

AWARD NUMBER:

W81XWH-14-1-0238

TITLE:

Targeting Histone Abnormality in Triple-Negative Breast Cancer

PRINCIPAL INVESTIGATOR:

Nancy E. Davidson, M.D.

CONTRACTING ORGANIZATION: University of Pittsburgh,
Pittsburgh, PA 15213

REPORT DATE: August 2016

TYPE OF REPORT:

Annual report

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Fort Detrick, Maryland 21702-5012

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14. ABSTRACT Increasing lines of evidence showed that epigenetic regulation of TNBC proliferation and gene expression could provide novel targets for molecularly directed therapies for this devastating disease. In the first year of this award, our team collaborated with Dr. Huang's lab to demonstrate the coordinated overexpression of HDAC5 and LSD1 proteins in human primary breast tumor specimens. By using <i>in vitro</i> and <i>in vivo</i> models, we identified that sulforaphane (SFN), a natural bioactive HDAC inhibitor, destabilized LSD1 protein through downregulation of HDAC5 transcription, and combined use of SFN with a potent LSD1 inhibitor HCl-2509 significantly enhanced antineoplastic efficacy of SFN in MDA-MB-231 xenografts in mice. On the basis of these novel findings, we carried out microarray assays to address the global effect of HDAC5-LSD1 axis on gene expression in TNBC cells. This study successfully identified a subset of genes including a group of tumor suppressor genes whose expression was regulated by HDAC5-LSD1 signaling. During this funding period, our lab also explored the molecular mechanism of SFN induced suppression of HDAC5 transcription and performed the histological and pathological examinations of tissues, and interpretation of the results generated from <i>in vivo</i> studies. The collaborative studies between two labs have resulted in publication of a research article in <i>Oncogene</i> .					
15. SUBJECT TERMS					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT Unclassified	18. NUMBER OF PAGES 83	19a. NAME OF RESPONSIBLE PERSON USAMRMC
a. REPORT Unclassified	b. ABSTRACT Unclassified	c. THIS PAGE Unclassified			19b. TELEPHONE NUMBER (include area code) N/A

1. INTRODUCTION

Emerging data indicate that epigenetic regulation of TNBC proliferation and metastasis may provide novel targets for molecularly directed therapies against this disease. Epigenetic changes include DNA methylation and modifications of the histone proteins that can switch genes on and off. The stepwise epigenetic changes have been implicated in transformation of normal breast epithelial cells into TNBC. The dysregulated epigenetic changes in TNBC frequently lead to loss of expression of important growth regulatory genes such as tumor suppressor genes (TSG) which facilitate malignant progression of this disease. Histone deacetylase 5 (HDAC5) and lysine specific demethylase 1 (LSD1) are two key epigenetic modifiers controlling chromatin levels of histone acetylation and methylation. In the first year of this award, we demonstrated that enhanced interaction between HDAC5 and LSD1 stabilizes LSD1 protein that in turn promotes tumor growth and metastasis of TNBC cells. We have also successfully identified that sulforaphane (SFN), a natural HDAC inhibitor, suppresses HDAC5 expression that in turn destabilizes LSD1 protein. Our preclinical data strongly suggest that targeting the HDAC5-LSD1 pathway by SFN in combination with a potent LSD1 inhibitor, HCI-2509, may represent a novel and effective approach for TNBC treatment. In the current funding year, in collaboration with Dr. Yi Huang's lab, we performed genome-wide gene expression analysis in MDA-MB-231 cells with stable knockdown of HDAC5 or LSD1 to define a comprehensive profile of genes whose expression is associated with the HDAC5 and LSD1 signaling pathways. The bioinformatic analysis revealed a subset of genes including a group of TSG whose expression was regulated by the HDAC5-LSD1 axis. We also explored the molecular mechanism of SFN induced suppression of HDAC5 transcription and performed the histological and pathological examinations of tissues, and interpretation of the results generated from *in vivo* studies. The collaborative study between the two PIs has led to a paper recently published in *Oncogene* (2016 May 23, Epub ahead of print, PMID: 27212032).

2. KEYWORDS

Triple negative breast cancer, HDAC5, LSD1, sulforaphane, HCI-2509, combination therapy, microarray study

3. ACCOMPLISHMENTS

a. What were the major goals of the project?

The major goal for the research award is to continue to understand the role of crosstalk between LSD1 and HDAC5 in promoting TNBC growth and metastasis, and seek for a novel therapeutic approach to target aberrant crosstalk between HDAC5 and LSD1 for poorly differentiated and aggressive TNBC. These goals are addressed with the close collaboration between two PIs through the following specific aims:

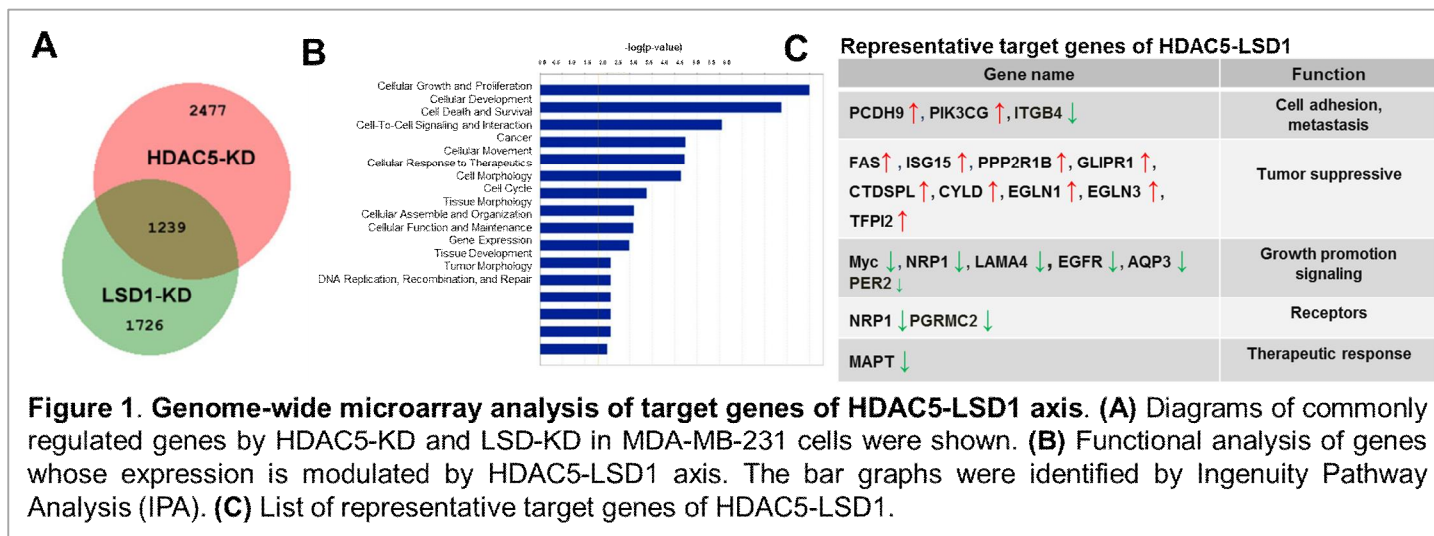
- i. Delineate the molecular basis by which inhibition of LSD1 promotes HDACi-induced apoptosis through reactivation of aberrantly silenced tumor suppressor genes.
- ii. Elucidate the role of LSD1 in HDACi therapy and chemoprevention of TNBC in animal models.
- iii. Evaluate therapeutic effects of combination strategies in patient-derived xenografts (PDXs).

We anticipate that the novel results obtained from these proposed studies would address an unmet need to develop novel methods to determine which epigenetic changes contribute directly to TNBC development and decipher through *in vitro* and *in vivo* models how to apply the novel epigenetic reagents in most favorable combination strategy. The information derived from these studies will likely validate if HDAC5-LSD1 axis has potential to serve as novel therapeutic biomarkers to predict or indicate the response to epigenetic therapy in TNBC.

b. What was accomplished under these goals?

Proposed Aims	Accomplishment
Specific Aim 1: Delineate the molecular basis by which inhibition of LSD1 promotes HDACi-induced apoptosis through reactivation of aberrantly silenced tumor suppressor genes.	The Davidson team used microarray technology to investigate the alteration of genome-wide gene expression in MDA-MB-231 cells with stable knockdown of HDAC5 by shRNA. With the assistance of UPCI biostatisticians, her team evaluated the comprehensive gene expression profile affected by HDAC5-KD, and compared the results with gene expression profile changes caused by LSD1-KD. The goal of this study is to identify the unique subset of genes whose expression is associated with HDAC5-LSD1 signaling pathway.
Major Task 3: Investigate genome-wide epigenetic gene silencing caused by crosstalk between LSD1 and HDACs. (Month 18-24)	To define a comprehensive profile of genes whose expression is associated with HDAC5 and LSD1 signaling pathways, we performed genome-wide gene expression analysis in MDA-MB-231 cells with stable knockdown of HDAC5 or LSD1 by shRNA. Microarray studies were performed at the UPCI Genomics Shared Facility. The array study was performed using Affymetrix Gene Chip U133A 2.0 array platform, which contains 20,928 probes representing all functionally characterized genes in the human genome. Raw intensity data were normalized by the Robust Multi-array Average (RMA). Student's t-tests were performed in R Bioconductor to identify differentially expressed genes. Probe level expression values were condensed to individual genes by choosing the individual probe with the lowest q-value. The list of genes significantly differentially expressed (FDR <0.10) was first filtered to remove probes with mean signal intensities of less than 50 units in both sample groups and to remove probes that are not unique to a single transcript or common among transcripts from the same gene ($\bar{n}_{at}$ or $\bar{n}_{s_{at}}$). Venn diagram was generated using the BioVenn-web application. Data were analyzed through the use of QIAGEN's Ingenuity® Pathway Analysis (Redwood City, CA). Heatmap was generated using TM4 system (Boston, MA). We identified 2477 and 1726 genes whose expression was significantly changed by inhibition of HDAC5 and LSD1, respectively. Strikingly, over 30% of genes in each group were changed by HDAC5-KD or LSD1-KD (Fig. 1A). This result reflects a comprehensive genome wide cooperative effect of HDAC5 and LSD1 on gene expression patterns. Ingenuity pathway analysis showed that these commonly targeted genes have important roles in a wide range of cellular functions in breast cancer (Fig.

1B). The in-depth bioinformatic analysis revealed a subset of genes including a group of TSG whose expression was reactivated by HDAC5-KD or LSD1-KD (**Fig. 1C**). These genes have the potential to play an important role in breast tumorigenesis and therapeutic response.



Proposed Aims	Accomplishment
Specific Aim 2: Elucidate the role of LSD1 in HDACi therapy and chemoprevention of TNBC in animal models.	In the first funding year, the Davidson lab successfully carried out the animal experiments and demonstrated that natural bioactive product, sulforaphane, in combination with a potent LSD1 inhibitor, HCI-2509, exhibited statistically significant enhanced inhibitory effect on MDA-MB-231 tumor growth in nude mice when compared with either drug alone. In the current funding period, the Davidson lab extended the tumor sample analysis, histological and pathological examinations of tissues, and interpretation of results generated from <i>in vivo</i> studies. In addition, her team carried out studies to investigate the mechanism underlying the regulation of SFN on HDAC5 transcriptional activity in breast cancer cells.
Major Task 4: Evaluate <i>in vivo</i> therapeutic effects of combination strategies using LSD1 inhibitors and HDACi in different subtypes of breast tumors.	
Subtask 2: Examine the <i>in vivo</i> effects of LSD1/HDAC signaling on tumorigenic transformation of MCF-10A cells (Month 8-	This study is being planned and we expect to start the experiment shortly.

16).	
Subtask 3: Evaluate combination strategies using LSD1i and HDACi in different subtypes of breast tumors (Month 10-26).	The poly(ADP-ribose) polymerase (PARP-1) is a 113 kDa nuclear enzyme which can be cleaved in fragments of 89 and 24 kDa during apoptotic cell death. Thus this cleavage has become a useful hallmark of apoptosis. To determine if combined therapy using SFN and HCI-2509 promotes MDA-MB-231 xenograft tumor cell apoptosis, level of full length PARP-1 cleavage was measured. MDA-MB-231 cells were transplanted into the mammary gland of nude mice. Seven days after implantation, sulforaphane (50 mg/kg), HCI-2509 (30 mg/kg), combination (SFN 50mg/kg+HCI-2509 30mg/kg) or vehicle (DMSO) were delivered via i.p. injection for 5 day/week x 4 weeks. Fifty micrograms of whole cell protein (n=9 for each group) per lane were analyzed for expression of full length PARP-1 and β-actin as a loading control. A quantitative analysis showed the combination induced significantly more PARP-1 cleavage in MDA-MB-231 xenograft tumor cells evidenced by significantly reduced level of full length PARP-1 compared with the single agent tumors (Fig. 2A). To further evaluate possible undesirable cytotoxic effects in treated animals, we performed hematoxylin-eosin (H&E) sections of animal livers and kidneys; these showed no apparent morphological changes in the tissues treated with SFN or HCI-2509 alone, or in combination (Fig. 2B). Collectively, these results indicate that SFN effectively inhibits growth of breast tumor <i>in vivo</i> but is more effective when used in combination with an LSD1 inhibitor; neither the single agents nor the combination led to histological evidence of liver or kidney toxicity.
Other reportable results	In first funding year, we demonstrated that sulforaphane (SFN), a natural HDAC inhibitor found in cruciferous vegetables, significantly inhibited mRNA expression of HDAC5 in MDA-MB-231 cells. In this award period, we compared the effect of SFN on expression of HDAC5, LSD1 and USP28 with some other HDACi that included hydroxamic acid derivatives SAHA (Vorinostat), TSA (Trichostatin A), LBH-589 (Panobinostat), and PXD-101 (Belinostat), a benzamide analog MS-275 (Entinostat), and a selective class II (IIa) histone deacetylase (HDAC II) inhibitor MC-1568. In MDA-MB-231 cells, treatment with most of the compounds led to significant increase of HDAC5

	mRNA expression with marginal effect on mRNA levels of LSD1 and USP28. However, among these HDACIs, SFN significantly inhibited mRNA expression of HDAC5 without altering mRNA levels of LSD1 and USP28 (Fig. 3). The above studies further confirm that SFN acts as a unique HDACI in suppression of HDAC5 mRNA expression in human breast cancer cells. The effects of selected HDAC inhibitors on HDAC5 transcription were studied using the element of -635 to -893 bp of HDAC5 promoter with full length construct (-1251 to + 666 bp) as control. This was based on results from the Huang lab that this element might play an essential role in mediating transcriptional activity of the HDAC5. cells/per well were seeded into 24 well plate, 250 ng plasmids pGL2-Enhancer or the constructs of pGL2-Enhancer-HDAC5 promoter was transiently co-transfected with 25 ng pRL-TK (Promega) into cells using Lipofectamine 3000 (Invitrogen), separately. 48 h post-transfection, cells were harvested and lysed in buffer from Dual-luciferase assay kit (Promega), with luciferase activity measured on a GLOMAX® 20/20 luminometer (Promega). Luciferase values (relative light units) were normalized to the Renilla luciferase activity and expressed as the fold change relative to pGL2-Enhancer transfected wells. Treatment with SFN significantly inhibited the reporter gene activity of the full length and -635 to -839 bp constructs in MDA-MB-231 cells. In contrast, exposure of MDA-MB-231 cells to SAHA led to increased reporter gene activity on the full length and -635 to -839 constructs (Fig. 4A and 4B). Similar results were observed in another breast cancer line MDA-MB-468 cells (data not shown). These data shed light on the mechanisms underlying transcriptional regulation of HDAC5 promoter activity in breast cancer cells and identify -635 to -839 as an important regulatory element for SFN at HDAC5 promoter. These results also suggest that upregulation of HDAC5 expression by other HDACs such as SAHA might act as a self-defense mechanism against antitumor effect of HDACIs and may contribute to refractoriness to SAHA therapy in breast cancer.
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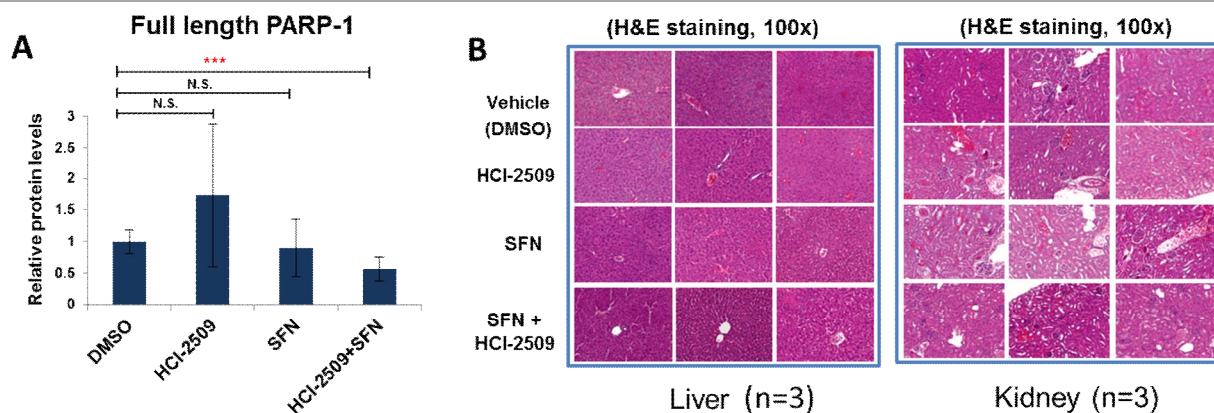


Figure 2. Effect of combination therapy on full length PARP-1 expression and histological evaluation of animal tissues (A) Whole cell proteins were extracted from tumor samples of MDA-MB-231 xenografts treated with vehicle, HCI-2509, SFN or combination for 4 weeks (n=9 from each group). Quantitative immunoblotting was used to determine the expression of full length PARP-1 protein. β -actin was used as control. Data were represented as the mean $\pm$ s.d of three independent experiments. The quantitative variables were analyzed by the two-tailed Student's t-test. P-value<0.05 was considered statistically significant for all tests. **(B)** Histological analysis of livers and kidney of xenograft mice treated with vehicle, HCI-2509, SFN or combination for 4 weeks (n=3 from each group). After the mice were euthanized, the organs were excised and stained with hematoxylin and eosin (H & E). The images of each group are depicted at an original magnification of 100 $\times$.

