Final Progress Report for Research Projects Funded by Health Research Grants

Instructions: Please complete all of the items as instructed. Do not delete instructions. Do not leave any items blank; responses must be provided for all items. If your response to an item is "None", please specify "None" as your response. "Not applicable" is not an acceptable response for any of the items. There is no limit to the length of your response to any question. Responses should be single-spaced, no smaller than 12-point type. The report **must be completed using MS Word**. Submitted reports must be Word documents; they should not be converted to pdf format. Questions? Contact Health Research Program staff at 717-783-2548.

1. **Grantee Institution:** Thomas Jefferson University

2. **Reporting Period (start and end date of grant award period):** 01/01/2011 – 12/31/2014

3. **Grant Contact Person (First Name, M.I., Last Name, Degrees):** Theodore F. Taraschi, PhD

4. **Grant Contact Person's Telephone Number:** 215-955-3900

5. **Grant SAP Number:** 4100054872

6. **Project Number and Title of Research Project:** 5- New Stem/Progenitor Cell-Related Biomarker(s) for Predicting DCIS Prognosis and Progression

7. **Start and End Date of Research Project:** 01/01/2011 – 09/01/2012

8. **Name of Principal Investigator for the Research Project:** Michael P. Lisanti, MD, PhD

9. **Research Project Expenses**.

   9(A) Please provide the total amount of health research grant funds spent on this project for the entire duration of the grant, including indirect costs and any interest earned that was spent:

   $ 350,824.58

   9(B) Provide the last names (include first initial if multiple individuals with the same last name are listed) of **all** persons who worked on this research project and were supported with health research funds. Include position titles (Principal Investigator, Graduate Assistant, Post-doctoral Fellow, etc.), percent of effort on project and total health research funds expended for the position. For multiple year projects, if percent of effort varied from year to year, report in the % of Effort column the effort by year 1, 2, 3, etc. of the project (x% Yr 1; z% Yr 2-3).

Last Name, First Name	Position Title	% of Effort on Project	Cost
Lisanti, Michael	Principal Investigator	2%	5,151
Danilo, Christina	Graduate Student	100%	17,702
Martinez-Outschoorn, Ubaldo	Assistant Professor	77%	24,634
Anselmo, Wanda	Visiting Researcher	100%	20,480
Avena, Paolo	Visiting Researcher	100%	23,779
Carito, Valentina	Visiting Research	100%	56,737

9(C) Provide the names of **all** persons who worked on this research project, but who *were not* supported with health research funds. Include position titles (Research Assistant, Administrative Assistant, etc.) and percent of effort on project. For multiple year projects, if percent of effort varied from year to year, report in the % of Effort column the effort by year 1, 2, 3, etc. of the project (x% Yr 1; z% Yr 2-3).

Last Name, First Name	Position Title	% of Effort on Project
NONE		

9(D) Provide a list of **all** scientific equipment purchased as part of this research grant, a short description of the value (benefit) derived by the institution from this equipment, and the cost of the equipment.

Type of Scientific Equipment	Value Derived	Cost
NONE		

10. Co-funding of Research Project during Health Research Grant Award Period. Did this research project receive funding from any other source during the project period when it was supported by the health research grant?

Yes_____ No___X_____

If yes, please indicate the source and amount of other funds:

11. Leveraging of Additional Funds

11(A) As a result of the health research funds provided for this research project, were you able to apply for and/or obtain funding from other sources to continue or expand the research?

Yes_____ No____X_____

If yes, please list the applications submitted (column A), the funding agency (National Institutes of Health—NIH, or other source in column B), the month and year when the application was submitted (column C), and the amount of funds requested (column D). If you have received a notice that the grant will be funded, please indicate the amount of funds to be awarded (column E). If the grant was not funded, insert "not funded" in column E.

Do not include funding from your own institution or from CURE (tobacco settlement funds). Do not include grants submitted prior to the start date of the grant as shown in Question 2. If you list grants submitted within 1-6 months of the start date of this grant, add a statement below the table indicating how the data/results from this project were used to secure that grant.

A. Title of research project on grant application	B. Funding agency (check those that apply)	C. Month and Year Submitted	D. Amount of funds requested:	E. Amount of funds to be awarded:
None	☐NIH ☐ Other federal (specify:_____) ☐ Nonfederal source (specify:_)		$	$

11(B) Are you planning to apply for additional funding in the future to continue or expand the research?

Yes_____ No___X_____

If yes, please describe your plans:

12. Future of Research Project. What are the future plans for this research project?

None.

13. New Investigator Training and Development. Did students participate in project supported internships or graduate or post-graduate training for at least one semester or one summer?

Yes___X_____ No_____

If yes, how many students? Please specify in the tables below:

	Undergraduate	Masters	Pre-doc	Post-doc
Male				
Female			1	
Unknown				
Total			**1**	

	Undergraduate	Masters	Pre-doc	Post-doc
Hispanic				
Non-Hispanic			1	
Unknown				
Total			**1**	

	Undergraduate	Masters	Pre-doc	Post-doc
White			1	
Black				
Asian				
Other				
Unknown				
Total			**1**	

14. Recruitment of Out-of–State Researchers. Did you bring researchers into Pennsylvania to carry out this research project?

Yes_____ No___X_____

If yes, please list the name and degree of each researcher and his/her previous affiliation:

15. Impact on Research Capacity and Quality. Did the health research project enhance the quality and/or capacity of research at your institution?

Yes____X_____ No_____

If yes, describe how improvements in infrastructure, the addition of new investigators, and other resources have led to more and better research.

This grant provided funds for the support and development of an important research project.

16. Collaboration, business and community involvement.

16(A) Did the health research funds lead to collaboration with research partners outside of your institution (e.g., entire university, entire hospital system)?

Yes_____ No___X_____

If yes, please describe the collaborations:

16(B) Did the research project result in commercial development of any research products?

Yes_____ No___X_____

If yes, please describe commercial development activities that resulted from the research project:

16(C) Did the research lead to new involvement with the community?

Yes_____ No____X_____

If yes, please describe involvement with community groups that resulted from the research project:

17. Progress in Achieving Research Goals, Objectives and Aims.

List the project goals, objectives and specific aims (as contained in the grant agreement). Summarize the progress made in achieving these goals, objectives and aims for the period that the project was funded (i.e., from project start date through end date). Indicate whether or not each goal/objective/aim was achieved; if something was not achieved, note the reasons why. Describe the methods used. If changes were made to the research goals/objectives/aims, methods, design or timeline since the original grant application was submitted, please describe the changes. Provide detailed results of the project. Include evidence of the data that was generated and analyzed, and provide tables, graphs, and figures of the data. List published abstracts, poster presentations and scientific meeting presentations at the end of the summary of progress; peer-reviewed publications should be listed under item 20.

