



FINAL REPORT

Project Title: Developing a MicroRNA-Based
Strategy for Targeting Uterine
Leiomyosarcoma

Project Number: SFA10-27

1. Date project was initiated: July 1, 2010
2. Period covered by this report: From: July 1, 2010 To: June 30, 2011
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:

Clinical Cancer Research (*in review*) x 2.
 - (3) Invited Articles:

SIIC Expertos Opinion Review (*in press*)
 - (4) Abstracts:

Upcoming abstract for SGO annual meeting (3/2012)
 - b. List presentations made during the last year (international, national, local societies, etc.). Use an asterisk (*) if presentation produced a manuscript.

Role of microRNAs in gynecologic Cancers. Cancer Biology Program, The University of Texas M.D. Anderson Cancer Center, October, 2011.

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

MicroRNA, Uterus, mir-31, miR-10a/b, proliferation, Non-coding RNA, Apoptosis

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:

Our previous work has found that the overexpression of multiple gene products important for driving the progression of human cells through the G2/M and spindle checkpoints is the dominant molecular feature of uterine leiomyosarcoma. Using support from a prior SFA award, we were able to examine the utility of a small molecule inhibitor that targets Aurora A kinase, one of the gene products most highly overexpressed in ULMS. Our results confirmed that this agent could be used to effectively inhibit the progression and/or metastasis of ULMS both *in vitro* and *in vivo*. These findings are an important proof of principle that the patterns of gene expression we observed play a critical role in ULMS. For the present proposal, we hypothesized that altered patterns of microRNA expression play a key role in driving the patterns of gene expression we previously identified in ULMS. Based on results of our NGS profiling, we planned to test the role of miR-143/145 in ULMS. Other investigators have reported that miR-143/145 play a key role in smooth muscle differentiation by mediating expression of the contractile apparatus in response to SRF, a key mediator of smooth muscle maturation and function. However, our initial experiments demonstrated that replacing the miR-143 lost in ULMS had little effect on the phenotype of cultured ULMS cell lines *in vitro* and were unlikely to prove important as a therapeutic strategy. Therefore, we refocused on our efforts and have gone on to study both miR-31 (overexpressed >130-fold) and individual members of the miR10a/b/99 families (downregulated >8 fold). Our results, currently in preparation for publication have identified novel mechanisms by which altered expression of these microRNAs contribute to ULMS. We are currently in the process of preparing our results for publication

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:

Our work has helped us to understand how microRNAs contribute to the key molecular phenotype and promote the progression and metastasis of ULMS. We have identified at least one novel approach that can be potentially used to treat women diagnosed with uterine leiomyosarcoma and are actively working to develop a clinical trial informed by our results.



January 16, 2012

Principal Investigator (signature)

Date



Department Chair (signature)

11/17/12.

Date