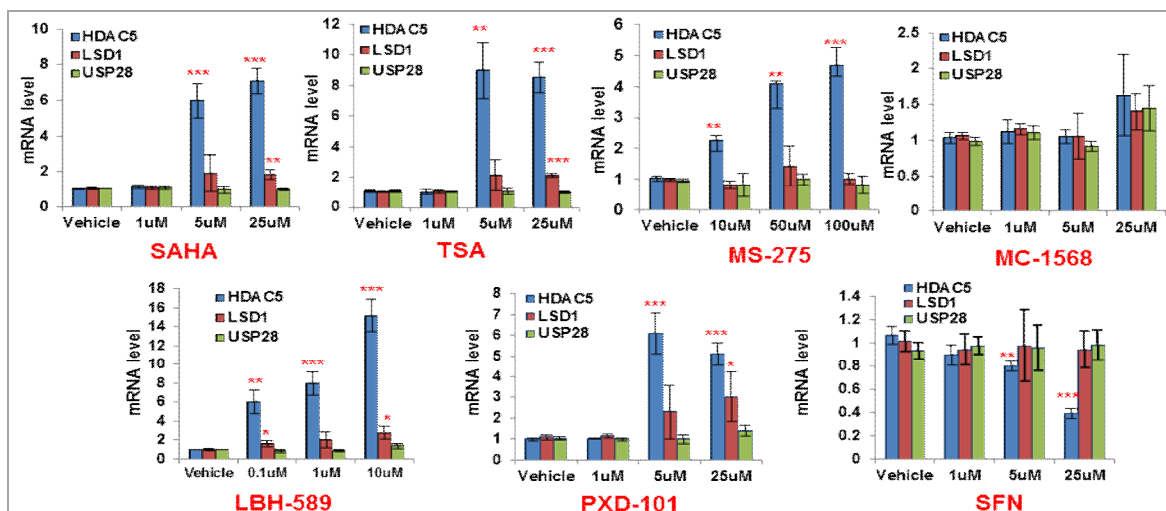
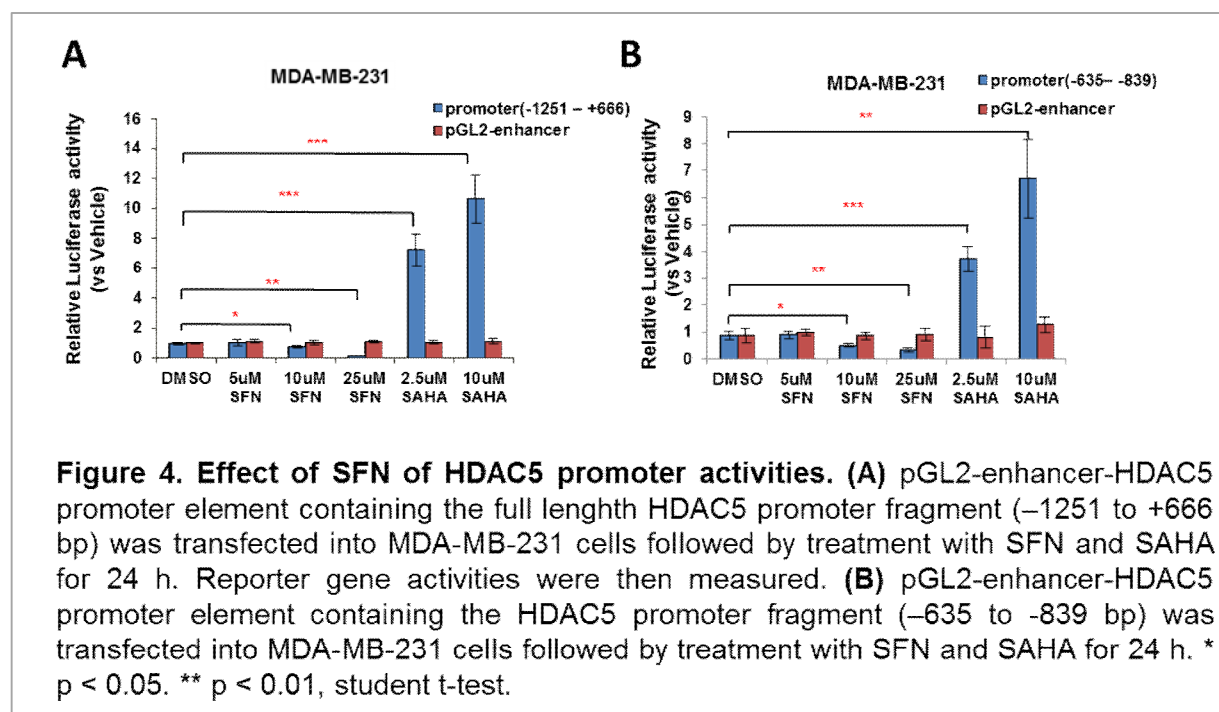


Figure 3. Effect of HDAC inhibitors on expression of HDAC5, LSD1 and USP28 in human breast cancer cells. After MDA-MB-231 cells were exposed to HDAC inhibitors for 24 h, cellular mRNA expression of HDAC5, LSD1 and USP28 was quantitatively measured by real-time PCR. Data were represented as the mean $\pm$ s.d of three independent experiments. The quantitative variables between HDACI treated sample and vehicle treated sample were analyzed by the two-tailed Student's t-test. P-value<0.05 was considered statistically significant for all tests.



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

The postdoc fellow who participates in this project has many opportunities for training and professional development. Travel costs for postdoc fellow to attend the local or national cancer conferences were supported by the project. There are numerous training sessions at the conferences and seminars inside or outside of our institute. Each of our fellows has many opportunities to present their work to their colleagues at these conferences. In addition, this project provided support and an excellent training opportunity for visiting and rotating scholars/students in the laboratory.

c. How were the results disseminated to communities of interest?

This work has been published in *Oncogene*: Cao C, Vasilatos SN, Bhargava R, Fine J, Oesterreich S, Davidson NE, Huang Y. Functional interaction of histone deacetylase 5 (HDAC5) and lysine-specific demethylase 1 (LSD1) promotes breast cancer progression. *Oncogene*, 2016. PMID: 27212032

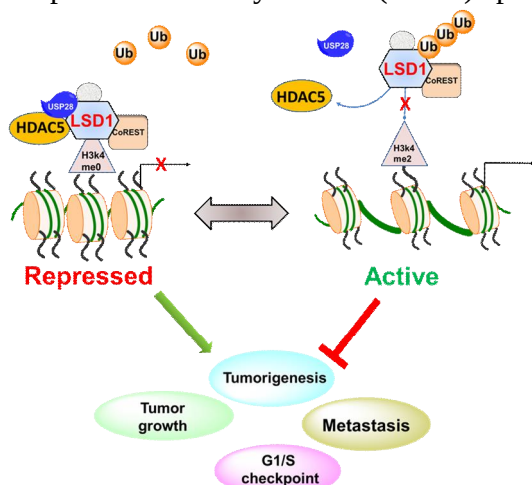


Figure 5. Proposed model of the role of HDAC5-LSD1 axis in breast cancer development.

d. What do you plan to do during the next reporting period to accomplish the goals?

As summarized in Figure 5, we have demonstrated that LSD1 protein stability is promoted by HDAC5 through the LSD1 associated ubiquitin-proteasome system, confirming that the regulation of LSD1 by HDAC5 is a posttranslational event. Our novel findings also provide supportive evidence that an orchestrated interaction between HDAC5 and LSD1 is a critical epigenetic mechanism to suppress transcriptional activities of important tumor suppressor genes that may contribute to breast cancer development. During the next

reporting period, we plan to perform the following studies to accomplish the goals: **(1)** in collaboration with Dr. Huang's team, we will further elucidate the mechanism of SFN-induced downregulation of HDAC5 transcription in breast cancer cells. Quantitative ChIP assays will be used to illustrate how SFN disrupts the DNA binding activity of the regulatory factors at Sulforaphane Response Element (SRE). Furthermore, the cellular sensitivity to SFN will be measured in cells overexpressing the key factors associated with SRE and to determine whether SFN hinders TNBC growth through disruption of the normal transcriptional activity at SRE. **(2)** To study the mechanisms of how HDAC5 inhibition sensitizes TNBC cells to novel LSD1 inhibitors. We will address this question through the following studies: (a) we will utilize the MCF10A progression model to examine the effect of combination therapy on transformation of MCF10A cells and assess whether combination therapy would more profoundly inhibit stem-cell-like traits of TNBC cells. (b) We will determine the potential synergistic effect of the combination treatment of SFN with novel LSD1 inhibitors on the expression of TSGs regulated by HDAC5-LSD1. **(3)** To further elucidate the *in vivo* function of HDAC5-LSD1 pathway in TNBC development and evaluate the effect of inhibition of HDAC5-LSD1 axis in TNBC therapy using murine models. We will test the *in vivo* effect of SFN on growth of TNBC cells overexpressing HDAC5 or LSD1. Moreover, animal work will be carried out to determine whether inhibition of the HDAC5-LSD1 axis effectively prevents the metastasis of TNBC *in vivo*.

4. IMPACT

(a) What was the impact on the development of the principal discipline(s) of the project? The proposed studies of this award addresses an unmet need to develop novel methods to define which epigenetic changes contribute directly to TNBC development and decipher through *in vitro* and *in vivo* models how to apply the novel epigenetic reagents in most favorable combination strategy. The information derived from these studies will likely validate if elements of the HDAC5-LSD1 axis have potential to serve as novel therapeutic biomarkers to predict response to epigenetic therapy in TNBC. Targeting HDAC5 inhibition with the natural product, sulforaphane, in combination with a newly developed potent LSD1 inhibitor, HCL-2509, showed superior antineoplastic activity both *in vitro* and *in vivo*. This proposal seeks to uncover how the HDAC5-LSD1 axis contributes to resistance to HDACi therapy in breast cancer. The information gained from this study could lead to validation and translation of our new strategy into future trials.

(b) What was the impact on other disciplines? Nothing to Report

(c) What was the impact on technology transfer? Nothing to Report

5. CHANGES/PROBLEMS

(a) Changes in approach and reasons for change

No major changes in approach have been made since the initiation of the award.

(b) Actual or anticipated problems or delays and actions or plans to resolve them

Nothing to Report

(c) Changes that had a significant impact on expenditures

Nothing to Report

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

Nothing to Report

6. PRODUCTS

- (a) **Publications, conference papers, and presentations**

Research Article:

Cao C, Vasilatos SN, Bhargava R, Fine J, Oesterreich S, Davidson NE, Huang Y. Functional interaction of histone deacetylase 5 (HDAC5) and lysine-specific demethylase 1 (LSD1) promotes breast cancer progression. Oncogene, 2016. PMID:27212032

Conference Abstract:

Vasilatos SN, Katz TA, Yatsenko TA, Chen L, Luthra S, Chandran UP, Oesterreich S, Davidson NE, Huang Y. Genome-wide effect of inhibition of lysine-specific demethylase 2 (LSD-2) on gene expression and chromosomal stability in human breast cancer. 2016 UPCI Annual Retreat

- (b) **Website(s) or other Internet site(s)** Nothing to Report

- (c) **Technologies or techniques** Nothing to Report

- (d) **Inventions, patent applications, and/or licenses** Nothing to Report

- (e) **Other Products** Nothing to Report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

- a) **Individuals have worked on the project**

Name:	Nancy Davidson	Yi Huang	Chunyu Cao	Shauna Vasilatos	Ye Qin
Project Role:	Co-PI	Co-PI	Postdoc Fellow	Technician	Postdoc Fellow
Researcher Identifier (e.g. ORCID ID):	N/A	N/A	N/A	N/A	N/A
Nearest person month worked:	1.2	3.6	6.0	9.0	6.0
Contribution to Project:	Oversaw epigenetic drug studies and animal experiments, and interpreted the results generated from combination	Designed and oversaw the studies to investigate the molecular mechanisms and biological	Studied molecular mechanisms by which LSD1 and HDAC5 interacted, and	Performed microarray studies and data analysis	Newly recruited postdoc fellow.

	and <i>in vivo</i> studies	consequences of the functional interplay between HDAC5 and LSD1 in TNBC	carried out animal study		
Funding Support:	CDMRP Breast Cancer Breakthrough Award and Breast Cancer Research Foundation	CDMRP Breast Cancer Breakthrough Award	CDMRP Breast Cancer Breakthrough Award	CDMRP Breast Cancer Breakthrough Award	CDMRP Breast Cancer Breakthrough Award

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

Dr. Chunyu Cao has completed his postdoctoral fellow training, and Dr. Ye Qin joined the laboratory to continue the work as a postdoctoral fellow. .

c) What other organizations were involved as partners?

Nothing to Report

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: Initiating PI, Dr. Yi Huang, will submit his annual report separately.

QUAD CHARTS: N/A

9. APPENDICES: updated curriculum vitae is attached

CURRICULUM VITAE

University of Pittsburgh
School of Medicine

BIOGRAPHICAL

Name:	Nancy Ellen Davidson, MD	Birth Place:	Denver, Colorado
Address:	537 North Neville Street Pittsburgh, PA 15213		
Home Phone:	412-683-7178	Citizenship:	United States
Business Address:	University of Pittsburgh Cancer Institute UPMC Cancer Pavilion 5150 Centre Avenue, Suite 500 Pittsburgh, PA 15232	Email Address:	davidsonne@upmc.edu
Business Phone:	412-623-3205	Business Fax:	412-623-3210

EDUCATION and TRAINING

UNDERGRADUATE:

1971-1975	Wellesley College Wellesley, Massachusetts	BA 1975	Molecular Biology
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GRADUATE:

1975-1979	Harvard Medical School Boston, Massachusetts	MD 1979	Medicine
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POSTGRADUATE:

1979-1980	Hospital of the University of Pennsylvania Philadelphia, Pennsylvania	Intern 1980	Internal Medicine
1980-1982	The Johns Hopkins Hospital Baltimore, Maryland	Resident 1982	Internal Medicine
1982-1985	National Cancer Institute National Institutes of Health Bethesda, Maryland	Medical Staff Fellow 1985	

APPOINTMENTS and POSITIONS

ACADEMIC:

1985-1987	Medical Breast Cancer Section, Medicine Branch, National Cancer Institute Bethesda, Maryland	Guest Worker
1985-1986	Uniformed Services University of Health Sciences Bethesda, Maryland	Research Assistant Professor of Pharmacology
1986-1992	The Johns Hopkins University Baltimore, Maryland	Assistant Professor of Oncology Associate Professor of Oncology
1995-2009	The Johns Hopkins University Baltimore, Maryland	Breast Cancer Research Chair of Oncology
1999-2009	The Johns Hopkins University Baltimore, Maryland	Professor of Oncology
1986-2009	Johns Hopkins Hospital Baltimore, Maryland	Active Staff
1994-2009	The Johns Hopkins Oncology Center Baltimore, Maryland	Director, Breast Cancer Program
1997-2009	The Johns Hopkins Bloomberg School of Public Health Baltimore, Maryland	Joint Appointment in Department of Biochemistry and Molecular Biology
2009-	The Johns Hopkins University Baltimore, Maryland	Adjunct Professor of Oncology
2009-2010	University of Pittsburgh Pittsburgh, PA	Chief, Division of Hematology/Oncology
2009-	University of Pittsburgh Pittsburgh, PA	Director, University of Pittsburgh Cancer Institute Professor of Medicine and Pharmacology and Chemical Biology Associate Vice Chancellor for Cancer Research Hillman Professor of Oncology

2010-	University of Pittsburgh Pittsburgh, PA	Professor, Clinical and Translational Science Institute
2013-	University of Pittsburgh Pittsburgh, PA	Distinguished Professor of Medicine

CERTIFICATION AND LICENSURE

SPECIALTY CERTIFICATION:

<u>Certifying Board</u>	<u>Year</u>
National Board of Medical Examiners	1980
American Board of Internal Medicine	1982
Medical Oncology	1985

Medical or other Professional Licensure:

State of Maryland	1982
Commonwealth of Pennsylvania	2009

MEMBERSHIPS in PROFESSIONAL and SCIENTIFIC SOCIETIES

<u>Organization</u>	<u>Year</u>
American Society of Clinical Oncology	1985-present
Member, Program Committee	1992, 1998, 2002, 2003
Session Chairman	1992, 1993, 1998
Member, Public Issues Committee	1992-1996
Member, Award Selection Committee	1992-1996
Chair, Award Selection Committee	1994-1995
Member, Ad hoc Technology Assessment Committee for Development of Growth Factor Clinical Practice Guidelines	1993-1994
Co-Chair, Breast Cancer Follow-up Testing Guidelines Expert Panel	1996- present
Member, Membership Committee	1997-1999
Member, Board of Directors	1996-1999
Member, Grants Selection Committee	1999-2002
Member, Task Force on Quality of Cancer Care	1999-2004
Member, Publications Committee	2004-2007
Chair, Publications Committee	2005-2006
Member, Translational Research Task Force	2005-2006
President-Elect, President, and Immediate Past President	2006-2009
Member, Value in Cancer Care Task Force	2007-present
Chair, Special Awards Selection Committee	2008-2009
Member, Translational Research Professorship Selection Committee	2008-2009
Government Relations Committee	2013-2016
By-laws Committee	2010-2014
	Chair, 2012-2014

American Association for Cancer Research	1988- present
Session Chair	1991, 1995, 1998 2004, 2006, 2013
Member, Maryland Legislative Committee	1993-1997
Member, Program Committee	2000-2001, 2002-2003 2003-2004
Co-Chair, Program Committee	2001
Member, Clinical Cancer Research Committee	1998-1999,
Member, AACR-Richard and Hinda Rosenthal Foundation Award Selection Committee	2001-2003
Member, Board of Directors	2002-2005
Chair, Education Committee	2003-2004
Member, Grants Selection Committee	2004-2005
Member, Lifetime Achievement Award Selection Committee	2004-2005
Member, Landon Award Selection Committee	2005-2006
Chair, AACR-Breast Cancer Research Foundation Grants Selection Committee	2008-2009
Member, Landon Translational Award Selection Committee	2008-2009
Co-Chair, Program Committee, 7 th Annual Frontiers in Cancer Prevention Research Conference	2008
Member and Chair (2010-11), AACR Nominating Committee	2010-2012
Member, Continuing Medical Education Committee, (Chair 2015-2016)	2010-2016
Member, Education Committee	2012-2013
Member, Program Committee, AACR-San Antonio Breast Cancer Symposium	2011-2014
President-Elect, President, and Immediate Past President	2015-2018
Eastern Cooperative Oncology Group	1987-present
Member, Breast Cancer Core Committee	1987-present
Chair, Breast Cancer Biology Committee	1992-1996
Co-Chair, Breast Cancer Committee	1992-1996
Chair - Breast Cancer Committee	1997-2002
American College of Physicians	2009-present
Member	
Member, National Surgical Adjuvant Bowel and Breast Project	2010-present
Member, Board of Directors, Association of American Cancer Institute's	2010-2013
Member, Association of American Physicians Council	2015-present

HONORS

Phi Beta Kappa	1974
Sigma X	1975
American Society of Clinical Oncology Young Investigator Award	1986-1987
Susan Komen Foundation Award	1987-1988
American Cancer Society Clinical Oncology Career Development Award	1988-1991
Merck Clinician Scientist Award	1989-1990
Breast Cancer Research Chair in Oncology, Johns Hopkins	1995-2009
ACS Research Award, American Cancer Society - Maryland Division	1998
Brinker International Award for Breast Cancer Research	1999
Wellesley College Alumnae Achievement Award	2000
William L. McGuire Memorial Lectureship, 24 th	2001
Annual San Antonio Breast Cancer Symposium	
Avon Foundation Medical Advancement Award	2003
President, American Society of Clinical Oncology	2007 - 2008
7 th Rosalind E. Franklin Award for Women in Science, National Cancer Institute	2008
11 th American Association for Cancer Research-Women in Cancer Research Charlotte Friend Award	2008
Johns Hopkins University Alumni Association Distinguished Alumna Award	2009
American Society of Clinical Oncology Gianni Bonadonna Breast Cancer Award	2010
Association of American Physicians	2010
National Academy of Medicine (formerly the Institute of Medicine)	2011
Pennsylvania Breast Cancer Coalition Potamkin Award	2012
Distinguished Professor of Medicine, University of Pittsburgh	2013
Thomson Reuters Highly Cited Researchers	2014, 2015
The Johns Hopkins Women's Medical Alumnae Assoc. Hall of Fame	2015
Johns Hopkins University Society of Scholars	2016
Fellow, American College of Physicians	2016