This response should be a DETAILED report of the methods and findings. It is not sufficient to state that the work was completed. Insufficient information may result in an unfavorable performance review, which may jeopardize future funding. If research findings are pending publication you must still include enough detail for the expert peer reviewers to evaluate the progress during the course of the project.

Health research grants funded under the Tobacco Settlement Act will be evaluated via a performance review by an expert panel of researchers and clinicians who will assess project work using this Final Progress Report, all project Annual Reports and the project's strategic plan. After the final performance review of each project is complete, approximately 12-16 months after the end of the grant, this Final Progress Report, as well as the Final Performance Review Report containing the comments of the expert review panel, and the grantee's written response to the Final Performance Review Report, will be posted on the CURE Web site.

There is no limit to the length of your response. Responses must be single-spaced below, no smaller than 12-point type. If you cut and paste text from a publication, be sure symbols print properly, e.g., the Greek symbol for alpha (α) and beta (ß) should not

print as boxes (☐) and include the appropriate citation(s). DO NOT DELETE THESE INSTRUCTIONS.

Project Title and Purpose

New Stem/Progenitor Cell-Related Biomarker(s) for Predicting DCIS Prognosis and Progression - Ductal Carcinoma *In Situ* (DCIS) is characterized by a clonal proliferation of malignant epithelial cells confined within the lumens of mammary ducts, without invasion into adjacent stroma. Since DCIS represents a group of biologically and morphologically heterogeneous diseases, its classification and management remains very challenging. Breast conserving therapy with or without radiotherapy is the accepted treatment for most cases of DCIS. However, the local recurrence rate with such therapy ranges from 10 to 40% with half of these patients developing invasive carcinoma. Previous studies have attempted to identify prognostic molecular markers. Many of the molecules thought to play critical roles in progression of invasive breast cancer have not been shown to be independent prognostic markers for local recurrence or progression of DCIS. Therefore, there is a critical need to identify novel predictors of DCIS progression and potential targets for therapy.

Project Overview

Breast cancer is a serious health threat and a common cause of death and disability. The understanding of this cancer is incomplete; however, certain abnormalities of the breast can be identified, such as ductal carcinoma *in situ* (DCIS), that commonly lead to invasive cancer. Not all of these early lesions lead to invasive breast cancer and this is a major source of concern for patients. Currently, women with these lesions typically receive toxic therapies with potentially serious side-effects, although many may not need or benefit from this treatment. In this study, a promising molecular marker of these early lesions will be examined, namely SPRR1A, that may predict which patients in this early stage of DCIS, will go on to develop invasive breast cancer.

SPRR1A is a novel stem/progenitor cell marker that has not yet been implicated in the pathogenesis of human breast cancer. Our unpublished preliminary results directly show that SPRR1A is upregulated during the transition from pre-malignancy (hyperplasia and DCIS) to invasive ductal carcinoma (IDC).

The two Specific Aims of the project are:

1) Examine the Role of SPRR1A in the Human Breast Cancer Onset and Progression, from Pre-Malignancy and DCIS to Invasive Ductal Carcinoma. The expression of SPRR1A in human pathology specimens will be examined, and its expression will be correlated with other biomarkers (ER, PR, HER2), patient progression, survival, and recurrence data. The possible use of SPRR1A as a diagnostic predictive biomarker for breast cancer progression from pre-malignancy will be assessed.

2) Determine the Functional Role of SPRR1A in Human Breast Cancer, using Xenograft Models. Our unpublished preliminary results show that SPRR1A is highly expressed in malignant breast cancer cell lines, such as MCF7 cells, but fails to be expressed in “normal”

immortalized cell lines, such as MCF10A cells. Thus, we will determine if over-expression of SPRR1A is sufficient to allow MCF10A cells to form tumors in nude mice. Conversely, it will be determined whether the expression of SPRR1A siRNA can prevent MCF7 tumor formation in nude mice.

Expected Research Outcomes and Benefits

Advanced medical technologies and therapeutic strategies are necessary for the successful detection, diagnosis, and treatment of breast cancer. This project will use novel technologies (tissue microarrays (TMA) and automated quantitative bioimaging (AQUA)) to identify new therapeutic and prognostic markers for human breast cancer. More specifically, the activation status of a new signaling pathway will be studied, which has been implicated in breast cancer pathogenesis, using both mouse animal models and cells in culture. For this purpose, the association of SPRR1A expression with pre-malignant lesions and progression from pre-malignancy to full-blown breast cancer will be studied.

Summary of Research Completed

SPRR1A promotes self-renewal of cancer stem/progenitor cells

We examined whether aberrant SPRR1A expression has an effect on the cancer stem/progenitor cell expansion. Mammosphere analyses were conducted in MDA-MB-231-GFP cells that either downregulated or overexpressed SPRR1A protein. Figure 1 shows that downregulation of SPRR1A in MDA-MB-231-GFP cells significantly reduced the number of MDA mammospheres ($p=0.0003$), whereas the overexpression significantly increased the number of mammospheres ($p=0.001$). Collectively, these results suggest that SPRR1A promotes self-renewal of cancer stem/progenitor cells.

SPRR1A promotes breast tumorigenesis.

The expansion of cell populations through self-renewal may contribute to tumor growth. Therefore, we assessed the ability of SPRR1A to promote breast tumor growth. MDA-MB-231cells overexpressing SPRR1A where injected in the flanks of nude mice. Three-weeks post injection, tumors were harvested. As shown in Figure 2, the overexpression of SPRR1A substantially promotes tumor growth, resulting in ~2.9-fold increase in tumor mass and ~4.4-fold increase in tumor volume. These results directly support that SPRR1A enhances the *in vivo* growth of breast cancer cells.

