has proven difficult to study because of the slow rate of tumor cell (LAM cell) growth with reliance on long duration treatment studies that have proven problematic in rare disease populations. Lung lesions are widely present at the time of diagnosis in all women. LAM cells line the lymphatics and spread diffusely through the lung exhibiting tiny nodules on computed tomography (CT).

LAM clinical care radically changed after the observation that patients with sporadic LAM exhibit activation of the mammalian target of rapamycin (mTOR) complex 1, a master kinase that regulates cell growth. mTOR activation is seen in several diseases, prompting clinical trials of sirolimus (also known as rapamycin). In LAM, these studies showed that inhibition of mTOR produced growth arrest in LAM cell cultures in many laboratories. Although inhibition of the mTOR complexes 1/2 (mTORC1/2) exerts cytostatic effects on tumor cells, the treatment is transient and not curative, with recurrence and/or growth of tumors noted upon cessation of therapy. This limitation in the therapeutic effects of mTOR pathway inhibitors could well be due to the fact that many LAM patient tumors do not exhibit *TSC* mutations and express the tuberin protein. These studies thus reveal the need to identify mTOR-independent pathologic mechanisms that can account for the timing of onset and growth of tumors in TS, LAM and sLAM patients, so as to inform more effective therapies.

Prior study in our group tested the use of Imatinib in LAM patients in a small pilot study. These studies documented the safety of the use of tyrosine kinase inhibitors in patients with LAM; the safety of concurrent use of tyrosine kinase and mTOR inhibitors; and short term variability in VEGF-D as a response to therapies. The limited study period and inclusion of multiple study groups did not allow for interpretations regarding lung function. The safety of imatinib in this study supports both additional preclinical studies examining the mechanism of tyrosine kinase inhibitors in LAM and supports the present proposal of a larger long-term clinical trial in disease. Our in vitro cell-based research studies during this time showed equally efficacious tumoricidal activity of nilotinib *in vitro.* We therefore propose longer-term clinical studies evaluating the safety and tolerability of nilotinib in patients with LAM.

This pilot trial would employ a dual agent design intended to generate safety and efficacy data sufficient to power and design a longer-term trial of nilotinib in the treatment of LAM. The hypothesis is that nilotinib can be safely co-administered with sirolimus and will result in change in serum biomarkers of LAM. Durability of response will not be tested. Importantly, the widely established LAM biomarker of disease activity, VEGF-D, will be used in this small clinical trial design using 20 participants.

KEYWORDS:
mTOR, Lymphangioleiomyomatosis, Nilotinib, Tyrosine Kinase Inhibitors, Tumoricidal

ACCOMPLISHMENTS:

What are the major goals of the project?

There are two major goals for this project. The first goal was to determine the safety and tolerability of nilotinib in the treatment of LAM with and without concurrent sirolimus treatment.

Our second goal was to evaluate the effect of nilotinib treatment on serum biomarkers of LAM.

1. **What was accomplished under these goals?**

The stand-alone protocol was created as required for the HRPO review and submitted to the Columbia IRB.

	Completed
Major Task 1: Secure Regulatory Documents to Begin Study	%
Subtask 1: Prepare Regulatory Documents and Research Protocol for Study	
Coordinate with Sites for material transfer agreements (MTAs) and clinical trial agreements (CTAs) submission	100
Submission of an Investigational New Drug (IND) application to the U.S. Food and Drug Administration	Not started
Refine eligibility criteria, exclusion criteria, screening protocol	100
Finalize consent form & human subjects protocol	100
Coordinate with Sites for IRB protocol submission	100
Coordinate with Sites for Military 2nd level IRB review (ORP/HRPO)	100
Submit amendments, adverse events and protocol deviations as needed	N/A
Coordinate with Sites for annual IRB report for continuing review	100
Milestone Achieved: Local IRB approval at MUSC, and Columbia	50%
Milestone Achieved: HRPO approval for all protocols	50%
Major Task 2: Coordinate Study Staff for Clinical Trials	
Subtask 1: Hiring and Training of Study Staff	
Select and Establish DSMB members	Not started
Training of Study coordinators in protocol specific tasks	50%
Milestone Achieved: Research staff trained	50%

Major Task 3: Participant Recruitment, Therapy, Participant Evaluation	
Coordinate with Sites for flow chart for all study steps, web data collection and database requirements	Not started
Finalize assessment measurements	Not started
Milestone Achieved: 1st participant consented, screened and enrolled	Not started
Begin subject recruitment	Not started
Complete follow-up assessments 6 months after initiation for first patient	Not started