PUBLICATIONS

Refereed Articles:

1. Kensler TW, Busby WF, Jr., Davidson NE, and Wogan GN. Aflatoxin inhibition of glucocorticoid binding capacity of rat liver nuclei. *Biochim. Biophys. Acta.* 473:200-10, 1976. PMID 181075
2. Kensler TW, Busby WF, Davidson NE, and Wogan GN. Effect of hepatocarcinogens on the binding of glucocorticoid-receptor complex in rat liver nuclei. *Cancer Res.* 36:4647-51, 1976. PMID 1000507

3. Michejda CJ, Davidson NE, and Keefer LK. Photochemical perturbation of Z=E equilibria in nitrosamines. *J. Chemistry Soc. Chem. Comm.* 633-634, 1976
4. Hochberg MC, Davidson NE, and Kim WS. Lupus nephritis. *Johns Hopkins Med. J.* 150:101-106, 1982. PMID 7062572
5. Davidson NE, Bronzert DA, Chambon P, Gelmann EP and Lippman ME. Use of two MCF-7 cell variants to evaluate the growth regulatory potential of estrogen-induced products. *Cancer Res.* 46:1904-08, 1986. PMID 3948173
6. Kasid A, Davidson NE, Gelmann EP and Lippman ME. Transcriptional control of thymidine kinase gene expression by estrogens and antiestrogens in MCF-7 human breast cancer cells. *J. Biol. Chem.* 261:5562-7, 1986. PMID 2420802
7. Lippman ME, Dickson R, Kasid A, Gelmann EP, Davidson NE, McManaway M, Huff K, Bronzert D, Bates S, Swain S and Knabbe C. Autocrine and paracrine growth regulation of human breast cancer. *J. Steroid Biochem.* 24:147-54, 1986. PMID 3486321
8. Bronzert DA, Davidson N, and Lippman M. Estrogen and antiestrogen resistance in human breast cancer cell lines. *Adv. Exp. Med. Biol.* 196:329-45, 1986. PMID 3521223
9. Kensler TW, Egner PA, Davidson NE, Roebuck BD, Pikul A, and Groopman JD. Modulation of aflatoxin metabolism, aflatoxin- N7-guanine formation, and hepatic tumorigenesis in rats fed ethoxyquin: role of induction of glutathione S-transferases. *Cancer Res.* 46:3924-31, 1986. PMID 2873884
10. Davidson NE, Gelmann EP, Lippman ME and Dickson RB. EGF receptor gene expression in estrogen receptor positive and negative human breast cancer cell lines. *Molecular Endocrinology*, 1:216-23, 1987. PMID 3502607
11. Lippman ME, Bates S, Huff KK, Davidson N and Dickson R. Estrogens regulate production of specific growth factors in hormone- dependent human breast cancer. *J. Lab. Clin. Med.* 109:230-5, 1987. PMID 3469292
12. Bronzert DA, Pantazis P, Antoniadis HN, Kasid A, Davidson NE, Dickson RB, and Lippman ME. Synthesis and secretion of PDGF-like growth factor by human breast cancer cell lines. *Proc. Natl. Acad. Sci. USA.* 84:5763-7, 1987. PMC298943
13. Bates SB and Davidson NE, Valverius EM, Dickson RB, Freter CE, Tam JP, Kudlow JE, Lippman ME and Salomon D. Expression of transforming growth factor alpha and its mRNA in human breast cancer: its regulation by estrogen and its possible functional significance. *Molecular Endocrinology.* 2:543-55, 1988. PMID: 3047555
14. Davidson NE and Lippman ME. The role of estrogens in growth regulation of breast cancer. *Crit. Rev. Oncogenesis.* 1:89-111, 1989. PMID 2488125
15. Geller RB, Boone LB, Karp JE, Davidson N, Selonick SE, Edwards J and Burke PJ. Secondary acute myelocytic leukemia after adjuvant therapy for early-stage breast carcinoma. A new complication of cyclophosphamide, methotrexate, and 5-fluorouracil therapy. *Cancer.* 64:629-34, 1989. PMID 2743258
16. Nigro JM, Baker SJ, Preisinger AC, Jessup JM, Hostetter R, Cleary K, Bigner SH, Davidson N, Baylin S, Devilee P, Glover T, Collins FS, Weston A, Modali R, Harris CC and Vogelstein B. p53 gene mutations occur in diverse human tumor types. *Nature.* 342:705-08, 1989. PMID 2531845
17. Davidson NE. Biology of breast cancer and its clinical implications. *Current Opinion in Oncology.* 1:269-76, 1989. PMID 2562285

18. Falco JP, Baylin SB, Lupu R, Borges M, Nelkin BD, Jasti R, Davidson NE, and Mabry M. v-ras induces non-small cell phenotype, with associated growth factors and receptors, in a small cell lung cancer cell line. *J Clin Inves.* 85:1740-05, 1990. PMC296635
19. Davidson NE, Egner PA and Kensler TW. Transcriptional control of glutathione S-transferase gene expression by the chemoprotective agent 5-(2-pyrazinyl)-4-methyl-1,2-dithiole-3-thione [Oltipraz] in rat liver. *Cancer Res*, 50:2251-5, 1990. PMID 2317812
20. Abeloff MD, Beveridge R, Donehower R, Fetting J, Davidson NE, Gordon G, Waterfield W and Damron D. Sixteen week dose-intense chemotherapy in adjuvant treatment of breast cancer. *J Natl Cancer Inst.* 82:570-4, 1990. PMID 2313733
21. Davidson NE. Biology and prognostic factors of breast cancer. *Current Opinion in Oncology.* 2:1025-30, 1990. PMID 1983088
22. Rowley SD, Piantadosi S, Marcellus DC, Jones RJ, Davidson NE, Davis JM, Kennedy J, Wiley JM, Wingard J, Yeager AM and Santos GW. Analysis of factors predicting speed of hematologic recovery after transplantation with 4 hydroperoxycyclophosphamide-purged autologous bone marrow grafts. *Bone Marrow Trans.* 7:183-91, 1991. PMID 2059755
23. Kyprianou N, English HF, Davidson NE and Isaacs JT. Programmed cell death during regression of the MCF-7 human breast cancer following estrogen ablation. *Cancer Res.* 51:162-6, 1991. PMID 1899037
24. Kennedy MJ, Beveridge RA, Rowley SD, Gordon GB, Abeloff MD and Davidson NE. High dose chemotherapy with reinfusion of purged autologous bone marrow following dose-intense induction as initial therapy for metastatic breast cancer. *J. Natl. Cancer Inst.* 83:920-6, 1991. PMID 1906111
25. Davidson NE. Biology of breast cancer. *Current Opinion in Oncology.* 3:988-94, 1991. PMID 1843117
26. Davidson NE. and Abeloff MD. Adjuvant systemic therapy for women with high risk early breast cancer. *J. Natl. Cancer Inst.* 84:301-5, 1992. PMID 1531367
27. Kennedy MJ, Prestigiacomo LJ, Tyler G, May WS. and Davidson NE. Differential effects of bryostatin 1 and phorbol ester on growth of human breast cancer cell lines. *Cancer Res.* 52:1278, 1992. PMID 1737390
28. Armstrong DK, Gordon GB, Hilton J, Streeper RT, Colvin OM, and Davidson, NE. Hepsulfam sensitivity in human breast cancer cell lines: the role of glutathione and glutathione-S transferase in resistance. *Cancer Res.* 52:1416-21, 1992. PMID 1540950
29. Armstrong DK, Isaacs JT, Ottaviano YL and Davidson NE. Programmed cell death in an estrogen-independent human breast cancer cell line, MDA-MB-468. *Cancer Res.* 52:3418-24, 1992. PMID 1534511
30. Sidransky D, Tokino T, Helzlsouer K, Zehnbauser B, Rausch G, Shelton B, Prestigiacomo L, Vogelstein B, and Davidson N. Inherited p53 gene mutations in breast cancer. *Cancer Res.* 52:2984-6, 1992. PMID 1581912
31. Davidson NE. Biology of breast cancer and its clinical implications. *Current Opinion in Oncology.* 4:1003-9, 1992. PMID 1457515
32. Armstrong DK, Fetting JH, Davidson NE, Gordon GB, Huelskamp AM and Abeloff, MD. Sixteen week dose intense chemotherapy for inoperable, locally advanced breast cancer. *Breast Cancer Res. Treat.* 28:277-84, 1993. PMID 8018956
33. Davidson NE, Prestigiacomo LJ and Hahm HA. Induction of jun gene family members by transforming growth factor alpha but not 17 beta-estradiol in human breast cancer cell lines. *Cancer Res.* 53:291-7, 1993. PMID 847822

34. Davidson NE, Mank AR, Prestigiacomo LJ, Bergeron RJ and Casero RA. Growth inhibition of hormone-responsive and -resistant human breast cancer cell lines by N¹,N¹²-bis(ethyl) spermine. *Cancer Res.* 53:2071-5, 1993. PMID 8481909
35. Kennedy MJ, Vogelsang GB, Beveridge RA, Farmer ER, Altomonte V, Huelskamp AM and Davidson NE. Phase I trial of intravenous cyclosporine A to induce graft-versus-host disease in women undergoing autologous bone marrow transplantation for breast cancer. *J Clin Oncol.* 11:478-84, 1993. PMID 8445424
36. Kaufmann SH, Desnoyers S, Ottaviano Y, Davidson NE and Poirier GG. Specific proteolytic cleavage of poly (ADP-ribose) polymerase: an early marker of chemotherapy-induced apoptosis. *Cancer Res.* 53:3976-85, 1993. PMID 8358726
37. Davidson NE and Abeloff MD. Menstrual effects on surgical treatment for breast cancer, *Cancer Treat Rev.* 19:105-12, 1993. PMID 8481925.
38. Tokino T, Davidson N, Helzlsouer K, Zehnbauser B, Nakamura Y, Vogelstein B, and Sidransky, D. Absence of germline prohibitin mutations in early onset breast cancer. *Int. J. Oncology.* 3:769-72, 1993. PMID 21573431
39. Kennedy MJ, Davis J, Passos-Coelho J, Noga SJ, Huelskamp AM, Ohly K and Davidson NE. Administration of human recombinant granulocyte-colony stimulating factor (Filgrastim) accelerates granulocyte recovery following high-dose chemotherapy and autologous marrow transplantation with 4-hydroperoxycyclophosphamide-purged marrow in women with metastatic breast cancer, *Cancer Res.* 53:5424-8, 1993. PMID 7693341
40. Ross AA, Cooper BW, Lazarus HM, Moss TJ, Ciobanu N, Tallman MS, Kennedy MJ, Davidson NE, Sweet D, Winter C, Alcard L, Jansen J, Copelan E, Meagher RC, Herzig RH, Klumpp TR, Kahn DG and Warner NE. Detection and viability of tumor cells in peripheral blood stem cell collections from breast cancer patients using immunocytochemical and clonogenic assay techniques, *Blood.* 82:2605-10, 1993. PMID 8219214
41. Kronthal AJ, Fishman EK, Gottlieb LM and Davidson NE. CT evaluation of breast cancer: spectrum of disease. *Critical Reviews in Diagnostic Imaging.* 34:159-237, 1993. PMID 8216816
42. Kennedy MJ, Vogelsang GB, Jones RJ, Farmer ER, Altomonte V, Huelskamp AM, Hess A, and Davidson NE. Phase I trial of interferon-gamma to potentiate cyclosporine A-induced graft-versus-host disease in women undergoing autologous bone marrow transplantation for breast cancer, *J. Clin. Oncol.* 12:249-57, 1994. PMID 8113833
43. Davidson NE. Ovarian ablation as treatment for young women with breast cancer. *J. Natl. Cancer Inst.* 16:95-9, 1994. PMID 7528032
44. Davidson NE and Abeloff MD. Adjuvant therapy of breast cancer. *World J Surg.* 18:112-6, 1994. PMID 8197765
45. Passos-Coelho J, Ross AA, Davis JM, Huelskamp A-M, Clarke B, Noga JS, Davidson NE and Kennedy MJ. Bone marrow micrometastases in chemotherapy-responsive advanced breast cancer - effect of ex vivo purging with 4-hydroperoxycyclophosphamide. *Cancer Res.* 54:2366-71, 1994. PMID 8162582
46. Ottaviano YL, Issa J-P, Parl FF, Smith HS, Baylin SB and Davidson NE. Methylation of the estrogen receptor gene CpG island marks loss of estrogen receptor expression in human breast cancer cells. *Cancer Res.* 54:2552-5, 1994. PMID 8168078
47. Issa J-P I, Ottaviano YL, Celano P, Hamilton SR, Davidson NE and Baylin SB. Methylation of the oestrogen receptor gene CpG island links ageing and neoplasia in human colon. *Nature Genetics.* 7:536-40, 1994. PMID 7951326

48. Cobleigh MA, Berris RF, Bush T, Davidson NE, Robert NJ, Sparano JA, Tormey DC and Wood WC. Estrogen replacement therapy in breast cancer survivors - a time for change. *JAMA*. 272:540-5, 1994. PMID 8046809
49. Armstrong DK, Kaufmann SH, Ottaviano YL, Furuya Y, Buckley JA, Isaacs JT and Davidson NE. Epidermal growth factor-mediated apoptosis of MDA-MB-468 human breast cancer cells. *Cancer Res*. 54:5280-3, 1994. PMID 7923154
50. May WS, Tyler PG, Ito T, Armstrong DK, Qatsha KA and Davidson NE. Interleukin-3 and bryostatin-1 mediate hyperphosphorylation of BCL2 in association with suppression of apoptosis. *J. Biol. Chem*. 269:26865-70, 1994. PMID 7929424
51. ASCO Ad Hoc Colony-Stimulating Factor Guideline Expert Panel, American Society of Clinical Oncology recommendations for the use of hematopoietic colony-stimulating factors: Evidence-based, clinical practice guidelines. *J. Clin. Oncol*. 12:2471-2508, 1994. PMID 7964965
52. Passos-Coelho JL, Ross AA, Moss TJ, Davis JM, Huelskamp A-M, Noga SJ Davidson NE and Kennedy MJ. Absence of breast cancer cells in a single day peripheral blood progenitor cell (PBPC) collection following priming with cyclophosphamide and granulocyte-macrophage colony-stimulating factor (GM-CSF). *Blood*. 85:1138-43, 1995. PMID 7849302.
53. Passos-Coelho JL, Braine HG, Davis JM, Huelskamp A-M, Schapers KG, Ohly K, Clarke B, Wright SK, Noga JS, Davidson NE and Kennedy MJ. Predictive factors for peripheral blood progenitor cell (PBPC) collection using a single large volume leukopheresis after cyclophosphamide and granulocyte-macrophage colony stimulating factor (GM-CSF) mobilization. *J. Clin. Oncol*. 13:705-14, 1995. PMID 7533827
54. Kennedy MJ, Armstrong DK, Huelskamp AM, Ohly K, Clark BV, Colvin OM, Grochow LB, Chen T-L and Davidson NE. Phase I and pharmacologic study of the alkylating agent modulator novobiocin in combination with high-dose chemotherapy for the treatment of metastatic breast cancer. *J. Clin. Oncol*. 13:1136-43, 1995. PMID 7738619
55. Ferguson AT, Lapidus RG, Baylin SB, and Davidson NE. Demethylation of the estrogen receptor gene in estrogen receptor-negative breast cancer cells can reactivate estrogen receptor gene expression. *Cancer Res*. 55:2279-83, 1995. PMID 7538900
56. Elledge RM, Gray R, Mansour E, Yu Y, Clark GM, Ravdin P, Osborne CK, Davidson NE, Robert N, Tormey DC and Allred DC. Accumulation of p53 protein as a possible predictor of response to adjuvant CMFP for breast cancer. *J. Natl. Cancer Inst*. 87:1254-6, 1995. PMID 7563172.
57. McCloskey DM, Casero, Jr. RA, Woster PM and Davidson NE. Induction of programmed cell death in human breast cancer cells by an unsymmetrically alkylated polyamine analogue. *Cancer Res*. 55:3233-6, 1995. PMID 7614453
58. Herman JG, Merlo A, Mao L, Lapidus RG, Issa J-P J, Davidson NE, Sidransky D and Baylin SB. Inactivation of the CDKN2/p16/MTS1 gene is frequently associated with aberrant DNA methylation in all common human cancers. *Cancer Res*. 55:4525-30, 1995. PMID 7553621
59. Graff JR, Herman JG, Lapidus RG, Chopra H, Xu R, Jarrard DF, Isaacs WB, Pitha PM, Davidson NE and Baylin SB. E-cadherin expression is silenced by DNA hypermethylation in human breast and prostate carcinomas. *Cancer Res*. 55:5195-9, 1995. PMID 7585573

60. M^cCloskey DM, Yang J, Woster PM, Davidson NE and Casero, Jr. RA. Polyamine analog induction of programmed cell death in human lung tumor cells. *Clinical Cancer Res.* 2:441-46, 1996. PMID 4816189
61. Issa J-P, Zehnbauser BA, Civin CI, Collector M, Sharkis SJ, Davidson NE, Kaufmann SH and Baylin SB. The estrogen receptor CpG island is methylated in most hematopoietic neoplasms. *Cancer Res.* 56:973-77, 1996. PMID 8640788
62. Lapidus RG, Ferguson AT, Ottaviano YL, Parl FF, Smith HS, Weitzman SA, Baylin SB, Issa J-P and Davidson NE. Methylation of estrogen and progesterone receptor genes 5' CpG islands correlates with lack of ER and PR expression in breast tumors. *Clinical Cancer Res.* 2:805-10, 1996. PMID 9816234
63. M^cCloskey DE, Kaufmann SH, Prestigiacomo LJ and Davidson NE. Paclitaxel induces programmed cell death in MDA-MB-468 human breast cancer cells. *Clinical Cancer Res.* 2:847-54, 1996. PMID 9816240
64. Pizer ES, Jackisch C, Wood FW, Pasternack GR, Davidson NE and Kuhajda FP. Inhibition of fatty acid synthesis induces programmed cell death in human breast cancer cells. *Cancer Res.* 56:2745-7, 1996. PMID 8665507
65. Passos-Coelho JL, Ross AA, Kahn DJ, Moss TJ, Davis JM, Huelskamp AM, Noga SJ, Davidson NE and Kennedy MJ. Similiar breast cancer cell contamination of single-day peripheral blood progenitor cell (PBPC) collections obtained after priming with hematopoietic growth factor alone or after cyclophosphamide followed by growth factors. *J. Clin. Oncol.* 14:2569-75, 1996. PMID 8823337
66. Ross AA, Layton TJ, Ostrander AB, Passos-Coelho JL, Davis JM, Huelskamp AM, Noga SJ, Davidson NE, Kennedy MJ, Cooper BW, Gerson SL, Lazarus HM, Holland K, Gluck S, Moss TJ, Kaubish A, Vahdat L and Antman K. Comparative analysis of breast cancer contamination in mobilized and nonmobilized hematopoietic grafts. *J. Hematotherapy.* 5:549-52, 1996. PMID 8938527
67. Jacobson LP, Zhang B-C, Zhu Y-R, Wang J-B, Wu Y, Zhang Q-N, Yu L-Y, Qian G-S, Kuang S-Y, Li Y-F, Fang X, Zarba A, Chen B, Enger C, Davidson NE, Gorman MB, Gordon GB, Prochaska HJ, Enger PA, Groopman JD, Muñoz A, Helzlsouer KJ and Kensler TW. Oltipraz chemoprevention trial in Qidong, People's Republic of China: Study design and clinical outcomes. *Cancer Epidemiol. Biomarkers Prev.* 6:257-65, 1997. PMID 9107431
68. ASCO Breast Cancer Surveillance Expert Panel (Schapira DV and Davidson, NE, co-chairs), Recommended breast cancer surveillance guidelines, *J. Clin. Oncol.* 15:2149-2156, 1997. PMID 9164230
69. Ferguson AT, Vertino PM, Spitzner JR, Baylin SB, Muller MT and Davidson NE. Role of estrogen receptor gene demethylation and DNA methyltransferase-DNA adduct formation in 5-aza-2'-deoxycytidine-induced cytotoxicity in human breast cancer cells. *J. Biol. Chem.* 272:32260-6, 1997. PMID 9405430
70. Dees EC and Davidson NE. Management of early stage breast cancer: interventions and their effectiveness. *Dis. Management Health Outcomes.* 2:270-280, 1997.
71. Ferguson AT and Davidson NE. Regulation of estrogen receptor α function in breast cancer. *Crit. Rev. Oncogenesis.* 8:29-46, 1997. PMID 9516085
72. Zhang B-C, Zhu Y-R, Wang J-B, Zhang Q-N, Qian G-S, Kuang S-Y, Li Y-F, Fang X, Yu L-Y, DeFlora S, Jacobson LP, Zarba A, Enger PA, He X, Wang J-S, Chen B, Enger CL, Davidson NE, Gordon GB, Gorman MB, Prochaska HJ, Groopman JD, Muñoz A, Helzlsouer KJ and Kensler TW. Oltipraz chemoprevention trial in Qidong, Jiangsu

- Province, People's Republic of China. *J. Cell. Biochem. Suppl* 28/29:166-173, 1997. PMID 9589363
73. Kensler TW, He X, Otieno M, Egner PA, Jacobson LP, Chen B, Wang J-S, Zhu Y-R, Zhang B-C, Wang J-B, Wu Y, Zhang Q-N, Qian GS, Kuang S-Y, Fang X, Li Y-F, Yu L-Y, Prochaska HJ, Davidson NE, Gordon GB, Gorman MB, Zarba A, Enger C, Muñoz A, Helzlsouer KJ, and Groopman JD. Oltipraz chemoprevention trial in Qidong, People's Republic of China: Modulation of serum aflatoxin albumin adduct biomarkers. *Cancer Epidemiol Biomarkers Prev.* 7:127-134, 1998. PMID 9488587
 74. Lapidus RG, Nass SJ and Davidson NE. The loss of estrogen and progesterone receptor gene expression in human breast cancer. *J. Mammary Gland Biol. Neoplasia.* 3:85-94, 1998. PMID 10819507
 75. Ferguson AT, Lapidus RG and Davidson NE. Demethylation of the progesterone receptor CpG island is not required for progesterone receptor gene expression. *Oncogene.* 17:577-83, 1998. PMID 9704923
 76. Lapidus RG, Nass SJ, Butash KA, Parl FF, Weitzman SA, Graff JG, Herman JG and Davidson NE. Mapping of ER gene CpG island methylation by methylation specific PCR. *Cancer Res.* 58:2515-9, 1998. PMID 9635570
 77. Davidson NE. Environmental estrogens and breast cancer risk. *Current Opinion in Oncology.* 10:475-478, 1998. PMID 9800120
 78. Hahm HA and Davidson NE. Apoptosis in the mammary gland and breast cancer. *Endocrine-Related Cancer.* 5:199-211, 1998.
 79. Hahm HA, Davidson NE, Giguere JK, DiBernardo C and O'Reilly S. Breast cancer metastatic to the choroid. *J. Clin. Oncol.* 16:2280-2, 1998. PMID 9626232
 80. Davidson NE, Hahm HA, McCloskey DE, Woster PM and Casero, Jr. RA. Clinical aspects of cell death in breast cancer: the polyamine pathway as a new target for treatment. *Endocrine-Related Cancer.* 6:69-73, 1999. PMID 10732790
 81. Mikhak B, Zahvrak M, Abeloff M, Fetting JH, Davidson NE, Donehower R, Waterfield W and Kennedy MJ. Long-term follow-up of women treated with 16-week dose intense adjuvant chemotherapy for high risk breast cancer. *Cancer.* 85:899-904, 1999. PMID 10091768
 82. Subramanyan S, Abeloff MD, Bond SE, Davidson NE, Fetting JH and Kennedy MJ. A phase I study of vinorelbine, doxorubicin, and methotrexate with leucovorin rescue as first-line treatment for metastatic breast cancer. *Cancer Chemother Pharmacol.* 43:497-502, 1999. PMID 10321510
 83. Kottke T, Blajeski AL, Martins M, Mesner, Jr. PW, Davidson NE, Earnshaw WC, Armstrong DK and Kaufmann SH. Comparison of paclitaxel, 5-fluoro-2-deoxyuridine-, and epidermal growth factor-induced apoptosis: evidence for EGF-induced anoikis. *J. Biol. Chem.* 274:15927-15936. 1999. PMID 10336499.
 84. Recht A, Gray R, Davidson NE, Fowble BL, Solin LJ, Cummings FJ, Falkson G, Falkson HC, Taylor, IV SG and Tormey DC. Local-regional failure ten years following mastectomy and adjuvant chemotherapy with or without tamoxifen without irradiation: experience of the Eastern Cooperative Oncology Group. *J. Clin. Oncol.* 17:1689-1700, 1999. PMID 10561205
 85. Smith TJ, Davidson NE, Schapira DV, et al. American Society of Clinical Oncology 1998 Update of recommended breast cancer surveillance guidelines. *J. Clin. Oncol.* 17:1080-1082, 1999. PMID 10071303

86. Nass SJ and Davidson NE. The biology of breast cancer. *Hematol. Oncol. Clin. North Am.* 13:311-332, 1999. PMID 10363133
87. Wolff AC and Davidson NE. New data on adjuvant therapy for breast cancer. *Curr. Oncol. Rep.* 1:31-37, 1999. PMID 11122795
88. Nass SJ, Ferguson AT, El-Ashry D, Nelson WG, and Davidson NE. Expression of DNA methyltransferase (DMT) and the cell cycle in human breast cancer cells. *Oncogene.* 18:7453-7461, 1999. PMID 10602504
89. McCloskey DE, Woster PM, Casero, Jr. RA, and Davidson NE. Effects of the polyamine analogs CPENSp^m and CHENSp^m in human prostate cancer cells. *Clinical Cancer Res.* 6:17-23, 2000. PMID 10656427.
90. Wolff AC and Davidson NE. Primary systemic therapy in breast cancer. *J. Clin. Oncol.* 18:1558-1569, 2000. PMID 10735905
91. Jackisch C, Hahm HA, Tombal B, McCloskey D, Butash K, Davidson NE and Denmeade SR. Delayed micromolar elevation in intracellular calcium precedes induction of apoptosis in thapsigargin-treated breast cancer cells. *Clin Cancer Res.* 6:2844-2850, 2000. PMID 10914733
92. Carlson RW, Anderson BO, Bensinger W, Cox CE, Davidson NE, Edge SB, Farrar WB, Goldstein LJ, Gradishar WJ, Lichter AS, McCormick B, Nabell LM, Reed EC, Silver SM, Smith ML, Somlo G, Theriault R, Ward JH, Winer EP, Wolff A; National Comprehensive Cancer Network. NCCN Practice Guidelines for Breast Cancer Oncology (Williston Park). 14(11A):33-49, 2000. PMID 11195418.
93. Hahm HA, Armstrong DK, Chen T-L, Grochow LB, Goodman SN, Davidson NE and Kennedy MJ. Novobiocin in combination with high-dose chemotherapy for the treatment of advanced breast cancer: a phase 2 study. *Biology of Blood and Marrow Transplantation.* 6:335-343, 2000. PMID 10905771
94. Nass SJ, Herman JG, Gabrielson E, Iversen PW, Parl FF, Davidson NE, and Graff JR. Aberrant methylation of the estrogen receptor and E-cadherin 5' CpG islands increases with malignant progression in human breast cancer. *Cancer Res.* 60:4346-4348, 2000. PMID 10969774
95. van der Wall E, Horn T, Bright E, Passos-Coelho JL, Bond S, Clarke B, Altomonte V, McIntyre K, Vogelsang G, Noga SJ, Davis JM, Thomassen J, Oly KV, Lee SM, Fetting J, Armstrong DK, Davidson NE, Hess AD and Kennedy MJ. Autologous graft-versus-host disease induction in advanced breast cancer: role of peripheral blood progenitor cells. *Br. J. Cancer.* 83:1405-1411, 2000. PMC2363431
96. Yang X, Ferguson AT, Nass SJ, Phillips DL, Butash KA, Wang SM, Herman JG and Davidson NE. Transcriptional activation of estrogen receptor α in human breast cancer cells by histone deacetylase inhibition. *Cancer Res.* 60:6890-6894, 2000. PMID 11156387
97. Anderson BO, Bensinger W, Cox CE, Davidson NE, Edge SB, Farrar WB, Goldstein LJ, Gradishar WJ, Lichter AS, McCormick B, Nabell LM, Reed EC, Silver SM, Smith ML, Somio G, Theriault R, Ward JH, Winer EP and Wolff A. NCCN practice guidelines for breast cancer. *Oncology (Huntingt)* 14:33-49, 2000. PMID 11195418
98. Wolff AC and Davidson NE. Early operable breast cancer. *Curr Treat Options Oncol.* 1(3): 210-220, 2000. PMID 12057163
99. Hahm HA, Dunn VR, Butash KA, Deveraux WL, Woster PM, Casero RA, Jr., and Davidson NE. Combination of standard cytotoxic agents with polyamine analogs in the treatment of breast cancer cell lines. *Clin. Cancer Res.* 7:391-399, 2001. PMID 11234895

100. Yan L, Yang X and Davidson NE. Role of DNA methylation and histone acetylation in steroid receptor expression in breast cancer. *J. Mammary Gland Biol. Neoplasia*. 6:183-192, 2001. PMID 11501578
101. Yang X, Yan L and Davidson NE. DNA methylation in breast cancer. *Endocrine-Related Reviews*. 8:115-127, 2001. PMID 11446343
102. Dees EC and Davidson NE. Ovarian ablation as adjuvant therapy for breast cancer. *Seminars in Oncology*. 28:322-33, 2001. PMID 11498826
103. Evron E, Dooley WC, Umbricht CB, Rosenthal D, Sacchi N, Gabrielson E, Soito AB, Hung DT, Ljung B-M, Davidson NE and Sukumar S. Detection of breast cancer cells in ductal lavage fluid by methylation-specific PCR. *The Lancet*. 357:1335-1336, 2001. PMID 11343741
104. Davidson NE. Ovarian ablation as adjuvant therapy for breast cancer. *J. Natl. Cancer Inst. Monograph*. 30:67-71, 2001. PMID 11773295
105. Yang X, Phillips DL, Ferguson AT, Nelson WG, Herman JG, and Davidson NE. Synergistic activation of functional estrogen receptor (ER)- α by DNA methyltransferase and histone deacetylase inhibition in human ER- α -negative breast cancer cells. *Cancer Res*. 61:7025-7029, 2001. PMID 11585728
106. Wolff AC and Davidson NE. Use of SERMs for the adjuvant therapy of early-stage breast cancer. *Ann N Y Acad Sci*. 949:80-88, 2001. PMID 11795384
107. Armstrong, D.K. and Davidson, N.E. Dose intensity for breast cancer. *Breast Disease*. 14:91-97, 2001. PMID 15687639
108. Wolff AC and Davidson NE. Preoperative therapy in breast cancer: lessons from the treatment of locally advanced disease. *The Oncologist*. 7:239-245, 2002. PMID 12065797.
109. Emens LA, Kennedy MJ, Fetting JH, Davidson NE, Garrett E and Armstrong DK. A phase I toxicity and feasibility trial of sequential dose-dense induction chemotherapy with doxorubicin, paclitaxel, and 5-fluorouracil followed by high dose consolidation for high-risk primary breast cancer. *Breast Cancer Res Treat*. 76:145-156, 2002. PMID 12452452
110. Roche PC, Suman VJ, Jenkins RB, Davidson NE, Martino S, Kaufman PA, Addo FK, Murphy B, Ingle JN and Perez EA. Concordance between local and central laboratory HER 2 testing in the Breast Intergroup Trial N9831. *J Natl Cancer Inst*. 94:855-7, 2002. PMID 12048274
111. Keen JC and Davidson NE. The biology of breast cancer. *Cancer*. 97 (3 supp): 825-833, 2003. PMID 12548582
112. Visvanathan K and Davidson NE. Aromatase inhibitors as adjuvant therapy in breast cancer. *Oncology*. 17:335-42, 2003. PMID 19577386
113. Citron ML, Berry DA, Cirincione C, Hudis C, Winder EP, Gradishar WJ, Davidson NE, Martino S, Livingston R, Ingle JN, Perez EA, Carpenter J, Hurd D, Holland JF, Smith BL, Sartor CI, Leung E, Abrams J, Schilsky RL, Muss HB and Norton L. Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: first report of Intergroup trial 9741/Cancer and Leukemia Group B trial 9741. *J Clin Oncol*. 21:1431-9, 2003. PMID 12668651
114. Yan L, Nass SJ, Smith D, Nelson WG, Herman JG and Davidson NE. Specific inhibition of DNMT 1 by antisense oligonucleotides induces re-expression of estrogen receptor α (ER) in ER-negative human breast cancer cell lines. *Cancer Biology and Therapy*. 2:552-6, 2003. PMID 14614325

115. Keen JC, Yan L, Mack KM, Pettit C, Smith D, Sharma D and Davidson NE. A novel histone deacetylase inhibitor, scriptaid, enhances expression of functional estrogen receptor alpha (ER) in ER-negative human breast cancer cells in combination with 5-aza-2' deoxycytidine. *Breast Cancer Res Treatment*. 81:177-86, 2003. PMID 14620913
116. Wolff AC, Armstrong DK, Fetting JH, Carducci MK, Riley CD, Bender JF, Casero, Jr. RA, and Davidson NE. A phase II study of the polyamine analog N1-N11-diethylnorspermine daily for five days every 21 days in patients with previously treated metastatic breast cancer. *Clinical Cancer Res*. 9:5922-5928, 2003. PMID 14676116
117. Davidson NE, Visvanathan K, Emens L. New findings about endocrine therapy for breast cancer. *The Breast*. 12:368-372, 2003. PMID 14659107
118. Zhu K, Davidson NE, Hunter S, Yang X, Payne-Wilks K, Roland CL, Phillips D, Bentley C, Dai M, Williams SM. Methyl-group dietary intake and risk of breast cancer among African-American women: a case-control study by methylation status of the estrogen receptor alpha gene. *Cancer Causes Control*. 14:827-836, 2003. PMID 14682440
119. Goss PE, Ingle JN, Martino S, Robert NJ, Muss HB, Piccart MJ, Castiglione M, Tu D, Shepherd LE, Pritchard KI, Livingston RB, Davidson NE, Norton L, Perez EA, Abrams JS, Therasse P, Palmer MJ and Pater JL. A randomized trial of letrozole in postmenopausal women after five years of tamoxifen therapy for early-stage breast cancer. *N Engl J Med*. 349:1793-1802, 2003. PMID 14551341
120. Emens LA and Davidson NE. The follow-up of breast cancer. *Semin Oncol*. 338-348, 2003. PMID 12870135
121. Huang Y, Hager ER, Phillips DL, Dunn VR, Hacker A, Frydman B, Kink JA, Valasinas AL, Reddy VK, Marton LJ, Casero RA, Jr. and Davidson NE. A novel polyamine analog inhibits growth and induces apoptosis in human breast cancer cells. *Clin Cancer Res*. 9:2769-2777, 2003. PMC3625930
122. Kumar SK, Hager E, Pettit C, Gurulingappa H, Davidson NE and Khan SR. Design, synthesis, and evaluation of novel boronic-chalcone derivatives as antitumor agents. *J Med Chem*. 46:2813-2815, 2003. PMID 12825923
123. Emens LA and Davidson NE. Adjuvant hormonal therapy for premenopausal women with breast cancer. *Clin Can Res*. 9(1 Pt 2):486S-94S, 2003. PMID 12538505.
124. Come SE, Buzdar AU, Arteaga CL, Brodie AM, Davidson NE, Dowsett M, Ingle JN, Johnston SR, Lee AV, Osborne CK, Pritchard KI, Vogel VG, Winer EP and Hart CS. Second international conference on recent advances and future directions in endocrine manipulation of breast cancer: summary consensus statement. *Clin Cancer Res*. 9(1 Pt 2) 443S-446S, 2003. PMID 12538498
125. Yang X, Groshen S, Formenti SC, Davidson NE and Press MF. P7 antigen expression in human breast cancer. *Clin Cancer Res*. 9:201-206, 2003. PMID 12538470.
126. Huang Y, Keen JC, Hager E, Smith R, Frydman B, Valasinas AL, Reddy VK, Marton LJ, Casero, Jr. RA and Davidson NE. Regulation of polyamine analogue cytotoxicity by c-jun in human MDA-MB-435 cancer cells. *Molecular Cancer Res*. 2:81-88, 2004. PMID 14985464
127. Stearns V, Davidson NE and Flockhart DA. Pharmacogenetics in the treatment of breast cancer. *The Pharmacogenomics Journal*. 4:143-53, 2004. PMID 15024382
128. Gabrielson E, Tully E, Hacker A, Pegg A, Davidson N and Casero R. Induction of spermidine/spermine N1-acetyltransferase (SSAT) in breast cancer tissues treated with the

- polyamine analogue N1-N11-diethylnorspermine. *Cancer Chemotherapy Pharmacol.* 54:122-6, 2004. PMID 15138709
129. Emens LA, Armstrong D, Biedrycki B, Davidson NE, Sproul-Davis, Janice, Fetting, John, Jaffee E, Onmiers B, Piantadosi S, Reilly RT, Stearns V, Tartakovsky I, Visvanathan K and Wolff A. A phase I vaccine safety and chemotherapy dose-finding trial of an allogeneic GM-CSF-secreting breast cancer vaccine given in a specifically timed sequence with immunomodulatory doses of cyclophosphamide and doxorubicin. *Human Gene Therapy.* 15:313-337, 2004. PMID 15018740
 130. Prowell TM and Davidson NE. What is the role of ovarian ablation in the management of primary and metastatic breast cancer today? *The Oncologist.* 9:507-17, 2004. PMID 15477635
 131. Emens LA and Davidson NE. Trastuzumab in breast cancer. *Oncology.* 18: 1117-1138, 2004. PMID 15471197.
 132. Perez EA, Suman VJ, Davidson NE, Kaufman PA, Martino S, Dakhil SR, Ingle JN, Rodeheffer RJ, Gersh BJ, Jaffe AS. Effect of doxorubicin plus cyclophosphamide on left ventricular ejection fraction in patients with breast cancer in the North Central Cancer Treatment Group N9831 Intergroup adjuvant trial. *J Clin Oncol.* 22:3700-4, 2004. PMID 15365066
 133. Mock V, Frangakis C, Davidson NE, Ropka ME, Pickett M, Poniatowski B, Stewart K, Cameron L, Zawacki K, Podewils LJ, Cohen G and McCorkle R. Exercise manages fatigue during breast cancer treatment: a randomized controlled trial. *Psycho-Oncology.* 14:464-77, 2005. PMID 15484202
 134. Jacobs MA, Ouwerkerk R, Wolff AC, Stearns V, Bottomley PA, Barker PB, Argani P, Khouri N, Davidson NE, Bhujwala ZM, and Bluemke DA. Multiparametric and multinuclear magnetic resonance imaging of human breast cancer: current applications. *Technology in Cancer Research & Treatment.* 3:543-50, 2004. PMID 15560711
 135. Sparano JA, Bernardo P, Stephenson P, Gradishar WJ, Ingle JN, Zucker S, and Davidson NE. Randomized phase III trial of marimastat versus placebo in patients with metastatic breast cancer who have responding or stable disease after first-line chemotherapy: Eastern Cooperative Group trial E2196. *J Clin Oncol.* 22:4683-90, 2004. PMID 15570070
 136. Keen JC, Garrett-Mayer E, Pettit C, Mack KM, Manning J, Herman JG, and Davidson NE. Epigenetic regulation of protein phosphatase 2A (PP2A), lymphotactin (XCL1) and estrogen receptor alpha (ER) expression in human breast cancer cells. *Cancer Biol Ther.* 3:1304-12, 2004. PMID 15662126
 137. Huang Y, Pledgie A, Casero RA and Davidson NE. Molecular mechanisms of polyamine analogues in cancer cells, *Anti-Cancer Drugs.* 16: 229-41, 2005. PMID 15711175
 138. Davis-Sproul JM, Harris MP, Davidson NE, Kobrin BJ, Jaffee EM, and Emens LA. Cost-effective manufacture of an allogeneic GM-CSF-secreting breast tumor vaccine in an academic cGMP facility. *Cytotherapy.* 1:46-56, 2005. PMID 16040383
 139. Agoston AT, Argani P, Yegnasubramanian S, De Marzo AM, Ansari-Lari MA, Hicks JL, Davidson NE, Nelson WG. Increased protein stability causes DNA methyltransferase 1 dysregulation in breast cancer. *J Biol Chem.* 280:18302-10, 2005. PMID 15755728
 140. Sharma D, Blum J, Yang X, Beaulieu N, Macleod AR, Davidson NE. Release of methyl CpG binding proteins and histone deacetylase 1 from the estrogen receptor alpha (ER) promoter upon reactivation in ER-negative human breast cancer cells. *Mol Endocrinol.* 19:1740-51, 2005. PMID 15746193

141. Goss P, Ingle J, Martino S, Robert N, Muss H, Piccart M, Castiglione M, Tu D, Shepherd L, Pritchard K, Livingston R, Davidson NE, Norton L, Perez E, Abrams J, Cameron DA, Palmer M, Pater J. Randomized trial of letrozole following tamoxifen as extended adjuvant therapy in receptor positive breast cancer: NCIC CTG MA.17. *J Natl Cancer Inst.* 97:1262-71, 2005. PMID 16145047
142. Davidson NE, O'Neill AM, Vukov AM, Osborne CK, Martino S, White DR, and Abeloff MD. Chemoendocrine therapy for premenopausal women with axillary lymph node-positive, steroid hormone receptor-positive breast cancer: results from INT 0101 (E5188). *J Clin Oncol.* 23:5973-82, 2005. PMID 16087950
143. Huang Y, Pledge A, Rubin E, Marton LJ, Woster PM, Casero RA, and Davidson NE. Role of p53/p21Waf1/Cip1 in the regulation on polyamine analogue-induced growth inhibition and cell death in human breast cancer cells. *Cancer Biol Ther.* 4:1006-13, 2005. PMC 3639297. NIHMS 453467
144. Keen JC, Zhou Q, Park BH, Pettit C, Mack KM, Blair B, Brenner K, and Davidson NE. Protein phosphatase 2A regulates estrogen receptor alpha (ER) expression through modulation of ER mRNA stability. *J Biol Chem.* 280:29519-24, 2005. PMID 15965230.
145. Li J, Orlandi R, White CN, Rosenzweig J, Zhao J, Seregini E, Morelli D, Yu Y, Meng XY, Zhang Z, Davidson NE, Fung ET, and Chan DW. Independent validation of candidate breast cancer serum biomarkers identified by mass spectrometry. *Clin Chem.* 51:2229-35, 2005. PMID 16223889
146. Romond EH, Perez EA, Bryant J, Suman VJ, Geyer CE Jr, Davidson NE, et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. *N Engl J Med.* 353:1673-84, 2005. PMID 16236738
147. Wolff AC, O'Neill A, Kennedy MJ, Stewart JA, Gradishar WJ, Lord RS 3rd, Davidson NE, Wood WC. Single-agent topotecan as first-line chemotherapy in women with metastatic breast cancer: final results of Eastern Cooperative Oncology Group trial E8193. *Clin Breast Cancer.* 4:334-9, 2005. PMID 16277884
148. Pledge A, Huang Y, Hacker A, Zhang Z, Woster PM, Davidson NE, Casero RA Jr. Spermine oxidase SMO (PAOh1), not N1-acetylpolyamine oxidase PAO, is the primary source of cytotoxic H₂O₂ in polyamine analogue-treated human breast cancer cell lines. *J Biol Chem.* 280: 39843-51, 2005. PMID 16207710
149. Davidson NE, Morrow M, Kopans DB, Koerner FC. Case records of the Massachusetts General Hospital. Case 35-2005. A 56-year-old woman with breast cancer and isolated tumor cells in a sentinel lymph node. *N Engl J Med.* 353: 2177-85, 2005. PMID 16291988
150. Yager JD and Davidson NE. Estrogen carcinogenesis in breast cancer. *N Engl J Med.* 354:270-82, 2006. PMID 16421368
151. Zucker S, Wang M, Sparano JA, Gradishar WJ, Ingle JI, Davidson NE. Plasma MMP-7 and MMP-9 in patients with metastatic breast cancer treated with marimastat or placebo: Results of an Eastern Cooperative Oncology Group Trial (E2196). *Clinical Breast Cancer.* 6:525-9, 2006. PMID 16595036
152. Modzelewska A, Pettit C, Achanta G, Davidson NE, Huang P, Khan SR. Anticancer activities of novel chalcone and bis-chalcone derivatives. *Bioorg Med Chem.* 14:3491-5, 2006. PMID 16434201
153. Ingle JI, Tu D, Pater JL, Martino S, Robert NJ, Muss HB, Piccart MJ, Castiglione M, Shepherd LE, Pritchard KI, Livingston RB, Davidson NE, Norton L, Perez EA, Abrams JS, Cameron DA, Palmer MJ, Goss PE. Duration of letrozole treatment and outcomes in the

- placebo-controlled NCIG CTG MA.17 extended adjuvant therapy trial. *Breast Cancer Res Treat.* 99:295-300, 2006. PMID 16541302
154. Carlson RW, O'Neill A, Goldstein L, Sikic BI, Abramson N, Stewart JA, Davidson NE, Wood WC., A pilot phase II trial of valspodar modulation of multidrug resistance to paclitaxel in the treatment of metastatic carcinoma of the breast (E1195): A trial of the Eastern Cooperative Oncology Group. *Cancer Investigation.* 24:677-81, 2006. PMID 17118777
 155. Fackler MJ, Malone K, Zhang Z, Schilling E, Garrett-Mayer E, Swift-Scanlon T, Lange J, Nayar R, Davidson NE, Khan SA, Sukumar S. Quantitative multiplex-methylation specific PCR analysis doubles detection of tumor cells in breast ductal fluid. *Clinical Cancer Res.* 12:3306-10, 2006. PMID 16740751
 156. Huang Y, Keen JC, Pledgie A, Marton LJ, Zhu T, Sukumar S, Park BH, Blair B, Brenner K, Casero RA Jr, Davidson NE. Polyamine analogues down-regulate estrogen receptor alpha expression in human breast cancer cells. *J Biol Chem.* 281:19055-63, 2006. PMC3623667
 157. Perez EA, Suman VJ, Davidson NE, Martino S, Kaufman PA, Lingle WL, Flynn PJ, Ingle JN, Visscher D, Jenkins RB. HER2 testing by local, central, and reference laboratories in specimens from the North Central Cancer Treatment Group N9831 Intergroup adjuvant trial. *J Clin Oncol.* 24:3032-8, 2006. PMID 16809727
 158. Brown RJ, Davidson NE. Adjuvant hormonal therapy for premenopausal women with breast cancer. *Seminars in Oncology.* 33:657-663, 2006. PMID 17145345
 159. Khatcheressian JL, Wolff AC, Smith TJ, Greenfield E, Muss HB, Vogel VG III, Halberg F, Somerfield MR, Davidson NE. American Society of Clinical Oncology 2006 update of the breast cancer follow-up and management guidelines in the adjuvant setting, *J Clin Oncol.* 24:5091-5097, 2006. PMID 17033037
 160. Wolff AC, Jones RJ, Davidson NE, Jeter SC, Stearns V. Myeloid toxicity in breast cancer patients receiving adjuvant chemotherapy with pegfilgrastim support. *J Clin Oncol.* 5:24: 2392-4, 2006. PMID 16710041
 161. Sharma D, Saxena NK, Davidson NE, Vertino PM, Restoration of tamoxifen sensitivity in estrogen receptor-negative breast cancer cells: tamoxifen-bound reactivated ER recruits distinctive corepressor complexes. *Cancer Res.* 66:6370-8, 2006. PMC2925469
 162. Abukhdeir AM, Blair BG, Brenner K, Karakas B, Konishi H, Lim J, Sahasranaman V, Huang Y, Keen J, Davidson N, Vitolo MI, Bachman KE, Park BH. Physiologic estrogen receptor alpha signaling in non-tumorigenic human mammary epithelial cells. *Breast Cancer Res Treat.* 99:23-33, 2006. PMID 16541319
 163. Visvanathan K, Santor D, Ali SZ, Hong IS, Davidson NE, Helzlsouer KJ. The importance of cytologic intrarater and interrater reproducibility: the case of ductal lavage. *Cancer Epidemiol Biomarkers Prev.* 15:2553-6, 2006. PMID 17164385
 164. Zhou Q, Atadja P, Davidson NE. Histone deacetylase inhibitor LBH589 reactivates silenced estrogen receptor alpha (ER) gene expression without loss of DNA hypermethylation. *Cancer Biol Ther.* 6:64-69, 2007. PMID 17172825
 165. Pledgie-Tracy A, Sobolewski MD, Davidson NE. Sulforaphane induces cell type-specific apoptosis in human breast cancer cell lines. *Mol Cancer Ther.* 6:1013-1021, 2007. PMID 17339367
 166. Visvanathan K, Santor D, Ali SZ, Brewster A, Arnold A, Armstrong DK, Davidson NE, Helzlsouer KJ. The reliability of nipple aspirate and ductal lavage in women at increased

- risk for breast cancer – a potential tool for breast cancer risk assessment and biomarker evaluation. *Cancer Epidemiol Biomarkers Prev.* 16:950-5, 2007. PMID 17507621
167. Goss PE, Ingle JN, Martino S, Robert NJ, Muss HB, Piccart MJ, Castiglione M, Tu D, Shepherd LE, Pritchard KI, Livingston RB, Davidson NE, Norton L, Perez EA, Abrams JS, Cameron DA, Palmer MJ, Pater JL. Efficacy of letrozole extended adjuvant therapy according to estrogen receptor and progesterone receptor status of the primary tumor: National Cancer Institute of Canada Clinical Trials Group MA.17. *J Clin Oncol.* 25:2006-11, 2007. PMID 17452676
 168. Briest S, Davidson NE. Aromatase inhibitors for breast cancer. *Rev Endocr Metab Disord.* 8:215-28, 2007. PMID 17486453
 169. Cornblatt BS, Ye L, Dinkova-Kostova AT, Erb M, Fahey JW, Singh NK, Chen MS, Stierer T, Garrett-Meyer E, Argani P, Davidson NE, Talalay P, Kensler TW, Visvanathan K. Preclinical and clinical evaluation of sulforaphane for chemoprevention in the breast. *Carcinogenesis.* 28:1485-90, 2007. PMID 17347138
 170. LHRH-agonists in Early Breast Cancer Overview group, Cuzick J, Ambrosine L, Davidson N, Jakesz R, Kaufmann M, Sainsbury R. Use of luteinising-hormone-releasing hormone agonists as adjuvant treatment in premenopausal patients with hormone-receptor-positive breast cancer: a metaanalysis of individual patient data from randomized adjuvant trials. *Lancet.* 369: 1711-23, 2007. PMID 17512856
 171. Sui M, Huang Y, Park BH, Davidson NE, Fan W. Estrogen receptor α mediates breast cancer cell resistance to paclitaxel through inhibition of apoptotic cell death. *Cancer Res.* 67:5337-44, 2007. PMID 17545614
 172. Miller K, Wang M, Gralow J, Dickler M, Cobleigh M, Perez EA, Shenkier T, Cella D, Davidson NE. Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. *N Engl J Med.* 357:2666-76, 2007. PMID 18160686
 173. Gralow J, Ozols RF, Bajorin DF, Cheson BD, Sandler HM, Winer EP, Bonner J, Demetri GD, Curran W Jr, Ganz PA, Kramer BS, Kris MG, Markman M, Mayer RJ, Raghavan D, Ramsey S, Reaman GH, Sawaya R, Schuchter LM, Sweentenham JW, Vahdat LT, Davidson NE, Schilsky RL, Lichter AS. Clinical cancer advances 2007: major research advances in cancer treatment, prevention, and screening. A report from the American Society of Clinical Oncology. *J Clin Oncol.* 26:313-25, 2008. PMID 18086794
 174. Stearns V, Zhou Q, Davidson NE. Epigenetic regulation as a new target for breast cancer therapy. *Cancer Invest.* 25:659-65, 2007. PMID 18058459
 175. Bao T, Davidson NE. How we maintain bone health in early stage breast cancer patients on aromatase inhibitors, *J Oncology Practice.* 3:323-5, 2007. PMC2793755
 176. Bao T, Davidson NE. Adjuvant endocrine therapy for premenopausal women with early breast cancer. *Breast Cancer Research.* 9:115-7, 2007. PMC2246185
 177. Goss PE, Ingle JN, Pater JL, Martino S, Robert NJ, Muss HB, Piccart MJ, Castiglione M, Shepherd LE, Pritchard KI, Livingston RB, Davidson NE, Norton L, Perez EA, Abrams JS, Cameron DA, Palmer MJ, Tu D. Late extended adjuvant treatment with letrozole improves outcome in women with early-stage breast cancer completing 5 years of tamoxifen. *J Clin Oncol.* 26:1948-55, 2008. PMID 18332475
 178. Perez EA, Suman VJ, Davidson NE, Sledge GW, Kaufman PA, Hudis CA, Martino S, Gralow JR, Dakhil SR, Ingle JN, Winer EP, Gelmon KA, Gersh BJ, Jaffe AS, and Rodeheffer RJ. Cardiac safety analysis of doxorubicin and cyclophosphamide followed by

- paclitaxel with or without trastuzumab in the North Central Cancer Treatment Group N9831 adjuvant breast cancer trial. *J Clin Oncol.* 26:1231-8, 2008. PMC 4048960, NIHMS 589003
179. Ingle JN, Tu D, Pater JL, Muss HB, Martino S, Robert NJ, Piccart MJ, Castiglione M, Shpeher LE, Pritchard KI, Livingston RB, Davidson NE, Norton L, Perez EA, Abrams JS, Cameron DA, Palmer MJ, Goss PE. Intent-to-treat analysis of the placebo-controlled trial of letrozole for extended adjuvant therapy in early breast cancer: NCIC CTG MA.17. *Ann Oncol.* 19:877-82, 2008. PMID 18332043
 180. Badve SS, Baehner FL, Gray RP, Childs BH, Maddala T, Liu M-L, Rowley SC, Shak SA, Perez ED, Shulman LJ, Martino SG, Davidson NE, Sledge GW, Goldstein LJ, Sparano JA. Estrogen and progesterone receptor status in ECOG 2197: comparison of immunohistochemistry by local and central laboratories and quantitative reverse transcription polymerase chain reaction by central laboratories. *J Clin Oncol.* 26:2473-81, 2008. PMID 18487567
 181. Wu JM, Fackler MJ, Halushka MK, Molavi DW, Taylor E, Teo WW, Griffin C, Fetting J, Davidson NE, Demarzo AM, Hicks JL, Chitale D, Ladanyi M, Sukumar S, Argani P. Heterogeneity of breast cancer metastases: comparison of therapeutic target expression and promoter methylation between primary tumors and their multifocal metastases. *Clinical Cancer Res.* 14:1938-46, 2008. PMC2965068
 182. Zhou Q, Agoston AT, Atadja P, Nelson V WG, and Davidson NE. Inhibition of histone deacetylases promotes ubiquitin-dependent proteasomal degradation of DNA methyltransferase 1 in human breast cancer cells, *Molecular Cancer Res.* 6:873-83, 2008. PMC3361136
 183. Goldstein L, Gray R, Badve S, Childs BH, Yoshizawa C, Rowley S, Shak S, Baehner FL, Ravdin PM, Davidson N, Sledge G, Perez E, Shulman L, Martino S, Sparano JA. Prognostic utility of the 21-gene assay in hormone receptor-positive operable breast cancer compared with classical clinicopathologic features. *J Clin Oncol.* 26:4063-71, 2008. PMC2654377
 184. Goldstein LJ, O'Neill AM, Sparano JA, Perez EA, Shulman LN, Martino S, Davidson NE. Concurrent doxorubicin plus docetaxel is not more effective than concurrent doxorubicin plus cyclophosphamide in operable breast cancer with 0-3 positive axillary nodes: results of North American Breast Cancer Intergroup Trial E2197, *J Clin Oncol.* 26:4092-9, 2008. PMC2654376
 185. Schneider BP, Wang M, Radovich M, Sledge GW, Badve S, Thor A, Flockhart DA, Hancock B, Davidson N, Gralow J, Dickler M, Perez EA, Cobleigh M, Shenkier T, Edgerton S, Miller KD. Association of VEGF and VEGFR-2 genetic polymorphisms with outcome in E2100. *J Clin Oncol.* 26:4672-8, 2008. PMC2653128
 186. Sparano JA, Wang M, Martino S, Jones V, Perez EA, Saphner T, Wolff AC, Sledge Jr GW, Wood WC, Davidson NE. Weekly paclitaxel in the adjuvant treatment of breast cancer. *N Engl J Med.* 358:1663-71, 2008. PMID 18420499. PMC2743943
 187. Davidson NE. Tracking 35 years of progress against breast cancer. *Oncology.* 22(6):593-53, 2008. PMID 18561549.
 188. Arteaga CL, O'Neill A, Moulder SL, Pins M, Sparano JA, Sledge GW, and Davidson NE. A phase I-II study of combined blockade of the erbB receptor network with trastuzumab and gefitinib in patients with HER2 (erbB-2)-overexpressing metastatic breast cancer. *Clin Cancer Res.* 14:6277-6283, 2008. PMC2925197