Next, we studied the possibility that the small, proline-rich repeat protein 1A (SPRR1A) may be a stem/progenitor cell marker that plays an important role in breast tumor malignancy. In support of this idea, we found that SPRR1A 1) is a specific target of Wnt-1 signaling pathway in mammary glands, consistent with the idea that SPRR1A is a stem/progenitor cell biomarker; 2) promotes mammosphere formation and the *in vivo* growth of the breast cancer cells MDA-MB-231; and 3) is upregulated during the transition from pre-malignancy (hyperplasia and DCIS) to invasive ductal carcinoma (IDC). Thus, these data suggest SPRR1A is a potential biomarker for breast cancer progression and that targeting SPRR1A may impair the cancer stem/progenitor cell self-renewal properties and, therefore, prevent breast tumor progression.

α-casein in mammary tumor development

We previously identified α-casein as a milk protein component with protective effects against the progression of human breast cancer and lung metastasis formation. To provide evidence supporting the important role of α-casein in decreasing mammary tumor development and metastasis formation, we used a novel cellular model based on Met-1 cells transfected with human α-casein cDNA, injected into the flank of nude mice.

DNA microarray analysis: α-Casein activates STAT1 signaling and decreases "stemness" in mammary tumor cells

To understand the mechanism(s) that underlies the protective effect of α-casein expression against the progression of human breast cancer and lung metastasis, we subjected the Met-1 cell lines to DNA microarray analysis. Figures 3A and 3B show the results from pathways analysis. Expression of α-casein induced the upregulation and downregulation of genes associated with different signaling pathways. This includes, most prominently, the interferon (IFN-α, -β, -gamma) signaling pathways. In particular, given that IFN-mediated signaling involves the activation of the classical Jak/STAT1 pathway, to validate our result obtained from this transcriptional profiling, we performed immunoblot analysis using an antibody directed against STAT1. In this pathway, JAKs associate with IFN-receptors and, following receptor interaction with IFN, Jak phosphorylates STAT1.

Figure 4 shows the results of this immunoblot analysis. Met-1 cells expressing α-casein displayed increased activation of STAT1 (phosphorylated at the Tyr701 position), together with a higher expression level of its non-phosphorylated form. Moreover, DNA microarray analysis also revealed that α-casein expression downregulated genes involved with focal adhesions. Thus, to validate our finding, we evaluated the expression levels of uPAR/PAI-1 that are important in the remodeling of the extracellular matrix during tumor cell invasion. Our results from immunoblot analysis show low or undetectable expression levels of uPAR and PAI-1 proteins after α-casein expression (Figure 5).

Finally, we found that α-casein expression downregulates genes that are highly expressed in stem/progenitor cells. To provide independent validation of this result obtained from our gene expression profiling study, we conducted FACS analysis. In these experiments, the antibody for the stem cell surface marker CD44 was used. Figure 6 shows the result of this analysis. Importantly, α-casein expression resulted in the reduction of the number of CD44(+) cancer stem cells.

Overall, these findings suggest that α-casein expression in mammary epithelial cancer cells may represent a potential therapeutic approach as an antitumor agent in breast cancer.

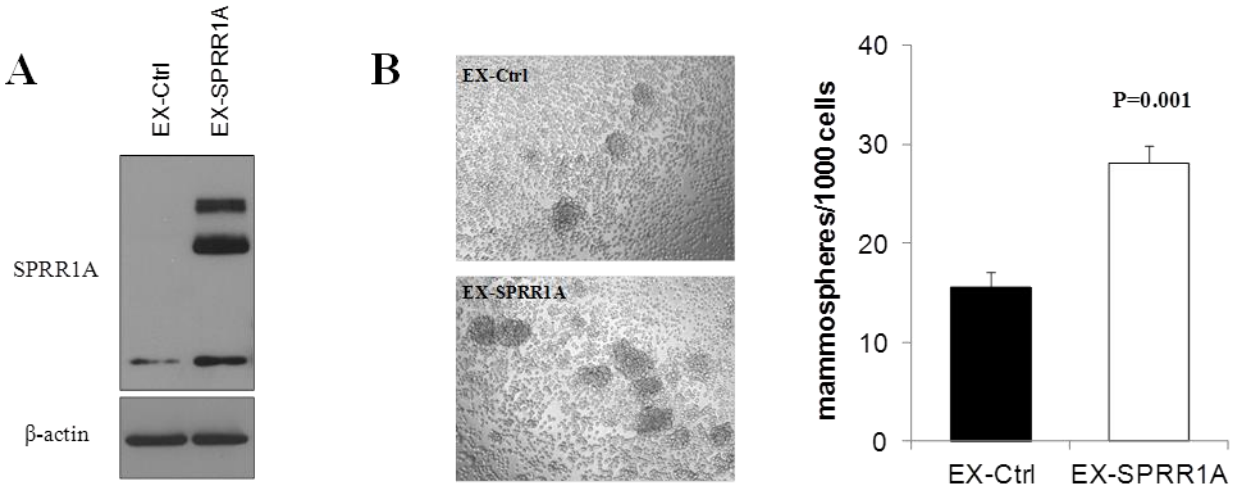

Figure 1: SPRR1A promotes mammary epithelial tumor stem cell expansion. A) Validation of SPRR1A overexpression in MDA-MB-231 cells by western blot. To confirm expression levels in SPRR1A transduced MDA cell lines, cells were cultured and lysates were prepared and subjected to immunoblot analysis with SPRR1A antibody. Increased levels of SPRR1A are observed in overexpressing (EX-SPRR1A) compared to control (EX-Ctrl). Note that the overexpression of SPRR1A resulted in formation of dimers. β-actin is shown as loading control. B) Mammosphere production by MDA-MB-231 overexpressing SPRR1A. Note that overexpression of SPRR1A leads to significant increased mammosphere production in these breast cancer cells (p=0.001). P-values are indicated in the graphs, as determined by the Student's t-test.

