



FINAL REPORT

Project Title: Targeting Centrosome in
Uterine Leiomyosarcoma

Project Number: SFA10-27

1. Date project was initiated: July 1, 2009
2. Period covered by this report: From: *July 1, 2009* To: *June 30, 2010*
3. Publications, Abstracts, and Presentations:
 - a. List all manuscripts submitted for publication during the period covered by this report resulting from this project. Include those in the categories of lay press, peer-reviewed scientific journals, invited articles, and abstracts. Each entry must include the author(s), article title, journal [book, editors(s), publisher, volume number, page number(s), and date.]

(1) **Lay Press:** None

(2) **Peer-Reviewed Scientific Journals:**

One in preparation. In addition, resources created for execution of this SFA grant were shared with Dr. Sandra Orsulic, leading to the following publication:

*Xing D, Scangas G, Nita M, Xu X, He L, Ioffe Y, Aspuria PJ, Hedvat C, **Anderson ML**, Oliva E, Karlan B, Mohapatra, G., Orsulic, S. "A Role for BRCA1 in Uterine Leiomyosarcoma" *Cancer Res.* 2009 Nov 1;69(21):8231-5. Epub 2009 Oct 20. PMID: 19843854.*

(3) **Invited Articles:** One in preparation

(4) **Abstracts:**

*Khan MF, Li Z, Olokpa A, Dziadzek O, Creighton CJ, Roden R, Thomas R, **Anderson ML**. "Overexpression of Centrosome-Regulating Pathways in Uterine Leiomyosarcoma" 2010 Annual Meeting, Society for Gynecologic Investigation, Orlando, FL, March, 2010.*

- b. List presentations made during the last year (international, national, local societies, etc.). Use an asterisk (*) if presentation produced a manuscript.

Invited Presentations:

4. Provide a brief list of keywords: (limit to 20 words)

Uterus, leiomyosarcoma, aurora kinase, MK-5108, small molecule kinase inhibitor, centrosome, metastasis, therapy.

5. Summarize the progress during the period of this report and its impact on your plans for the remainder of the project. Include a summary of the progress toward the achievement of the originally stated aims and list the significant results:

We have successfully executed each of the proposed objectives. Using both Western blot and quantitative PCR, our work has successfully confirmed that the overexpression of Aurora A and B kinases as well as their downstream targets CENPE, CENPA is a robust feature of uterine leiomyosarcoma. We have also been able to use siRNA to specifically target both Aurora A and B kinase and have found that both are critical for the continue proliferation of both an established leiomyosarcoma cell lines (sk-lms) as well as several novel cell strains derived from pulmonary metastases of uterine leiomyosarcoma. Our results indicate that knockdown of AurkA particularly results in an profound arrest of leiomyosarcoma growth by blocking the cell cycle at its G2-M interface. Reduction in AurkA levels also produces a dramatic, dose-dependent induction of apoptosis. Similar results were obtained when cultures of cell strains derived from ULMS were treated with a novel small molecule inhibitor of Aurora A kinase in culture. Dose-responses for MK05108 were determine both alone and in combination with chemotherapeutic agents currently used to treat ULMS clinically. As part of our original proposal, we initially planned to use a novel model of ULMS to examine the impact of targeting centrosome overexpression. However, genotyping demonstrated that the cells that we thought had undergone were derived from primary cultures of uterine smooth muscle were in fact a contamination with HELA-S2 cells that occurred prior to the cells arriving in my laboratory. This sad fact led me to withdraw an article describing our characterization of this work that had been accepted for publication. However, as an aside, we have subsequently expanded on these findings to demonstrate a potential role for MK-5108, a novel small molecule inhibitor for Aurora A kinase, in treating cervical cancer. This has resulted in 2 additional abstracts and a paper in preparation that are not included in the summary above. Once this contamination was discovered, we explored whether cell strains shared by Dr. Dina Lev (UTMDACC) could be used to create in vivo models for ULMS. As this was not successful, we moved on to determine to test whether MK-5108 could be used to inhibit the growth of LMS in vivo using a xenograft model created using sk-lms cells. Our results indicate that oral administration of this drug can be successfully used to impair LMS growth as monotherapy.

6. In layperson’s terms, summarize the progress during the period of this report. Explain any medical significance or implications of your results to date:

We have found that specific components of the machinery used by cells to divide can be targeted to successfully impair the growth and proliferation of leiomyosarcoma both in cultured cells and in vivo models of this disease. Our results suggest that small molecule inhibitors that target these gene products may provide an effective treatment alternative for this lethal disease.



9/4/2010

Principal Investigator (signature)

Date



9/22/2010

Department Chair (signature)

Date