189. Bao T, Davidson NE. Gene expression profiling of breast cancer. *Adv Surg.* 42:249-60, 2008. PMC2775529
190. Fall-Dickson JM, Mock V, Berk RA, Grimm PM, Davidson N, Gaston-Johansson F. Stomatitis-related pain in women with breast cancer undergoing autologous hematopoietic stem cell transplant. *Cancer Nurs.* 31:452-61, 2008. PMC3508511
191. Carraway HE, Wang S, Blackford A, Guo M, Powers P, Jeter S, Davidson NE, Argani P, Terrell K, Herman JG, Lange JR. Promoter hypermethylation in sentinel lymph nodes as a marker for breast cancer recurrence. *Breast Cancer Res Treat.* 114:315-25, 2009. PMC3422075
192. Shabeer S, Sobolweski M, Anchoori R, Kachhap S, Davidson N, Carducci M, Khan SR. Fenugreek: A naturally occurring edible spice as an anticancer agent. *Cancer Biol Ther.* 8: 3, 272-8, 2009. PMC3095649
193. Halyard MY, Pisansky TM, Dueck A, Pierce LG, Solin LJ, Marks LB, Davidson NE, Martino S, Kaufman PA, Kutteh LA, Dakhil DR, Perez EA. Radiotherapy and adjuvant trastuzumab in operable breast cancer: tolerability and adverse event data from the North Central Cancer Treatment Group Phase 3 trial N9831. *J Clin Oncol.* Jun 1;27: 2638-44, 2009. PMC2690390
194. Higgins MJ, Davidson NE. What is the current status of ovarian suppression/ablation in women with premenopausal early-stage breast cancer? *Curr Oncol Rep.* 11:45-50, 2009. PMID 19080741
195. Billam M, Witt AE, Davidson NE. The silent estrogen receptor: Can we make it speak? *Cancer Biology & Therapy.* 8:6, 485-496, 2009. PMC 3901993, NIHMS 529864
196. Zellars R, Stearns V, Frassica D, Asrari F, Tsangaris T, Lyers L, DiPasquale S, Lange JR, Jacobs LK, Emens L, Armstrong DK, Fetting JH, Garrett-Mayer E, Davidson NE, Wolff AC. Feasibility trial of partial breast irradiation and concurrent dose-dense doxorubicin and cyclophosphamide. *J Clin Oncol.* 27:2816-22, 2009. PMID 19332718
197. Hughes LL, Wang M, Page DL, Gray R, Solin LJ, Davidson NE, Lowen MA, Ingle JN, Recht A, Wood WC. Local excision alone with irradiation for ductal carcinoma in situ of the breast: A trial of the Eastern Cooperative Oncology Group. *J Clin Oncol.* 27:5319-24, 2009. PMC2773217
198. Emens LA, Asquith JM, Leatherman JM, Kobrin BJ, Petrick S, Laiko M, Levi J, Daphtary MM, Biedrzycki B, Wolff AC, Stearns V, Disis ML, Ye X, Piantadosi S, Fetting JH, Davidson NE, Jaffee EM. Time sequential treatment with cyclophosphamide, doxorubicin and an allogeneic granulocyte-macrophage colony-stimulating factor secreting breast tumor vaccine: A chemotherapy dose-ranging factorial study of safety and immune activation. *J Clin Oncol.* 27:5911-8, 2009. PMC2793039
199. Billam M, Sobolewski MD, Davidson NE. Effects of a novel DNA methyltransferase inhibitor zebularine on human breast cancer cells. *Breast Cancer Res Treat.* 120:581-92, 2010. PMC 3901992, NIHMS 529877
200. Balmanoukian A, Zhang Z, Jeter S, Slater S, Armstrong DK, Emens LA, Fetting JH, Wolfe AC, Davidson NE, Jacobs L, Lanage J, Tsangaris TN, Zellars R, Gabrielson E, Stearns V. African American women who receive primary anthracycline-and taxane-based chemotherapy for triple-negative breast cancer suffer worse outcomes compared with white women. *J. Clin. Oncol.* 27:e35-7, 2009. PMID 19564528

201. Zhou Q, Shaw PG, Davidson NE. Epigenetics meets estrogen receptor: regulation of estrogen receptor by direct lysine methylation. *Endocr Relat Cancer*. 16:316-23, 2009. PMC 3901989
202. Zhou Q, Shaw PG, Davidson NE. Inhibition of histone deacetylase suppresses EGF signaling pathways by destabilizing EGFR mRNA in ER-negative human breast cancer cells. *Breast Cancer Res Treat*. 117:443-51, 2009. PMID 18683042
203. Madar I, Huang Y, Ravert H, Dalrymple SL, Davidson NE, Isaacs JT, Dannals RF, Frost JJ. Detection and quantification of the evolution dynamics of apoptosis using the PET voltage sensor 18F-fluorobenzyl triphenyl phosphonium. *J. Nucl Med*. 50:774-80, 2009. PMID 19372481
204. Sparano JA, Goldstein LJ, Childs BH, Shak S, Brassard D, Badve S, Baehner FL, Bugarini R, Rowley S, Perez E, Shulman LN, Martino S, Davidson NE, Sledge GW Jr, Gray R. Relationship between topoisomerase 2A RNA expression and recurrence after adjuvant chemotherapy for breast cancer. *Clin Cancer Res*. 7693-7700, 2009. PMC3396025
205. Emens LA, Davidson NE. Post operative endocrine therapy for invasive breast cancer. *Cancer Treat Res*. 151:139-61, 2009. PMC3086398
206. Puhalla S, Brufsky A, Davidson NE. Adjuvant endocrine therapy for premenopausal women with breast cancer. *Breast*. 18:2122-30, 2009
207. Pledge-Tracy, A, Billam M, Hacker A, Sobolewski MD, Woster PM, Zhang Z, Casero RA, Davidson NE. The role of the polyamine catabolic enzymes SSAT and SMO in the synergistic effects of standard chemotherapeutic agents with a polyamine analogue in human breast cancer cell lines. *Cancer Chemother Pharmacol*. 65: 1067, 2010. PMC2840063
208. Yao Y, Li H, Gu Y, Davidson NE, Zhou Q. Inhibition of SIRT1 deacetylase suppresses estrogen receptor signaling. *Carcinogenesis*. 31:382-387, 2010: PMC2832546
209. Zhou Q, Chaerkady R, Shaw PG, Kensler TW, Pandey A, Davidson NE. Screening for therapeutic targets of vorinostat by SILAC-based proteomic analysis in human breast cancer cells. 2010 Jan 4. *Proteomics*. 10:1029-39, 2010. PMC3337220
210. Yao Y, Brodie AM, Davidson NE, Kensler TW, Zhou Q. Inhibition of estrogen signaling activates the NRF2 pathway in breast cancer. *Breast Cancer Res Treat*. 121:111-20, 2010. PMC3417311
211. Albain KS, Barlow WE, Shak S, Hortobagyi GN, Livingston RB, Yeh IT, Ravdin P, Bugarini R, Baehner FL, Davidson NE, Sledge GW, Winer EP, Hudis C, Ingle JN, Perez EA, Pritchard KI, Shepherd L, Gralow JR, Yoshizawa C, Allred DC, Osborn CK, Hayes DF; for the Breast Cancer Intergroup of North American. Prognostic and predictive value of the 21-gene recurrence score assay in postmenopausal women with node-positive, oestrogen-receptor-positive breast cancer on chemotherapy: a retrospective analysis of a randomized trial. *Lancet Oncol*. 11:55-65, 2010 PMC3058239
212. King JC, Lawrence TS, Murphy SB, Davidson NE, Mayer RJ. The American Society of Clinical Oncology Cancer Foundation Grants Program: a 25-year report and a look toward the future. *J Clin Oncol*. 28:1616-21, 2010. PMID: 20177012
213. Wolff AC, Wang M, Li H, Pins MR, Pretorius FJ, Rowland KM, Sparano JA, Davidson NE. Phase II trial of pegylated liposomal doxorubicin plus docetaxel with and without trastuzumab in metastatic breast cancer: Eastern Cooperative Oncology Group trial E3198. *Breast Cancer Res Treat*. 121:111-20, 2010. PMC3112234
214. Burstein HJ, Prestrud AA, Seidenfeld J, Anderson H, Buchholz TA, Davidson NE et al. American Society of Clinical Oncology clinical practice guideline: update on adjuvant

- endocrine therapy for women with hormone receptor-positive breast cancer. *J Clin Oncol.* 28:3784-96, 2010 PMID 20625130
215. Perez E, Reinholz MM, Hillman DW, Tenner KS, Schroeder MJ, Davidson NE, et al. HER2 and chromosome 17 effect on patient outcome in the N9831 adjuvant trastuzumab trial. *J Clin Oncol.* 28:4307-15, 2010. PMC2954132
 216. Jacobs MA, Stearns V, Wolff AC, Macura K, Argani P, Khouri N, Tsangaris T, Barker PB, Davidson NE, Bhujwalla ZM, Bluemke DA, Ouwerkerk R. Multiparametric magnetic resonance imaging spectroscopy and multinuclear (^{23}Na) imaging monitoring of preoperative chemotherapy for locally advanced breast cancer. *Acad Radiol.* 17:1477-85, 2010. PMC3401079
 217. Davidson, NE. HER2-targeted therapies: how far we've come—and where we're headed. *Oncology.* 25(5):425-6, 2011. PMID 21710840
 218. Davidson, NE. Retrospective on the last quarter-century in medical oncology. *Oncology.* 25(5):396, 2011. PMID 21710831
 219. Connolly RM, Rudek MA, Garrett-Mayer E, Jeter SC, Donehower MG, Wright LA, Zhao M, Fetting JH, Emens LA, Stearns V, Davidson NE, Baker SD, Wolff AC. Docetaxel metabolism is not altered by imatinib: findings from an early phase study in metastatic breast cancer. *Breast Cancer Res Treat.* 127(1):153-62, 2011. PMC3111459
 220. Perez EA, Jenkins RB, Dueck AC, Wiktor AE, Bedroske PP, Anderson SK, Ketterling RP, Sukov WR, Kanehira K, Chen B, Geiger XJ, Andorfer CA, McCullough AE, Davidson NE, Martino S, Sledge GW, Kaufman PA, Jutte LA, Gralow JR, Harris LN, Ingle JN, Lingle WL, Reinholz MM. C-MYC alterations and association with patient outcome in early-stage HER2-positive breast cancer from the North Central Cancer Treatment Group N9831 adjuvant trastuzumab trial. *J Clin Oncol.* 29(6):651-9, 2011. PMID 2124520
 221. Perez EA, Suman VJ, Davidson NE, Gralow JR, Kaufman PA, Visscher DW, Chen B, Ingle JN, Dakhil SR, Jejewski J, Moreno-Aspitia A, Pisansky TM, Jenkins RB. Sequential versus concurrent trastuzumab in adjuvant chemotherapy for breast cancer. *J Clin Oncol.* 29(34):4491-7, 2011. PMC3236650
 222. Shaw PG, Chaerkady R, Zhang Z, Davidson NE, Pandey A. Monoclonal antibody cocktail as an enrichment tool for acetylome analysis. *Anal Chem.* 83(10):3623-6, 2011. PMC3205458
 223. Perez EA, Romond EH, Suman VJ, Jeong JH, Davidson, NE, Geyer CE Jr., Martino S, Mamounas EP, Kaufman PA, Wolmark N. Four-year follow up of trastuzumab plus adjuvant chemotherapy for operable human epidermal growth factor receptor 2-positive breast cancer: Joint analysis of data from NCCTG N9831 and NSABP B-31. *J Clin Oncol.* 29(25):3366-73, 2011. PMC3164242
 224. Sparano JA, Goldstein LJ, Childs BH, Shak S, Brassard D, Badve S, Baehner FL, Bugarini R, Rowley S, Perez EA, Shulman LN, Martino S, Davidson NE, Kenny PA, Sledge GW Jr, Gray R. Relationship between quantitative GRB7 RNA expression and recurrence after adjuvant anthracycline chemotherapy in triple-negative breast cancer. *Clin Cancer Res.* 17(22):7194-7203, 2011. PMC3570203
 225. Huang Y, Shaw PG, Davidson NE. Inhibition of histone deacetylases. *Methods Mol Biol.* 791:297-311, 2011. PMID 21913088
 226. Huang Y, Nayak S, Jankowitz R, Davidson NE, Oesterreich S. Epigenetics in breast cancer: what's new? *Breast Cancer Res.* 13(6):225, 2011. PMC3326545

227. Griggs JJ, Somerfield MR, Anderson H, Henry NL, Hudis CA, Khatcheressian JL, Partridge AH, Prestrud AA, Davidson NE. American Society of Clinical Oncology endorsement of the Cancer Care Ontario practice guidelines on adjuvant ovarian ablation in the treatment of premenopausal women with early-stage invasive breast cancer. *J Clin Oncol.* 29(29): 3939-42, 2011. PMID 21900112
228. Prowell TM, Blackford AL, Byrne C, Khouri NF, Dowsett M, Folkert E, Tarpinian KS, Powers PP, Wright LA, Donehower MG, Jeter SC, Armstrong DK, Emens LA, Fetting JH, Wolff AC, Garrett-Mayer E, Skaar TC, Davidson NE, Stearns V. Changes in breast density and circulating estrogens in postmenopausal women receiving adjuvant anastrozole. *Cancer Prev Res (Phila).* 4:1993-2001, 2011. PMC3700336
229. Perez EA, Suman VJ, Davidson NE, Gralow JR, Kaufman PA, Visscher DW, Chen B, Ingle JN, Dakhil SR, Zujewski J, Moreno-Aspitia A, Pisansky TM, Jenkins RB. Sequential versus concurrent trastuzumab in adjuvant chemotherapy for breast cancer. *J Clin Oncol.* 29(34):4491-7, 2011. PMC3236650
230. Shaw PH, Boyiadzis M, Tawbi H, Welsh A, Kemerer A, Davidson NE, Kim Ritchey A. Improved clinical trial enrollment in adolescent and young adult (AYA) oncology patients after the establishment of an AYA oncology program uniting pediatric and medical oncology divisions. *Cancer.* 10, 15:118(14):3614-7, 2012. PMID 22213134
231. Jin K, Kong X, Shah T, Penet MF, Wildes F, Sgroi DC, Ma XJ, Huang Y, Kallioniemi a, Landberg G, Bieche I, Wu X, Lobi PE, Davidson NE, Bhujwalla ZM, Zhu T, Sukumar S. The HOXB7 protein renders breast cancer cells resistant to tamoxifen through activation of the EGFR pathway. *Proc Natl Acad Sci,* 109(8):2736-41, 2012. PMC3286915
232. Agyman AS, Chaerkady R, Shaw PG, Davidson NE, Visvanathan K, Pandey A, Kensler TW. Transcriptomic and proteomic profiling of KEAP1 disrupted and sulforaphane-treated human breast epithelial cells reveals common expression profiles. *Breast Cancer Res Treat.* 132(1): 175-87, 2012. PMC3564494
233. Huang Y, Vasilatos SN, Boric L, Shaw PG, Davidson NE. Inhibitors of histone demethylation and histone deacetylation cooperate in regulating gene expression and inhibiting growth in human breast cancer cells. *Breast Cancer Res Treat.* 131(3):777-89, 2012. PMC3624096
234. Bardia A, Arieas ET, Zhang Z, DeFilippis A, Tarpinian K, Jeter S, Nguyen A, Henry NL, Flockhart DA, Hayes DF, Hayden J, Hayden J, Storniolo AM, Armstrong DK, Davidson NE, Fetting J, Ouyang P, Wolff AC, Blumenthal RS, Ashen MD, Stearns V. Comparison of breast cancer recurrence risk and cardiovascular disease incidence risk among postmenopausal women with breast cancer. *Breast Cancer Res Treat.* 131(3):907-14, 2012. PMC3582017
235. Zhu Q, Huang Y, Marton LJ, Woster PM, Davidson NE, Casero RA Jr. Polyamine analogs modulate gene expression by inhibiting lysine-specific demethylase 1 (LSD1) and altering chromatin structure in human breast cancer cells. *Amino Acids.* 42(2-3):887-98, 2012. PMC3240695
236. Higgins MJ, Prowell TM, Blackford AL, Byrne C, Khouri NF, Slater SA, Jeter SC, Armstrong DK, Davidson NE, Emens LA, Fetting JH, Powers PP, Wolff AC, Green H, Thibert JN, Rae JM, Folkert E, Dowsett M, Blumenthal RS, Garber JE, Stearns V. A short-term biomarker modulation study of simvastatin in women at increased risk of a new breast cancer. *Breast Cancer Res Treat.* 131(3):915-24, 2012. PMC3536477

237. Perez EA, Dueck AC, McCullough AE, Reinholz MM, Tenner KS, Davidson NE, Gralow J, Harris LN, Kutteh LA, Hillman DW, Jenkins RB, Chen B. Predictability of adjuvant trastuzumab benefit in N9831 patients using the ASCO/CAP HER2-positivity criteria. *J Natl Cancer Inst.* 18:104(2):159-62, 2012. PMC3260130
238. Sparano JA, Wang M, Zhao F, Stearns V, Martino S, Ligibel JA, Perez EA, Saphner T, Wolff AC, Sledge GW Jr, Wood WC, Davidson NE. Race and hormone receptor-positive breast cancer outcomes in a randomized chemotherapy trial. *J Natl Cancer Inst.* 104(5) 406-14, 2012. PMID 22250182. PMC3295746
239. Sparano JA, Wang M, Zhao F, Stearns V, Martino S, Ligibel JA, Perez EA, Saphner T, Wolff AC, Sledge W Jr, Wood WC, Fetting J, Davidson NE. Obesity at diagnosis is associated with inferior outcomes in hormone receptor-positive operable breast cancer. *Cancer.* 118(23):5937-46, 2012. PMC3586227
240. Hu D, Zhou Z, Davidson NE, Huang Y, Wan Y. Novel insight into KLF4 proteolytic regulation in estrogen receptor signaling and breast carcinogenesis. *J Biol Chem.* 287(17) 13584-97, 2012. PMC3340146
241. Puhalla S, Battacharya S, Davidson NE. Hormonal therapy in breast cancer: A model disease for the personalization of cancer care. *Mol Oncol.* 6(2):222-36, 2012. PMID 22406404
242. Puhalla S, Battacharya S, Davidson NE. Hematopoietic growth factors: Personalization of risks and benefits. *Mol Oncol.* 6(2):237-41, 2012. PMID 22497867
243. Sparano JA, Goldstein LJ, Davidson NE, Sledge GW Jr, Gray R. TOP2A RNA expression and recurrence in estrogen receptor-positive breast cancer. *Breast Cancer Res Treat.* 134(2):751-7, 2012. PMID 22706628
244. Solin LJ, Gray R, Goldstein LJ, Recht A, Baehner FL, Shak S, Badve S, Perez EA, Shulman LN, Martino S, Davidson NE, Sledge GW Jr, Sparano JA. Prognostic value of biologic subtype and the 21-gene recurrence score relative to local recurrence after breast conservation treatment with radiation for early stage breast carcinoma: results from the Eastern Cooperative Oncology Group E2197 study. *Breast Cancer Res Treat.* 134(2):683-92, 2012. PMC3552372
245. Schneider BP, Zhao F, Wang M, Stearns V, Martino S, Jones V, Perez EA, Saphner T, Wolff AC, Sledge GW Jr, Wood WC, Davidson NE, Sparano JA. Neuropathy is not associated with clinical outcomes in patients receiving adjuvant taxane-containing therapy for operable breast cancer. *J Clin Oncol.* 30(25):3051-7, 2012. PMC3732004
246. Zhu Q, Jin L, Casero RA, Davidson NE, Huang Y. Role of ornithine decarboxylase in regulation of estrogen receptor alpha expression and growth in human breast cancer cells. *Breast Cancer Res Treat.* 136(1):57-66, 2012. PMC3715085
247. Goss PE, Ingle JN, Martino S, Robert NJ, Muss HB, Livingston RB, Davidson NE, Perez EA, Chavarri-Guerra Y, Cameron DA, Pritchard KI, Whelan T, Shepherd LE, Tu D. Impact of premenopausal status at breast cancer diagnosis in women entered on the placebo-controlled NCIC CTG MA17 trial of extended adjuvant letrozole. *Ann Oncol.* (2):355-61, 2013. PMC3551482
248. Khatcheressian JL, Hurley P, Bantug E, Esserman LJ, Grunfield H, Halberg F, Hantel A, Henry NL, Muss HB, Smith TJ, Vogel VG, Wolff AC, Somerfield MR, Davidson NE. Breast Cancer Follow-up and management after primary treatment: American Society of Clinical Oncology Clinical Practice Guidelines Update. *J Clin Oncol.* 31(7):961-5, 2013. PMID 23129741.

249. Tevaarwerk AJ, Gray RJ, Schneider BP, Smith ML, Wagner LI, Fetting JH, Davidson N, Goldstein LJ, Miller KD, Sparano JA. Survival in patients with metastatic recurrent breast cancer after adjuvant chemotherapy: Little evidence of improvement over the past 30 years. *Cancer*. 15:119(6):1140-8, 2013. PMC 3593800
250. Schneider BP, Gray FJ, Radovich M, Shen F, Vance G, Li L, Jiang G, Miller KD, Gralow JR, Dickler MN, Cobleigh MA, Perez EA, Schenkler TN, Vang Nielsen K, Muller S, Thor A, Sledge GW Jr, Sparano JA, Davidson NE, Badve SS. Prognostic and predictive value of tumor vascular endothelial growth factor gene amplification in metastatic breast cancer treated with paclitaxel with and without bevacizumab; results from ECOG 2100 trial. *Clin Cancer Res*. 1:19(5):1281-9, 2013. PMC 3594423
251. Vasilatos SN, Katz TA, Oesterreich S, Wan Y, Davidson NE, Huang Y. Crosstalk between lysine-specific demethylase 1 (LSD1) and histone deacetylases mediates antineoplastic efficacy of HDAC inhibitors in human breast cancer cells. *Carcinogenesis*. 34(6):1196-207, 2013. PMC3670252
252. Rudek MA, Connolly RM, Hoskins JM, Garrett-Mayer E, Jeter SC, Armstrong DK, Fetting JH, Stearns V, Wright LA, Zhao M, Watkins SP Jr., McLeod HL, Davidson NE, Wolff AC. Fixed-dose capecitabine is feasible: results from a pharmacokinetic and pharmacogenetic study in metastatic breast cancer. *Breast Cancer Res Treat*. 139(1):135-43, 2013. PMC3673300
253. Solin LJ, Gray R, Baehner FL, Butler SM, Hughes LL, Yoshizawa C, Cherbavaz DB, Shak S, Page DL, Sledge GW Jr, Davidson NE, Ingle JN, Perez EA, Wood WC, Sparano JA, Badve S. A multigene expression assay to predict local recurrence risk for ductal carcinoma in situ of the breast. *J Natl Cancer Inst*. 15;105(10):701-10, 2013. PMC3653823
254. Davidson NE. Fifteen years of anti-HER2 therapy. *Oncology*. 27(3):151, 2013. PMID 23687781
255. Perez EA, Dueck AC, McCullough AE, Chen B, Geiger XJ, Jenkins RB, Lingle WL, Davidson NE, Martino S, Kaufman PA, Kutteh LA, Sledge GW, Harris LN, Gralow JR, Reinholz MM. Impact of PTEN protein expression on benefit from adjuvant trastuzumab in early-stage human epidermal growth factor receptor 2-positive breast cancer in the north central cancer treatment group N9831 trial. *J Clin Oncol*. 31(17):2115-22, 2013. PMC3731983
256. Stearns V, Jacobs LK, Fackler MJ, Tsangaris TN, Rudek MA, Higgins MJ, Lange JR, Cheng Z, Slater SA, Jeter SC, Powers P, Briest, Chao C, Yoshizawa C, Sugar E, Espinoza-Delgado I, Sukumar S, Gabrielson E, Davidson NE. Biomarker modulation following short term vorinostat in women with newly-diagnosed primary breast cancer. *Clin Cancer Res*. 19(14):4008-16, 2013. PMID 2371926. PMC3718062
257. Moreno-Aspitia A, Hillman DW, Dyer SH, Tenner KS, Gralow J, Kaufman PA, Davidson NE, Lafky JM, Reinholz MM, Lingle WL, Kutteh LA, Carney WP, Dueck AC, Perez EA. Soluble human epidermal growth factor receptor 2 (HER2) levels in patients with HER2-positive breast cancer receiving chemotherapy with or without trastuzumab: Results from North Central Cancer Treatment Group adjuvant trial N9831. *Cancer*. 119(15): 2675-82, 2013. PMID 23744760
258. Visvanathan K, Hurley P, Bantug E, Brown P, Col NF, Cuzick J, Davidson NE, Decensi A, Fabian C, Ford L, Garber J, Katapodi M, Kramer B, Marrow M, Parker B, Runowicz C, Vogel VG 3rd, Wade JL, Lippman SMA. Use of pharmacologic interventions for breast

- cancer risk reduction: American Society of Clinical Oncology Clinical Practice Guidelines. *J Clin Oncol.* 31(23): 2942-62, 2013. PMID 23835710
259. Yang L, Zahid M, Liao Y, Rogan EG, Cavalieri EL, Davidson NE, Yager JD, Visvanathan K, Groopman, JD, Kensler TW. Reduced formation of depurinating estrogen-DNA adducts by sulforaphane or KEAP1 disruption in human mammary epithelial MCF-10A cells. *Carcinogenesis.* 34 (11):2587-92, 2013. PMID 23843041. PMC3888356
 260. van Londen GJ, Beckjord EB, Dew MA, Cooper KL, Davidson NE, Bovbjerg DH, Donovan HS, Thurston RC, Morse JQ, Nutt S, Rechis R. Associations between adjuvant endocrine therapy and onset of physical and emotional concerns among breast cancer survivors. *Support Care Cancer.* 22(4):937-45, 2014. [Epub ahead of print] PMID 24271937, PMC 3987952, NIHMS 544009
 261. Shaw PG, Chaerkady R, Wang T, Vasilatos S, Huang Y, Van Houten B, Pandey A, Davidson NE. Integrated proteomic and metabolic analysis of breast cancer progression. *PLoS One.* 8(9):e76220, 2013. PMID 24086712. PMC3785415
 262. Jankowitz RC, McGuire KP, Davidson NE. Optimal systemic therapy for premenopausal women with hormone receptor-positive breast cancer. *Breast.* 22 Suppl 2:S165-70, 2013. PMID: 24074781[PubMed - in process]
 263. Dueck AC, Reinholz MM, Geiger XJ, Tenner K, Ballman K, Jenkins RB, Riehle D, Chen B, McCullough AE, Davidson NE, Martino S, Sledge GW, Kaufman PA, Kutteh LA, Gralow J, Harris LN, Ingle JN, Lingle WL, Perez EA. Impact of c-MYC protein expression on outcome of patients with early-stage HER2+ breast cancer treated with adjuvant trastuzumab NCCTG (alliance) N9831. *Clin Cancer Res.* 19(20):5798-807, 2013. PMID 23965903. PMC3805021
 264. Goldhirsch A, Winer EP, Coates AS, Gelber RD, Piccart-Gebhart M, Thürlimann B, Senn HJ; Panel members. Personalizing the treatment of women with early breast cancer: highlights of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2013 *Ann Oncol.* (9):2206-23, 2013. PMID 23917950. PMC3755334.
 265. Jankowitz RC, Davidson NE. Adjuvant endocrine therapy for breast cancer: how long is long enough? *Oncology.* 27(12):1210-6, 2013. PMID: 24624537
 266. Pathiraja TN, Nayak SR, Xi Y, Jiang S, Garee JP, Edwards DP, Lee AV, Chen J, Shea MJ, Santen RJ, Gannon F, Kangaspeska S, Jenlinek J, Issa JP, Richer JK, Elias A. McIlroy M, Young LS, Davidson NE, Schiff R, Li W, Oesterreich S. Epigenetic reprogramming of HOXC10 in endocrine-resistant breast cancer. *Sci Transl Med.* 26;6(229):229ra-41, 2014 PMID: 24670685
 267. Sikora MJ, Cooper KL, Bahreini A, Luthra S, Wang G, Chandran UR, Davidson NE, Dabbs DJ, Welm AL, Oesterreich S. Invasive lobular carcinoma cell lines are characterized by unique estrogen-mediated gene expression patterns and altered tamoxifen response. *Cancer Res.* 1;74(5):1463-74, 2014. PMID 24425047
 268. Lee AV, Davidson NE. Breast cancer in 2013: Genomics, drug approval, and optimal treatment duration. *Nat Rev Clin Oncol.* 11(2):71-2, 2014. PMID 24419301
 269. Katz TA, Vasilatos SN, Harrington E, Oesterreich S, Davidson NE, Huang Y. Inhibition of histone demethylase, LSD2 (KDM1B), attenuates DNA methylation and increases sensitivity to DNMT inhibitor-induced apoptosis in breast cancer cells. *Breast Cancer Res Treat.* 46(1)99-108, 2014. PMID 24924415
 270. Burstein HJ, Temin S, Anderson H, Buchholz TA, Davidson NE, Gelmon KE, Giordano SH, Hudis CA, Rowden D, Solky AJ, Stearns V, Winer EP, Griggs JJ. Adjuvant endocrine

- therapy for women with hormone receptor-positive breast cancer: American Society of Clinical Oncology Practice Guidelines focused update. *J Clin Oncol.* 20; 32(21) 2255-69, 2014. PMID 24868023
271. Ramakrishna N, Temin S, Chandarlapaty S, Crews JR, Davidson NE, Esteva FJ, Giordano SH, Gonzalez-Angulo AM, Kirshner JJ, Krop I, Levinson J, Modi S, Patt DA, Perez EA, Perlmutter J, Winer EP, Lin NU. Recommendation on disease management for patients with advanced human epidermal growth factor receptor 2-positive breast cancer and brain metastases: American Society of Clinical Oncology Clinical Practice Guidelines. *J Clin Oncol.* 32(19)2100-8, 2014. PMID: 24799487
 272. Giordano SH, Temin S, Kirshner JJ, Chandarlapaty S, Crews JR, Davidson NE, Esteva FJ, Gonzalez-Angulo AM, Krop I, Levinson J, Lin NU, Modi S, Patt DA, Perez EA, Perlmutter J, Ramakrishna N, Winer EP. Systemic therapy for patients with advanced human epidermal growth factor receptor 2-positive breast cancer: American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol.* 32(19) 2078-99, 2014. PMID 24799465
 273. Partridge AH, Rumble RB, Carey LA, Come SE, Davidson NE, Di Leo A, Gralow J, Hortobagyi GN, Moy B, Yee D, Brundage SB, Danso MA, Wilcox M, Smith IE. Chemotherapy and targeted therapy for women with human epidermal growth factor receptor 2-negative (or unknown) advanced breast cancer: American Society of Clinical Oncology Clinical Practice Guidelines. *J Clin Oncol.* 32(29): 3307-29, 2014. PMID 25185096. [Epub ahead of print]
 274. Schneider BP, Li L, Shen F, Miller KD, Radovich M, O'Neill A, Gray RJ, Lane D, Flockhart DA, Jiang G, Wang Z, Lai D, Koller D, Pratt JH, Dang CT, Northfelt D, Perez EA, Shenkier T, Cobleigh M, Smith ML, Railey E, Patridge A, Gralow J, Sparano J, Davidson NE, Foroud T, Sledge GW. Genetic variant predicts bevacizumab-induced hypertension in ECOG-5103 and ECOG-2100. *Br J Cancer.* 111(6):1241-1248, 2014. PMID 25117820
 275. Cheng H, Ballman K, Vassilakopoulou M, Dueck AC, Reinholz MM, Tenner K, Gralow J, Hudis C, Davidson NE, Fountzilas G, McCullough AE, Chen B, Psyrris A, Rimm DL, Perez EA. EGFR expression is associated with decreased benefit from trastuzumab in the NCCTG N9831 (Alliance) trial. *Br J Cancer.* 111(6):1065-1071, 2014. PMID 25117817
 276. Chen G, Gupta R, Petrik S, Laiko M, Leatherman JM, Asquith JM, Daphtary MM, Garrett-Mayer E, Davidson NE, Hirt K, Berg M, Uram J, Dausies T, Fetting JH, Duus EM, Atay-Rosenthal S, Ye X, Wolff AC, Stearns V, Jaffee EM, Emens LA. A feasibility study of cyclophosphamide, trastuzumab, and an allogeneic GM-CSF-secreting breast tumor vaccine for HER-2+ metastatic breast cancer. *Cancer Immunol Res.* 2(10):949-61, 2014 [Epub ahead of print] PMID 25116755
 277. Adams S, Gray RJ, Demaria S, Goldstein L, Perez EA, Shulman LN, Martino S, Wang M, Jones VE, Saphner TJ, Wolff AC, Wood WC, Davidson NE, Sledge GW, Sparano JA, Badve SS. Prognostic value of tumor infiltrating lymphocytes in triple-negative breast cancers from two Phase III randomized adjuvant breast cancer trials: ECOG 2197 and ECOG 1199. *J Clin Oncol.* 20; 32(27) 2959-67, 2014 PMID 25071121
 278. Katz TA, Huang Y, Davidson NE, Jankowitz RC. Epigenetic reprogramming in breast cancer: From new targets to new therapies. *Ann Med.* 46(6):397-408, 2014. PMID: 250581777

279. Li H, Chiappinelli KB, Guzzetta AA, Easwaran H, Yen RW, Vata-palli R, Topper MJ, Luo J, Connolly RM, Azad NS, Stearns V, Pardoll DM, Davidson N, Jones PA, Slamon DJ, Baylin SB, Zahnow CA, Ahuja N. Immune regulation by low doses of the DNA methyltransferase inhibitor 5-azacitidine in common human epithelial cancers. *Oncotarget*. 5(3):587-98, 2014. PMID 24583822. PMC 3996658
280. VanLonden GJ, Donovan HS, Beckjord EB, Cardy AL, Bovbjerg DH, Davidson NE, Morse JQ, Switzer GE, Verdonck-deLeeuw IM, Dew MA. Perspectives of postmenopausal breast cancer survivors on adjuvant endocrine therapy-related symptoms. *Oncol Nurs Forum*. 41(6) 660-8, 2014. PMID 25355021
281. Perez EA, Romond EH, Suman VJ, Jeong JH, Sledge G, Geyer CE Jr, Martino S, Rastogi P, Gralow J, Swain SM, Winer EP, Colon-Otero G, Davidson NE, Mamounas E, Zujewski JA, Wolmark N. Trastuzumab plus adjuvant chemotherapy for human epidermal growth factor receptor 2-positive breast cancer: planned joint analysis of overall survival from NSABP B-31 and NCCTG N9831. *J Clin Oncol*. 32(33):3744-52, 2014. PMID 25332249
282. Francis PA, Regan MM, Fleming GF, Lang I, Ciruelos E, Bellet M, Bonnefoi HR, Climent MA, Prada GA, Burstein HJ, Martino S, Davidson NE, Geyer CE Jr, Walley BA, Coleman R, Kerbrat P, Buchholz S, Ingle JN, Winer EP, Rabaglio-Poretti M, Maibach R, Ruepp B, Giobbie-Hurder A, Price KN, Colleoni M, Viale G, Coates AS, Goldhirsch A, Gelber RD; the SOFT Investigators and the International Breast Cancer Study Group. Adjuvant Ovarian suppression in premenopausal breast cancer. *N Eng J Med*. 372(5):436-46, 2015. PMID: 25495490.
283. Connolly RM, Leal JP, Goetz MP, Zhang Z, Zhou XC, Jacobs LK, Mhlanga J, O JH, Carpenter J, Storniolo AM, Watkins S, Fetting JH, Miller RS, Sideras K, Jeter SC, Walsh B, Powers P, Zorzi J, Boughey JC, Davidson NE, Carey LA, Wolff AC, Khouri N, Gabrielson E, Wahl RL, Stearns V. TBCRC 008: early change in 18F-FDG uptake on PET predicts response to preoperative systemic therapy in human epidermal growth factor receptor 2-negative primary operable breast cancer. *J Nucl Med*. 56(1):31-37, 2015. PMID 25476537.
284. Lee AV, Oesterreich S, Davidson NE. MCF-7 cells-changing the course of breast cancer research and care for 45 years. *J Natl Cancer Inst*. 31;17(7), 2015. PMID 25828948.
285. Reeder A, Attar M, Nazario L, Bathula C, Zhang A, Hochbaum D, Roy E, Cooper KL, Oesterreich S, Davidson NE, Neumann CA, Flint MS. Stress hormones reduce the efficacy of paclitaxel in triple negative breast cancer through induction of DNA damage. *Br J Cancer*. 28:112(9): 1461-70, 2015. PMID 25880007.
286. Coates AS, Winer EP, Goldhirsch A, Gelber RD, Gnant M, Piccart-Gebhart M, Thurlimann B, Seen HJ; Panel members. Tailoring therapies-improving the management of early breast cancer: St. Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2015. *Ann Oncol*. 26:153-46, 2015. PMID 25939896.
287. Willis S, De P, Dey N, Long B, Young B, Sparano JA, Wang V, Davidson NE, Leyland-Jones BR. Enriched transcription factor signatures in triple negative breast cancer indicates possible targeted therapies with existing drugs. *Meta Gene*. 15;4:129-41, 2015. PMID 26005638. PMCID 4438509.
288. Sparano JA, Zhao F, Martino S, Ligibel JA, Perez EA, Saphner T, Wolff AC, Sledge GW Jr, Wood WC, Davidson NE. Long-term follow-up of the E1199 Phase III trial evaluating the role of taxane and schedule in operable breast cancer. *J Clin Oncol*. 20;33(21):2353-60, 2015. PMID 26077235.