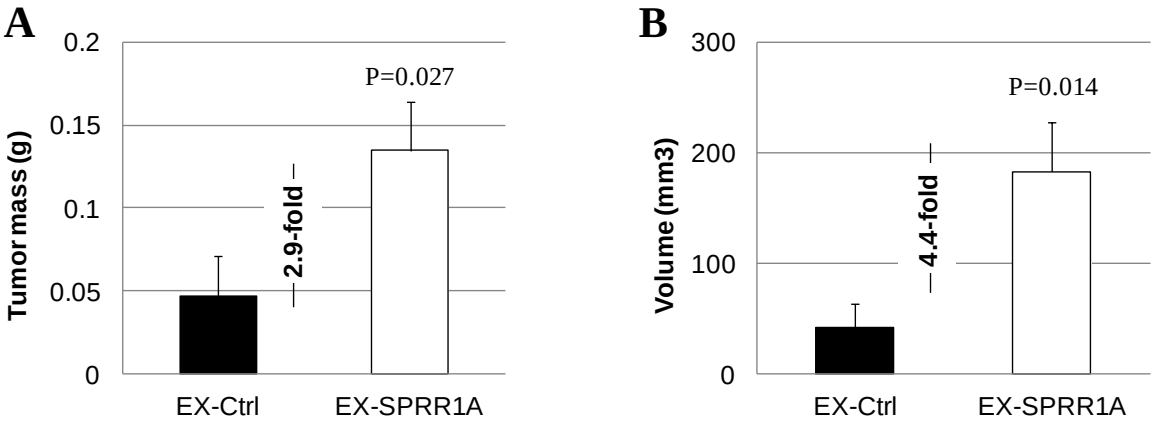

Figure 2: SPRR1A promotes breast tumor growth. SPRR1A overexpressing MDA-MB-231 cells were injected into the flanks of nude mice along with their respective controls. 3 weeks post-injection tumors were excised and the mass and tumor volume were determined. Relative to controls, overexpression of SPRR1A in MDA-MB-231 cells stimulated tumor growth, resulting in near 3-fold increase in tumor mass (A) and 4.4-fold increase in tumor volume (B) as compared to controls. P-values are indicated in the graphs, as determined by the Student's t-test.

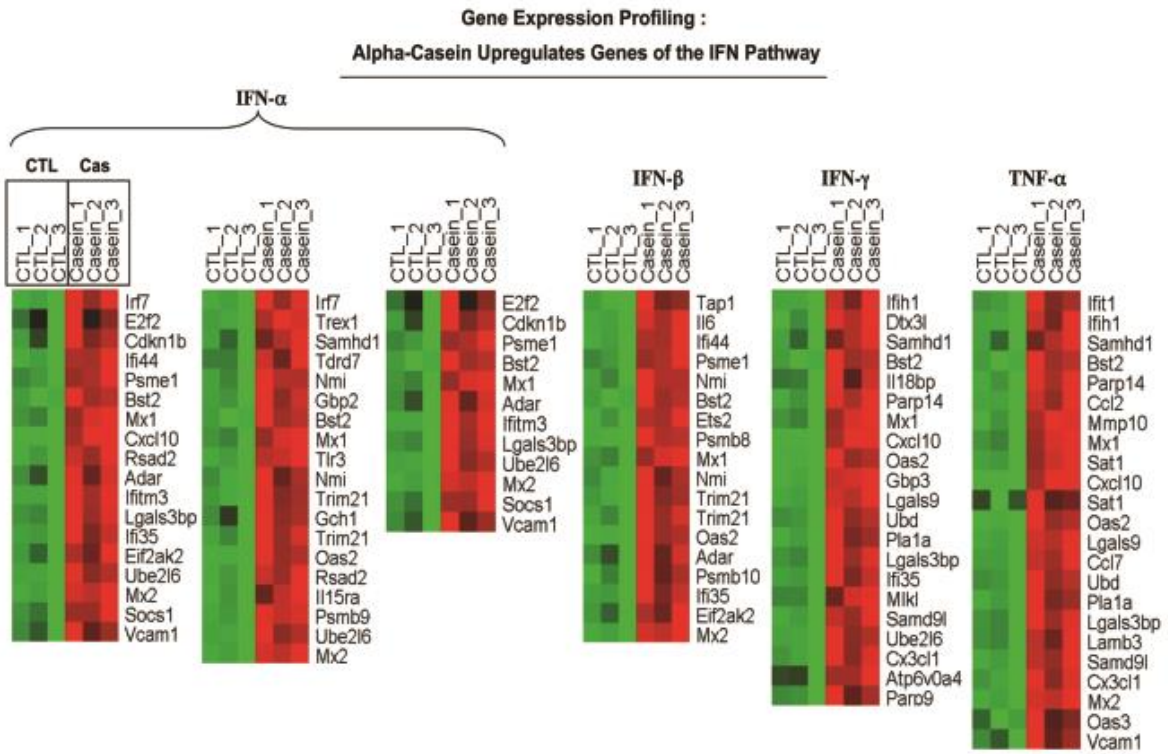

Figure 3A. α-casein transcriptional profiling. Results from pathway analysis with ASSESS. We performed pathway analysis using ASSESS (analysis of sample set enrichment scores). Note that α-casein upregulates gene transcripts associated with inflammatory interferon/STAT1 signaling (IFN-α) and decreases gene transcripts associated with "stemness" (IFN-β, IFN–γ, TNF–α).