Last patient enrolled	Not started
Last patient, last data entered	Not started
	Timeline
Milestone Achieved: Report findings from 6 month follow-up assessments	Not started
Major Task 4: Data Analysis	
Coordinate with Sites & Data Core for monitoring data collection rates and data quality	Not started
Perform all analyses according to specifications, share output and finding with all investigators	Not started
Work with data core and dissemination of findings (abstracts, presentation, publications, DOD)	Not started
Milestone Achieved: Report findings from 2 month follow-up assessments	Not started

Continue to work with Robert Zahid, Director, Healthcare Association Engagement and Innovation. He will present the study to the Pulmonary group with the hopes that this division in Novartis could assist in obtaining the drug for our trial.

Studies funded from internal sources are ongoing to utilize tyrosine kinase inhibitors in mice to document efficacy of the inhibitor in vivo. The study requires six-month-old animals to be treated with the compound for one month. Mice are being aged to the six-month time point (presently 4 months of age) and will be treated with the compound at that point. Tumors will be measured utilizing ultrasound imaging.

2. **What opportunities for training and professional development has the project provided?**

N/A

- **How were the results disseminated to communities of interest?**

Nothing to Report

- **What do you plan to do during the next reporting period to accomplish the goals?**

Will work with the Novartis pulmonary group to obtain the interventional drug from Novartis. Our new contact Robert Zahid will address whether the project could be moved from the hematology group and into pulmonary where we can obtain the compound.

IMPACT:

- **What was the impact on the development of the principal discipline(s) of the project?**

If we are successful in this study, we could potentially identify a novel therapy in LAM. A disease which has not had a new drug in development in 15 years.

- **What was the impact on other disciplines?**

  Nothing to Report

- **What was the impact on technology transfer?**

  Nothing to Report

-
- **What was the impact on society beyond science and technology?**

  Nothing to Report

CHANGES/PROBLEMS:

- **Changes in approach and reasons for change**

  We have not made any changes from our original plans in the project.

- **Actual or anticipated problems or delays and actions or plans to resolve them**

  We have been delayed due to the continued difficulties with the company and the delay in agreeing to send us the compound as they had committed to doing. Our new contact within Novartis will attempt to move the project into the pulmonary group to allow us to perform the study. He has had internal meetings with the hematology group that oversees the drug distribution and is presently working on setting up a meeting with us for the entire group.

- **Changes that had a significant impact on expenditures**

  Nothing to Report

- **Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents**

  Nothing to Report

- **Significant changes in use or care of human subjects**
  Nothing to Report

- **Significant changes in use or care of vertebrate animals.**
  Nothing to Report

- **Significant changes in use of biohazards and/or select agents**
  Nothing to Report

PRODUCTS:

Publications, conference papers, and presentations

- **Journal publications.**

  Nothing to Report.

- **Books or other non-periodical, one-time publications.**

  Nothing to Report.

- **Other publications, conference papers, and presentations.**

  Nothing to Report.

- **Website(s) or other Internet site(s)**

  Nothing to Report.

- **Technologies or techniques**

  Nothing to Report

- **Inventions, patent applications, and/or licenses**

  Nothing to Report.

- **Other Products**

  Nothing to Report.

PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

- **What individuals have worked on the project?**

Name:	Jeanine D'Armiento, MD, Ph.D.
Project Role:	Principal Investigator
Research Identifier:	0000-0002-6219-6083
Nearest Person Month Worked:	0.45
Contribution to Project:	Dr. D'Armiento oversaw submission of all regulatory documents and interactions with Novartis.

Name:	Charlie Strange, MD
Project Role:	Co-Investigator
Research Identifier:	0000-0002-8109-8067
Nearest Person Month Worked:	0.45
Contribution to Project:	Dr. Strange helped design and prepare the protocol and submission for the MUSC site.

Name:	Monica Goldklang, MD
Project Role:	Co-Investigator
Research Identifier:	0000-0002-7019-3130
Nearest Person Month Worked:	0.30
Contribution to Project:	Dr. Goldklang assisted in submission of the IRB and trial protocol.

- **Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?**

  Nothing to Report

- **What other organizations were involved as partners?**

  Nothing to Report

SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS:

Not applicable

QUAD CHARTS:

Not applicable

APPENDICES: