



FINAL REPORT

Project Title: A preclinical mouse model for targeted therapy in uterine leiomyosarcoma

Project Number: SFA09-16

1. Date project was initiated: 07/01/09
2. Period covered by this report: From 07/01/09 To 06/30/10
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:

Ioffe YJM, Xing D, Aspuria P-J, Karlan BY, **Orsulic S**. A preclinical mouse model for uterine leiomyosarcoma. Electronic Sarcoma Update Newsletter, Volume 6, Number 4, 2009.

(2) Peer-Reviewed Scientific Journals:

Xing D, Scangas G, Nita M, He L, Xu X, Ioffe YJM, Aspuria P-J, Hedvat CY, Anderson ML, Oliva E, Karlan BY, Mohapatra G, **Orsulic S**. A Role for BRCA1 in Uterine Leiomyosarcoma. Cancer Research 2009; 69:8231-8235.

(3) Invited Articles:

Cheon D-J and **Orsulic S**. Mouse Models of Cancer. Annual Review of Pathology: Mechanisms of Disease. Volume 6, 2011, *in press*

(4) Abstracts:

D. Xing, G. Scangas, M. Nita, X. Xu, L. He, Y.J.M. Ioffe, P.J. Aspuria, C.Y. Hedvat, M.L. Anderson, E. Oliva, B.Y. Karlan, G. Mohapatra, and **S. Orsulic**. A Mouse Model Reveals a Possible Function for BRCA1 in Human Uterine Leiomyosarcoma. Current Oncology 2009; 16: 91-110.

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

Basic Research in Ovarian Cancer, Research Grand Rounds, Cedars-Sinai Medical Center, September 18, 2009, Los Angeles, CA

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

Animal models, breast cancer, BRCA1, cancer progression, LMS, mouse, murine, myoepithelium, oncogene, ovarian cancer, p53, preclinical models, promoter methylation, tumor suppressor gene, uterine leiomyosarcoma

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 are pleased to report significant progress on our proposed project. Specifically, we have obtained additional evidence that BRCA1 may play a role in human uterine leiomyosarcoma (ULMS) development. Our immunohistochemistry results from a larger number of patient samples (85 ULMS and 76 benign uterine leiomyoma tissue specimens) showed a significant difference in BRCA1 protein expression between ULMS and benign uterine leiomyoma. BRCA1 protein expression was absent in 29% of ULMS samples and in 4% of benign leiomyoma samples. Consistent with the view that *BRCA1* silencing may play a role in the development or progression of ULMS, we demonstrated that the *BRCA1* promoter is methylated in samples with negative BRCA1 immunohistochemical staining.

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 shown that the loss of BRCA1 function may be an important step in the progression of uterine leiomyosarcoma in a mouse model. The work funded by the Sarcoma Foundation of America resulted in a publication that was featured as a Priority Report in the journal *Cancer Research*. Recently, our reported finding was corroborated by two independent research groups who published similar findings in the journal *PLoS ONE*.

These animal models will be useful for the investigation of therapies that target BRCA1 deficiency in uterine leiomyosarcoma, which is an important step towards initiating clinical trials to test these therapies in patients.



Principal Investigator (signature)

07/11/10

Date



Department Chair (signature)

7.22.10

Date