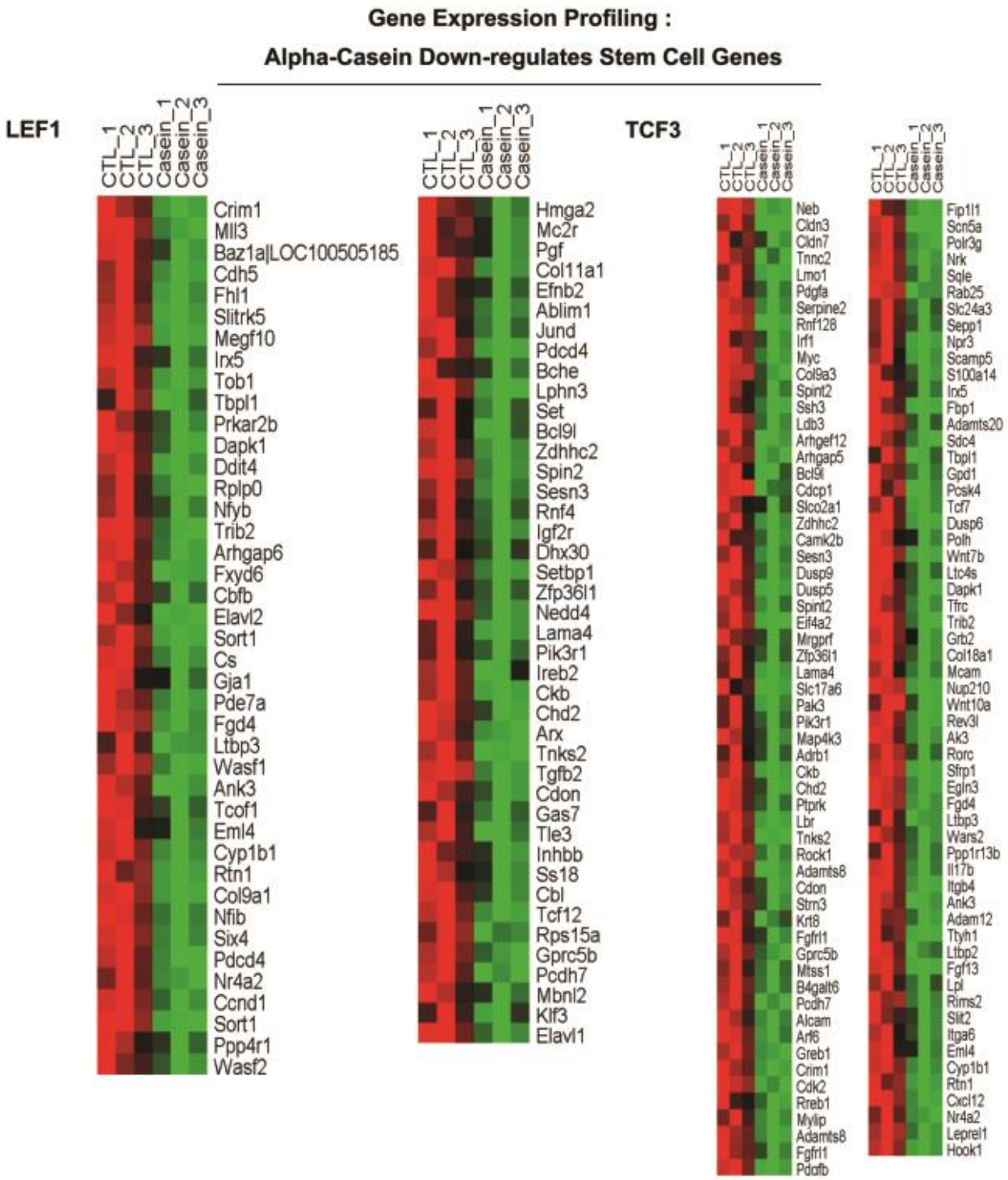

Figure 3B. α-casein transcriptional profiling. Results from pathway analysis with ASSESS. We performed pathway analysis using ASSESS (analysis of sample set enrichment scores). Note that α-casein upregulates gene transcripts associated with inflammatory interferon/STAT1 signaling (LEF1) and decreases gene transcripts associated with "stemness" (TCF3).

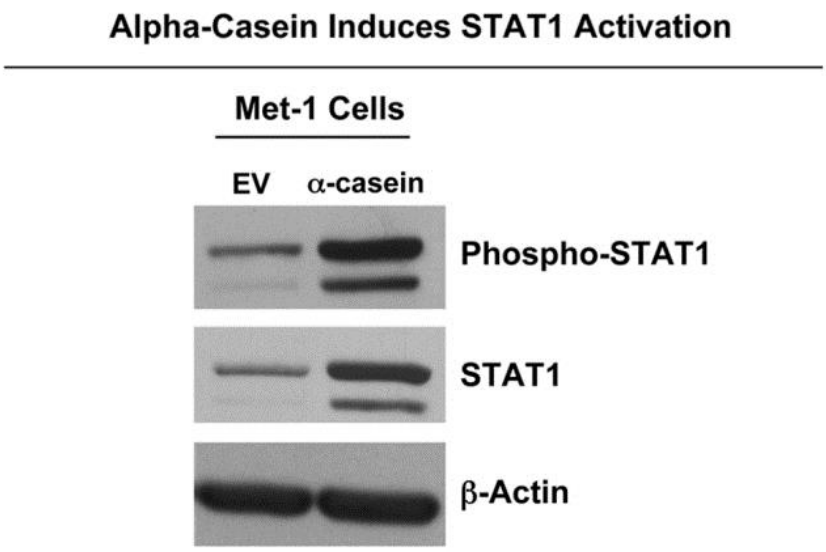

Figure 4. α-casein induces STAT1 activation. Results from DNA microarray analysis suggested that α-casein expression induces the upregulation of the IFN-signaling pathway. Activation of this pathway results in STAT1 phosphorylation. Thus, we performed immunoblot analysis on Met-1 cell lystates. Interestingly, both total STAT1 and phospho-STAT1expression levels were clearly increased by the expression of α-casein.

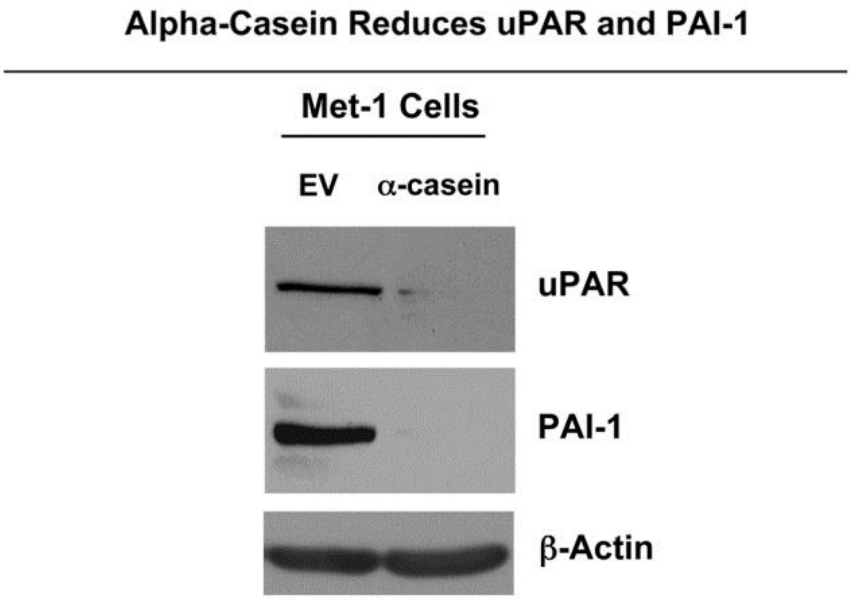

Figure 5. α-casein decreases the expression of uPAR and PAI-1. Lysates were prepared from Met-1 cells recombinantly expressing α-casein or the vector alone control. Then, they were subjected to immunoblot analysis with specific antibody probes. Note that expression of α-casein dramatically reduces the expression of uPAR and PAI-1, as predicted. Immunoblotting with β-actin is shown as a control for equal loading.

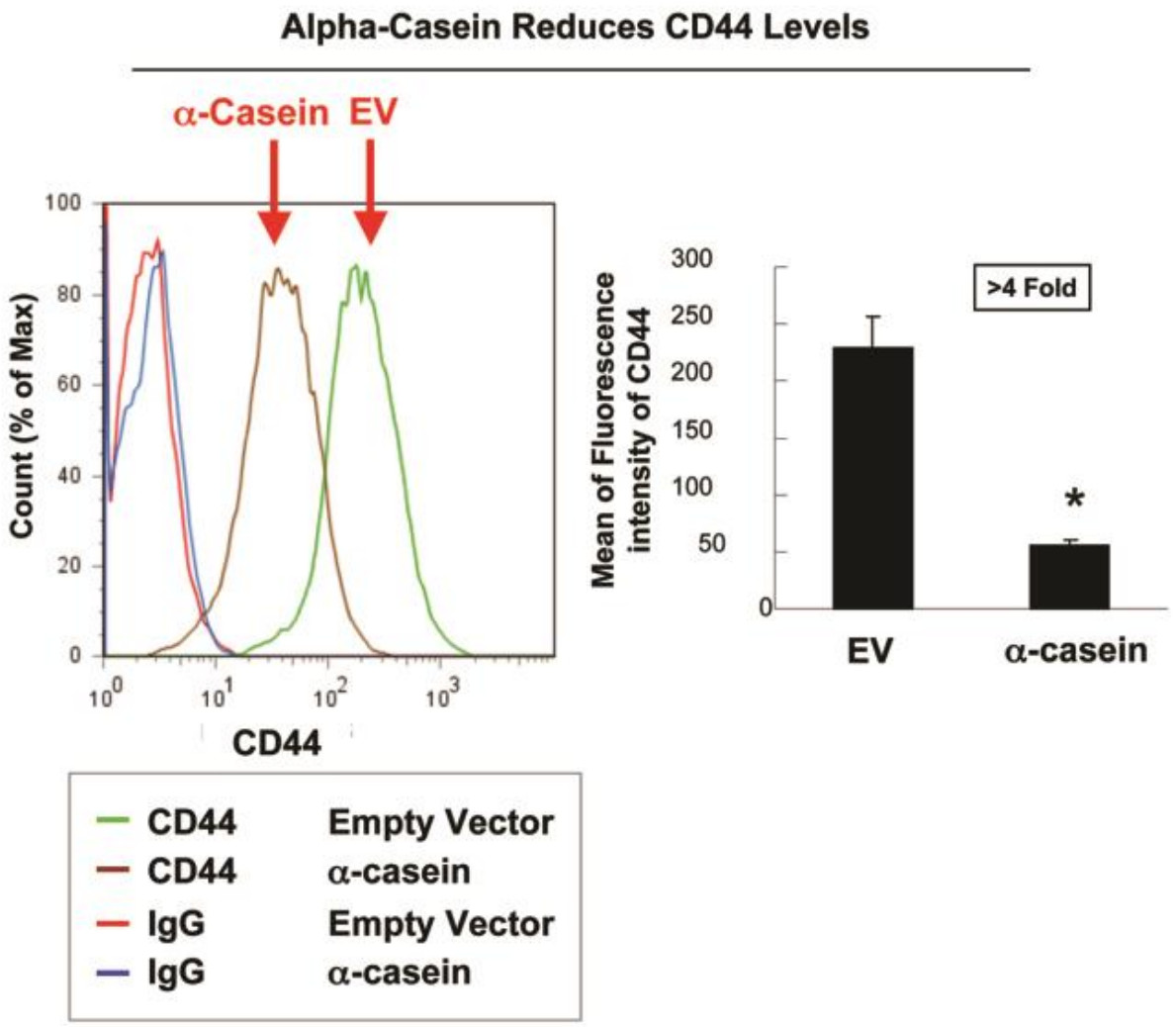

Figure 6. α-casein decreases the number of mammary cancer "stem" cells. (Left Panel) We performed FACS analysis on Met-1 cell cultures to investigate the expression of the cell surface stem/progenitor marker CD44. Note that the proportion of CD44(+) cells was lower in Met-1 cells expressing α-casein (brown line) as compared with Met-1 empty vector control cells (green line). (Right Panel) Graphic representation of the mean values. *$p < 0.01$.

18. Extent of Clinical Activities Initiated and Completed. Items 18(A) and 18(B) should be completed for all research projects. If the project was restricted to secondary analysis of clinical data or data analysis of clinical research, then responses to 18(A) and 18(B) should be "No."

18(A) Did you initiate a study that involved the testing of treatment, prevention or diagnostic procedures on human subjects?

_____Yes
__X___No

18(B) Did you complete a study that involved the testing of treatment, prevention or diagnostic procedures on human subjects?

_____Yes
__X___No

If "Yes" to either 18(A) or 18(B), items 18(C) – (F) must also be completed. (Do NOT complete 18(C-F) if 18(A) and 18(B) are both "No.")

18(C) How many hospital and health care professionals were involved in the research project?

_____Number of hospital and health care professionals involved in the research project

18(D) How many subjects were included in the study compared to targeted goals?

_____Number of subjects originally targeted to be included in the study
_____Number of subjects enrolled in the study

Note: Studies that fall dramatically short on recruitment are encouraged to provide the details of their recruitment efforts in Item 17, Progress in Achieving Research Goals, Objectives and Aims. For example, the number of eligible subjects approached, the number that refused to participate and the reasons for refusal. Without this information it is difficult to discern whether eligibility criteria were too restrictive or the study simply did not appeal to subjects.

18(E) How many subjects were enrolled in the study by gender, ethnicity and race?

Gender:
_____Males
_____Females
_____Unknown

Ethnicity:
_____Latinos or Hispanics
_____Not Latinos or Hispanics
_____Unknown

Race:
_____American Indian or Alaska Native
_____Asian
_____Blacks or African American
_____Native Hawaiian or Other Pacific Islander
_____White
_____Other, specify:_____
_____Unknown

18(F) Where was the research study conducted? (List the county where the research study was conducted. If the treatment, prevention and diagnostic tests were offered in more than one county, list all of the counties where the research study was conducted.)

19. Human Embryonic Stem Cell Research. Item 19(A) should be completed for all research projects. If the research project involved human embryonic stem cells, items 19(B) and 19(C) must also be completed.

19(A) Did this project involve, in any capacity, human embryonic stem cells?
_____Yes
__X___ No

19(B) Were these stem cell lines NIH-approved lines that were derived outside of Pennsylvania?
_____Yes
_____ No

19(C) Please describe how this project involved human embryonic stem cells:

20. Articles Submitted to Peer-Reviewed Publications.

20(A) Identify all publications that resulted from the research performed during the funding period and that have been submitted to peer-reviewed publications. Do not list journal abstracts or presentations at professional meetings; abstract and meeting presentations should be listed at the end of item 17. **Include only those publications that acknowledge the Pennsylvania Department of Health as a funding source** (as required in the grant agreement). List the title of the journal article, the authors, the name of the peer-reviewed publication, the month and year when it was submitted, and the status of publication (submitted for publication, accepted for publication or published.). Submit an electronic copy of each publication or paper submitted for publication, listed in the table, in a PDF version 5.0.5 (or greater) format, 1,200 dpi. Filenames for each publication should include the number of the research project, the last name of the PI, and an abbreviated title of the publication. For example, if you submit two publications for Smith (PI for Project 01), one publication for Zhang (PI for Project 03), and one publication for Bates (PI for Project 04),

the filenames would be:

Project 01 – Smith – Three cases of isolated
Project 01 – Smith – Investigation of NEB1 deletions
Project 03 – Zhang – Molecular profiling of aromatase
Project 04 – Bates – Neonatal intensive care

If the publication is not available electronically, provide 5 paper copies of the publication.

Note: The grant agreement requires that recipients acknowledge the Pennsylvania Department of Health funding in all publications. Please ensure that all publications listed acknowledge the Department of Health funding. If a publication does not acknowledge the funding from the Commonwealth, do not list the publication.

Title of Journal Article:	Authors:	Name of Peer-reviewed Publication:	Month and Year Submitted:	Publication Status (check appropriate box below):
1. Mitochondrial oxidative stress in cancer-associated fibroblasts drives lactate production, promoting breast cancer tumor growth: understanding the aging and cancer connection	Balliet RM, Capparelli C, Guido C, Pestell TG, Martinez-Outschoorn UE, Lin Z, Whitaker-Menezes D, Chiavarina B, Pestell RG, Howell A, Sotgia F, Lisanti MP	Cell Cycle	September 2011	☐Submitted ☐Accepted ☒Published
2. Pyruvate kinase expression (PKM1 and PKM2) in cancer-associated fibroblasts drives stromal nutrient production and tumor growth.	Chiavarina B, Whitaker-Menezes D, Martinez-Outschoorn UE, Witkiewicz AK, Birbe RC, Howell A, Pestell RG, Smith J, Daniel R, Sotgia F, Lisanti MP.	Cancer Biol Ther.	November 2011	☐Submitted ☐Accepted ☒Published
3. Caveolin-1 and Accelerated Host Aging in the Breast Tumor Microenvironment	Mercier I,J Camacho, K Titchen, DM Gonzales, K Quann, KG Bryant, A Molchansky, JN Milliman, D Whitaker-Menezes, F Sotgia, JF Jasmin, R Schwarting, RG Pestell, MV Blagosklonny, and MP Lisanti	Am. J. Path	March 2012	☐Submitted ☐Accepted ☒Published

20(B) Based on this project, are you planning to submit articles to peer-reviewed publications in the future?

Yes_____ No__X_____

If yes, please describe your plans:

21. Changes in Outcome, Impact and Effectiveness Attributable to the Research Project. Describe the outcome, impact, and effectiveness of the research project by summarizing its impact on the incidence of disease, death from disease, stage of disease at time of diagnosis, or other relevant measures of outcome, impact or effectiveness of the research project. If there were no changes, insert "None"; do not use "Not applicable." Responses must be single-spaced below, and no smaller than 12-point type. DO NOT DELETE THESE INSTRUCTIONS. There is no limit to the length of your response.

Ultimately, we believe that these studies will lead to the development of new biomarkers for treatment stratification of breast cancer patients.

22. Major Discoveries, New Drugs, and New Approaches for Prevention Diagnosis and Treatment. Describe major discoveries, new drugs, and new approaches for prevention, diagnosis and treatment that are attributable to the completed research project. If there were no major discoveries, drugs or approaches, insert "None"; do not use "Not applicable." Responses must be single-spaced below, and no smaller than 12-point type. DO NOT DELETE THESE INSTRUCTIONS. There is no limit to the length of your response.

High-risk patients might benefit from treatment with mTOR inhibitors, such as rapamycin or other rapamycin-related compounds (rapalogues).

23. Inventions, Patents and Commercial Development Opportunities.

23(A) Were any inventions, which may be patentable or otherwise protectable under Title 35 of the United States Code, conceived or first actually reduced to practice in the performance of work under this health research grant? Yes_____ No___X_____

If "Yes" to 23(A), complete items a – g below for each invention. (Do NOT complete items a - g if 23(A) is "No.")

a. Title of Invention:

b. Name of Inventor(s):

c. Technical Description of Invention (describe nature, purpose, operation and physical, chemical, biological or electrical characteristics of the invention):

d. Was a patent filed for the invention conceived or first actually reduced to practice in the performance of work under this health research grant?
Yes_____ No___

If yes, indicate date patent was filed:

e. Was a patent issued for the invention conceived or first actually reduced to practice in the performance of work under this health research grant?
Yes_____ No___
If yes, indicate number of patent, title and date issued:
Patent number:
Title of patent:
Date issued:

f. Were any licenses granted for the patent obtained as a result of work performed under this health research grant? Yes_____ No___

If yes, how many licenses were granted?_____

g. Were any commercial development activities taken to develop the invention into a commercial product or service for manufacture or sale? Yes__ No___

If yes, describe the commercial development activities:

23(B) Based on the results of this project, are you planning to file for any licenses or patents, or undertake any commercial development opportunities in the future?

Yes_____ No____X_____

If yes, please describe your plans:

24. Key Investigator Qualifications. Briefly describe the education, research interests and experience and professional commitments of the Principal Investigator and all other key investigators. In place of narrative you may insert the NIH biosketch form here; however, please limit each biosketch to 1-2 pages.

NAME Michael P. Lisanti, M.D.-Ph.D.	POSITION TITLE PI: Professor of Cancer Biology
eRA COMMONS USER NAME MPL001	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
New York University, NY, NY	BA	1985	Chemistry
Cornell University Medical College, NY,	MD-PhD	1992/1991	Cell Biology &
Rockefeller University, NY, NY	Visiting	1992	Molecular
Whitehead Institute/ MIT, Cambridge, MA	Fellow	1992-97	Molecular Cell
University of Manchester, Manchester, UK		2012	Cancer Biology

A. Professional Experience

2012- Professor of Cancer Biology, Director of the Manchester Breakthrough Breast Cancer Research Unit, University of Manchester, UK

2006-2012 Leader/Director, *Program in Cancer Genetics and Molecular Biology*, Kimmel Cancer Center, Thomas Jefferson University (TJU)

2006-2012 Member, *Executive Steering Committee*, Kimmel Cancer Center, TJU

2006- 2012 Professor, Dept., of *Cancer Biology*, Kimmel Cancer Center, TJU

2006- 2012 Professor, Dept., of *Biochemistry and Molecular Biology*, Kimmel Cancer Center, TJU

2002-2006 Professor, Dept. of *Medicine*, The Albert Einstein College of Medicine (*Secondary Appointment*)

2001-2006 Professor, Dept. of *Molecular Pharmacology*,The Albert Einstein College of Medicine; Member, Albert Einstein's *Cancer, Diabetes and Liver Centers*

1998-2001 Associate Professor, Dept. of *Molecular Pharmacology*,The Albert Einstein College of Medicine; Member, Albert Einstein's *Cancer, Diabetes and Liver Centers*

1997-1998 Assistant Professor, Dept. of *Molecular Pharmacology*,The Albert Einstein College of Medicine; Member, Albert Einstein's *Cancer, Diabetes and Liver Centers*

1992-1997 Whitehead Institute Fellow, Whitehead Institute for Biomedical Research, Massachusetts Institute of Technology (MIT). Affiliated with Dr. Harvey Lodish's laboratory

July 1991- June 1992 Visiting Scientist, with Dr. A. K. Menon, Laboratory of Molecular Parasitology, The Rockefeller University

1988-1991 Ph.D., with Dr. Rodriguez-Boulan, Dept. of Cell Biology, Cornell University Medical College

B. Publications (Selected from over 500 publications)

1. Martinez-Outschoorn UE, Goldberg AF, Lin Z, Ko YH, Flomenberg N, Wang C, Pavlides S, Pestell RG, Howell A, Sotgia F, Lisanti MP. 2011. Anti-estrogen resistance

in breast cancer is induced by the tumor microenvironment and can be overcome by inhibiting mitochondrial function in epithelial cancer cells. Cancer Biology and Therapy., 12: 924-38.

2. Martinez-Outschoorn UE, Lin Z, Flomenberg N, Wang C, Pavlides S, Pestell RG, Howell A, Sotgia F, Lisanti MP. 2011. Cancer cells metabolically "fertilize" the tumor microenvironment with hydrogen peroxide, driving the reverse Warburg effect: Implications for PET imaging of human tumors. Cell Cycle, 10: 2504-20.
3. Martinez-Outschoorn UE, Lin Z, Flomenberg N, Wang C, Pavlides S, Pestell RG, Howell A, Sotgia F, Lisanti MP. 2011. Understanding the metabolic basis of drug resistance: Therapeutic induction of the Warburg effect kills cancer cells. Cell Cycle, 10: 2521-28.
4. Bryant KG, Camacho J, Jasmin JF, Wang C, Addya S, Casimiro MC, Fortina P, Balasubramaniam S, Knudsen KE, Schwarting R, Lisanti MP, Mercier I. 2011.
5. Caveolin-1 overexpression enhances androgen-dependent growth and proliferation in the mouse prostate. Int J Biochem Cell Biol., 43: 1318-29.
6. Janowski E, Jiao X, Katiyar S, Lisanti MP, Liu M, Pestell RG, Morad M. 2011. c-Jun is required for TGF-beta-mediated cellular migration via nuclear Ca(2+) signaling. Int J Biochem Cell Biol., 43: 1104-13.
7. Martinez-Outschoorn UE, Whitaker-Menezes D, Lin Z, Flomenberg N, Howell A, Pestell RG, Lisanti MP, Sotgia F. 2011. Cytokine production and inflammation drive autophagy in the tumor microenvironment: Role of stromal caveolin-1 as a key regulator. Cell Cycle. 10: 1784-93.
8. Whitaker-Menezes D, Martinez-Outschoorn UE, Lin Z, Ertel A, Flomenberg N, Witkiewicz AK, Birbe RC, Howell A, Pavlides S, Gandara R, Pestell RG, Sotgia F, Philp NJ, Lisanti MP. 2011. Evidence for a stromal-epithelial "lactate shuttle" in human tumors: MCT4 is a marker of oxidative stress in cancer-associated fibroblasts. Cell Cycle. 10: 1772-83.
9. Li T, Sotgia F, Vuolo MA, Li M, Yang WC, Pestell RG, Sparano JA, **Lisanti MP.** 2006. Caveolin-1 Mutations in Human Breast Cancer: Functional Association with Estrogen Receptor (ER□) Positive Status. Am J Pathol. 168: 1998-2013.

Relevant Review Articles

10. Sotgia F, Martinez-Outschoorn UE, Howell A, Pestell RG, Pavlides S, Lisanti MP. 2012. Caveolin-1 and Cancer Metabolism in the Tumor Microenvironment: Markers, Models, and Mechanisms. Annual Review of Pathology: Mechanisms of Disease, Vol. 7; In Press (Publication date: February 2012).
11. Velasco-Velázquez MA, Popov VM, Lisanti MP, Pestell RG. 2011. The role of breast cancer stem cells in metastasis and therapeutic implications. Am J Pathol. 179: 2-11.
12. Lisanti , M.P., Martinez-Outschoorn, U.E.,, Lin, Z., Pavlides, S., Whitaker-Menezes, D., Pestell, R.G., Howell, A., Sotgia, F. 2011. Accelerated aging in the tumor microenvironment: Connecting aging, inflammation and cancer metabolism with personalized medicine. Cell Cycle., 10: 2059-63.
13. Martinez-Outschoorn, U.E., Pavlides, S., Howell, A., Pestell, R.G., Tanowitz, H.B., Sotgia, F., and Lisanti , M.P. 2011. Stromal –Epithelial Metabolic Coupling in Cancer: Integrating Autophagy and Metabolism in the Tumor Microenvironment. Int J Biochem Cell Biol., 43: 1045-51.