289. Schnipper LE, Davidson NE, Wollins DS, Tyne C, Blayney DW, Blum D, Dicker AP, Ganz PA, Hoverman JR, Langdon R, Lyman GH, Meropol NJ, Mulvey T, Newcomer L, Peppercorn J, Polite B, Raghavan D, Rossi G, Saltz L, Schrag D, Smith TJ, Yu PP, Hudis CA, Schilsky RL. American Society of Clinical Oncology statement: A conceptual framework to assess the value of cancer treatment options. *J Clin Oncol.* 10;33(23):2563-77, 2015. PMID 26077235.
290. Nayak SR, Harrington E, Hartmaier R, Chen J, Pathiraja TN, Cooper KL, Fine JL, Sanfilippo J, Davidson NE, Lee AV, Dabbs D, Oesterreich S. A role for histone H2B variants in endocrine-resistant breast cancer. *Horm Cancer.* 6(5-6) 214-24, 015. PMID 26113056.
291. Schneider BP, Li L, Radovich M, Shen F, Miller C, Flockhart DA, Jiang G, Vance GH, Gardner L, Vatta M, Bai C, Lai D, Koller D, Zhao F, O'Neill A, Smith ML, Railey E, White C, Partridge A, Sparano JA, Davidson NE, Foroud T, Sledge GW. Genome-wide association studies for taxane-induced peripheral neuropathy (TIPN) in ECOG-5103 and ECOT-1199. *Clin Cancer Res.* 21:5082-1 2015. PMID 26138065.
292. Katz TA, Liao S, Palmieri VJ, Dearth RK, Pathiraja TN, Hou Z, Shaw P, Small S, Davidson NE, Peters DG, Tseng G, Oesterreich S, Lee AV. Targeted DNA methylation screen in the mouse mammary genome reveals a parity-induced hypermethylation of IGF 1R which persists long after parturition. *Cancer Prev Res.* 8(10):1000-9, 2015. PMID 26290394.
293. Brown DD, Dabbs DJ, Lee AV, McGuire KP, Ahrendt GM, Bhargava R, Davidson NE, Brufsky AM, Johnson RR, Oesterreich S, McAuliffe PF. Developing in vitro models of human ductal carcinoma in situ from primary tissue explants. *Breast Cancer Res Treat.* 153(2):311-21, 2015. PMID 26283301.
294. Mathew A, Davidson NE. Adjuvant endocrine therapy for premenopausal women with hormone-responsive breast cancer. *Breast.* Nov; 24 Suppl 2:S120-5. 2015. PMID 26255743.
295. Liao S, Hartmaier RJ, McGuire KP, Puhalla SL, Luthra S, Chandran UR, Ma T, Bhargava R, Modugno F, Davidson NE, Benz S, Lee AV, Tseng GC, Oesterreich S. The molecular landscape of premenopausal breast cancer. *Breast Cancer Res.* 17:104. 2015. PMID 26251034.
296. Schneider BP, Li L, Radovich M, Shen F, Miller C, Flockhart DA, Jiang G, Vance GH, Gardner L, Vatta M, Bai C, Lai D, Koller D, Zhao F, O'Neill A, Smith ML, Railey E, White C, Partridge A, Sparano JA, Davidson NE, Foroud T, Sledge GW. Genome-wide association studies for taxane-induced peripheral neuropathy (TIPN) in ECOG-5103 and ECOG-1199. *Clin Cancer Res.* 2015 [Epub ahead of print].
297. Solin LJ, Gray R, Hughes LL, Wood WC, Lowen MA, Badve SS, Baehner FL, Ingle JN, Perez EA, Recht A, Sparano JA, Davidson NE. Surgical excision without radiation for ductal carcinoma in situ breast: 12-year results from the ECOG-ACRIN E5194 study. *J Clin Oncol.* 33(33):3938-44, 2015. PMID: 26152014
298. Perez EA, Baehner FL, Butler SM, Thompson EA, Dueck AC, Jamshidian F, Cherbavaz D, Yoshizawa C, Shak S, Kaufman PA, Davidson NE, Gralow J, Asmann YW, Ballman KV. The relationship between quantitative human epidermal growth factor receptor 2 gene expression by the 21-gene reverse transcriptase polymerase chain reaction assay and adjuvant trastuzumab benefit in Alliance N9831. *Breast Cancer Res.* 1:17(1):133, 2015. PMID: 2589954.
299. Wang P, Bahreini A, Gyanchandani R, Lucas P, Hartmaier RJ, Watters RJ, Jonnalagadda AR, Trejo Bitta HE, Berg A, Hamilton RL, Kurland BF, Weiss K, Mathew A, Leone JP,

- Davidson NE, Nikiforova MN, Brufsky AM, Ambros TF, Stern AM, Puhalla S, Lee AW, Oesterreich S. Sensitive detection of mono-and polyclonal ESR1 mutations in primary tumors, metastatic lesions and cell free DNA of breast cancer patients. *Clin Cancer Res*. 2015 [Epub ahead of print].
300. Azim HA, Jr., Davidson NE, Ruddy KJ. Challenges in Treating Premenopausal Women with Endocrine-Sensitive Breast Cancer. American Society of Clinical Oncology educational book / ASCO American Society of Clinical Oncology Meeting. 35:23-32, 2016. PMID: 27249683.
 301. Bhargava R, Davidson NE. "Take two"? The role of second opinions for breast biopsy specimens. *Bmj*. 2016;353:i3256, 2016. PMID: 27339037.
 302. Burstein HJ, Lacchetti C, Anderson H, Buchholz TA, Davidson NE, Gelmon KE, Giordano SH, Hudis CA, Solky AJ, Stearns V, Winer EP, Griggs JJ. Adjuvant endocrine therapy for women with hormone receptor-positive breast cancer: American Society of Clinical Oncology Clinical Practice Guideline Update on Ovarian Suppression. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 34(14):1689-701, 2016. PMID: 26884586.
 303. Cao C, Vasilatos SN, Bhargava R, Fine JL, Oesterreich S, Davidson NE, Huang Y. Functional interaction of histone deacetylase 5 (HDAC5) and lysine-specific demethylase 1 (LSD1) promotes breast cancer progression. *Oncogene*. DOI:10.1038/onc.2016.186 (Epub ahead of print), 2016 May 23. PMID: 27212032.
 304. Davidson NE. Serendipity and purpose. *Endocrine-related cancer*. 23(5):P1-3, 2016. PMID: 27059549.
 305. Davidson NE. Conquering Metastatic Breast Cancer. *J Oncol Pract*. 12(1):11-2, 2016.
 306. Dowsett M, Lonning PE, Davidson NE. Incomplete Estrogen Suppression With Gonadotropin-Releasing Hormone Agonists May Reduce Clinical Efficacy in Premenopausal Women With Early Breast Cancer. *J Clin Oncol*. 34(14):1580-1583, 2016.
 307. Gyanchandani R, Lin Y, Lin HM, Cooper KL, Normolle DP, Brufsky AM, Fastuca M, Crosson W, Oesterreich S, Davidson NE, Bhargava R, Dabbs DL, Lee AV. Intra-tumor heterogeneity affects gene expression profile test prognostic risk stratification in early breast cancer. *Clinical cancer research : an official journal of the American Association for Cancer Research*. DOI: 10.1158/1078-0432.2016; (Epub ahead of print), 2016. PMID: 27185370.
 308. Kensler TW, Spira A, Garber JE, Szabo E, Lee JJ, Dong Z, Dannenberg AJ, Hait WN, Blackburn E, Davidson NE, Foti M, Lippman SM. Transforming Cancer Prevention through Precision Medicine and Immune-oncology. *Cancer Prev Res (Phila)*. 9(1):2-10, 2016.
 309. Puhalla SL, Davidson NE. Breast cancer: The 21-gene recurrence score - biology remains at the forefront. *Nature reviews Clinical oncology*. 13(8):470-2, 2016. PMID: 27296295.
 310. Schnipper LE, Davidson NE, Wollins DS, Blayney DW, Dicker AP, Ganz PA, Hoverman JR, Langdon R, Lyman GH, Meropol NJ, Mulvey T, Newcomer L, Peppercorn J, Polite B, Raghavan D, Rossi G, Soltz L, Schrag D, Smith TJ, Yu PP, Hudis CA, Vose JM, Schilsky RL. Updating the American Society of Clinical Oncology Value Framework: Revisions and reflections in response to comments received. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. DOI:10.1200/JCO.2016.68.2518 (Epub ahead of print), 2016 May 31. PMID: 27247218.
 311. Solin LJ, Gray R, Hughes LL, Wood WC, Lowen MA, Badve SS, Baehner FL, Ingle JN, Perez ED, Recht A, Sparano JA, Davidson NE. Reply to C. Shah et al. *Journal of clinical*

oncology : official journal of the American Society of Clinical Oncology. 34(15):1824-5, 2016. PMID: 27001578.

312. Wang P, Bahreini A, Gyanchandani R, Lucas PC, Hartmaier RJ, Watters RJ, Jonnalagadda AR, Trejo Bittar HE, Berg A, Hamilton RL, Kurland BF, Weiss KR, Mathew A, Leone JP, Davidson NE, Nikiforova MN, Brufsky AM, Ambros TF, Stern AM, Puhalla SL, Lee AV, Oesterreich S. Sensitive Detection of Mono- and Polyclonal ESR1 Mutations in Primary Tumors, Metastatic Lesions, and Cell-Free DNA of Breast Cancer Patients. *Clinical cancer research : an official journal of the American Association for Cancer Research*. 22(5):1130-7, 2016. PMCID: 4775406.

Editorials:

1. Davidson NE and Lippman ME. Combined therapy in advanced breast cancer. *Eur. J. Cancer Clin. Oncol.* 21:1123-6, 1985
2. Davidson NE and Lippman ME. Stimulation of breast cancer with estrogens: how much clinical value? *Eur. J. Cancer Clin. Oncol.* 23:897-900, 1987. PMID: 3311768.
3. Davidson NE. Out of the courtroom and into the clinic. *J. Clin. Oncol.* 10:517-9, 1992. PMID: 1548515.
4. Davidson NE. Tamoxifen - panacea or Pandora's box? *N. Engl. J. Med.* 326:885-6, 1992
5. Davidson NE. Hormone replacement therapy: Breast vs heart vs bone. *N. Engl. J. Med.* 332:1638-9, 1995
6. Davidson NE. and Yager JD. Pesticides and breast cancer: fact or fad? *J. Natl. Cancer Inst.* 89:17434, 1997. PMID: 9392608.
7. Nass SJ, Hahm HA and Davidson NE. Breast cancer biology blossoms in the clinic. *Nature Medicine.* 4:761, 1998. PMID: 9662357.
8. Davidson NE. Combined endocrine therapy for breast cancer - new life for an old idea? *J. Natl. Cancer Inst.* 92:859-60, 2000. PMID: 10841814.
9. Davidson NE and Levine ME. Breast cancer consensus meetings: vive la difference? *J Clin Oncol.* 20:1719-20, 2002. PMID: 11919226.
10. Davidson NE and Helzlsouer KJ. Good news about oral contraceptives. *N. Engl. J. Med.* 346:2078-9, 2002. PMID: 12087145.
11. Park BH and Davidson NE. Estrogen receptor status, cell cycling and paclitaxel looking for a "hormone"-ious explanation. *Cancer Biology & Therapy* 3:468-9, 2004. PMID: 15153814.
12. Stearns V and Davidson NE. Déjà vu for breast cancer two? *J Natl Cancer Inst* 96: 497-499, 2004. PMID: 15069104.
13. Davidson NE and Morrow M. Sometimes a great notion--an assessment of neoadjuvant systemic therapy for breast cancer. *J Natl Cancer Inst.* 97:159-61, 2005. PMID: 15687353
14. Davidson NE and Sukumar S. Of Snail, mice and women. *Cancer Cell.* 8:173-4, 2005. PMID: 16169460.
15. Kominsky SL and Davidson NE. A "bone" fide predictor of metastasis? Predicting breast cancer metastasis to bone. *J Clin Oncol*, 24:2227-9, 2006. PMID: 16636338. EPub.
16. Zhou Q and Davidson NE. Silencing estrogen receptor alpha in breast cancer cells. *Cancer Biol Ther.* 5:848-9, 2006. PMID: 16921265. EPub.
17. Wolff AC and Davidson NE. Still waiting after 110 years: the optimal use of ovarian ablation as adjuvant therapy for breast cancer. *J Clin Oncol*, 24:4949-4951, 2006. PMID: 17075110.

18. Visvanathan K, Sukumar S and Davidson, NE. Epigenetic biomarkers and breast cancer: cause for optimism. *Clinical Cancer Research* 12:6591-92, 2006. PMID: 17121875.
19. Stebbing J, Stearns V, and Davidson NE. Role of CYP2D6 testing in selection of endocrine therapy for breast cancer. *Pharmacogenomics*. 8:1-3, 2007. PMID: 17187500
20. Davidson, NE. The maturation of medical oncology. *Lancet Oncol*. 8:457-8, 2007
Park BH and Davidson NE. PI3 kinase activation and response to trastuzumab therapy: What's new with Herceptin resistance? *Cancer Cell* 4:297-9, 2007. PMID: 17936554.
21. Davidson NE. In memoriam. Martin D. Abeloff, *J Clin Oncol* 26:1573-4, 2008
22. Chivukula M, Brufsky A., Davidson NE. Small beginnings: do they matter? The importance of lymphovascular invasion in early breast cancer. *J Natl Cancer Inst*. 101(10) 698-9, 2009. PMID: 19436037.
23. Rastogi P, Davidson NE. Trastuzumab as single agent therapy for HER2-positive metastatic breast cancer. *Onkologie* 33:420-1, 2010. PMID: 20838056.
24. Oesterreich, S, Lee AV, Davidson NE. Is it time to reSET the standard for estrogen receptor testing in breast cancer? *J Clin Oncol* 28:4101-3, 2010. PMID: 2069707.
25. Davidson, NE, Kensler TW. "MAPping" the course of chemoprevention in breast cancer. *N Engl J Med* 364(25):2463-4, 2011. PMID: 21639807.
26. Puhalla S, Jankowitz RC, Davidson NE. Adjuvant endocrine therapy for breast cancer: don't ditch the switch! *J Natl Cancer Inst* 103:1280-2, 2011. PMID: 21859987
27. Bhargava R, Brufsky AM, Davidson NE. Prognostic/predictive immunohistochemistry assays for estrogen receptor-positive breast cancer: back to the future? *J Clin Onc* 30(36):4451-3, 2012. PMID: 23045595
28. McAuliffe PF, Danoff S, Shapiro SD, Davidson NE. Treatment for breast cancer: is time really of the essence? *J Natl Cancer Inst* 105(2):8-2, 2012. PMID 23264682
29. Sharma D, Davidson NE. Obesity and breast cancer: a multipartite connection. *J Mammary Gland Biol Neoplasia*. 18(3-4):253-5, 2013. PMID:24190309
30. Oesterreich S, Brufsky AM, Davidson NE. Using mice to treat (wo)men: mining genetic changes in patient xenografts to attack breast cancer. *Cell Rep*. 4(6):1061-2, 2013
PMID24075202[PubMed - in process]
31. Oesterreich S, Davidson NE. The search for ESR1 mutations in breast cancer. *Nat Genet*. 45(12):1415-6, 2013. PMID 24270445
32. Jankowitz RC, Puhalla S, Davidson NE. Should we embrace or ablate our urge to (ovarian) suppress? *J Clin Oncol*. 32(35): 3920-2, 2014. PMID 25366692.
33. Mathew A, Brufsky AM, Davidson NE. Can circulating tumor cells predict resistance in metastatic breast cancer? *Clin Cancer Res* 2:2967, 2014. PMID 25645864
34. Davidson NE, Rimm DL. Expertise vs evidence in assessment of breast biopsies: an atypical science. *JAMA* 17:313(11):1109-10, 2015. PMID 25781438

Articles in the Lay Press:

1. Davidson NE. Is hormone replacement a risk? *Scientific American*. 275:101, 1996.
2. Davidson NE. Hormone replacement therapy in perspective; *Medical and Health Annual*, Encyclopedia Britannica, Inc., Chicago, IL pp. 361-6, 1997.

Book Reviews:

1. Davidson NE. *Molecular Endocrinology and Steroid Hormone Action: Progress in Clinical*
2. *and Biologic Research*, Volume 322, *J Natl Cancer Inst*. 82:1150, 1990.

3. Davidson NE. The Breast: Comprehensive Management of Benign and Malignant Diseases. J. Natl. Cancer Inst. 84:806, 1992.
4. Davidson NE. Diseases of the Breast. J Natl Cancer Inst. 89:85, 1997.
5. Davidson NE. Emperor of All Maladies: A Biography of Cancer. Lancet 377:801, 2011.

Books Edited:

The Breast Comprehensive Management of Benign and Malignant Disease (Second edition), Edited by Bland KI, Copeland EM, III, Davidson NE, Mendenhall NP, Page DL, and Wilkinson EJ. W.B. Saunders Company, Philadelphia, PA, 1998.

The Breast Comprehensive Management of Benign and Malignant Disorders (Third edition) Edited by Bland KI, Copeland, III, EM, Davidson NE, Page DL, Recht A, and Unst MM. Saunders, Philadelphia, PA, 2004.

Book Chapters:

1. Lippman ME, Dickson RB, Gelmann EP, Kasid A, Bates S, Knabbe C, Swain SM, McManaway M, Wilding G, Davidson N, Huff K, and Bronzert D. Mechanisms of growth regulation of human breast cancer. In: Advances in Gene Technology. Molecular Biology of the Endocrine System. Ed. by Paett, D., Ahmeod, F., Beah, S., and Whelon, W.J. ISCU Short Reports, Vol. 4, 1986, p. 254-257.
2. Davidson NE and Lippman ME. Adjuvant therapy for breast cancer. In Diagnosis and Management of Breast Cancer, Lippman, ME, Lichter, AS, and Danforth, DN (eds). W.B. Saunders and Co., Philadelphia, 1988, pp 348-374.
3. Davidson NE and Lippman ME. Treatment of metastatic breast cancer. In Diagnosis and Management of Breast Cancer, Lippman, ME, Lichter, AS, and Danforth, DN (eds). W.B. Saunders and Co., Philadelphia, 1988, pp 375-406.
4. Dickson RB, Knabbe C, Bates SE, Huff K, Davidson NE, Bronzert D, Swain S, Valverius E, Gelmann EP, and Lippman ME. Growth factors, receptors, and oncogenes in breast cancer. In: Current Perspectives in Breast Cancer, Ed by I Mittra, Mata & McGraw Hill Publishing Co. Ltd, Bombay, India, 1988, pp 73-80.
5. Kensler TW, Davidson NE, Egner PA, Guyton KZ, Groopman JD, Liu Y-L and Roebuck BD. Mechanisms of chemoprotection against aflatoxin-induced hepatocarcinogenesis by oltipraz. In: Anticarcinogenesis & Radiation Protection 2, Ed by Nygaard OF and Upton AC, Plenum, New York, 1991, pp 315-322.
6. Antman K, Bearman SI, Davidson N, deVries E, Gianni AM, Gisselbrecht C, Kaiser H, Lazarus HM, Livingston RB, Maraninchi D, McElwain TJ, Ogawa M, Peters W, Rosti G, Slease RB, Spitzer G, Tajima T, Vaughan WP and Williams S. Dose intensive therapy in breast cancer: current status. In: New Strategies in Bone Marrow Transplantation. Ed by: Gale, RP and Champlin, RE. Wiley-Liss, Inc. New York, 1991, pp 423-436.
7. Davidson NE and Abeloff MD. Adjuvant chemotherapy for axillary lymph node-positive breast cancer. In: Adjuvant Therapy of Breast Cancer. Ed by Henderson, IC, Kluwer Academic Publishers, Norwell, MA, 1992, pp 115-145.
8. Kensler TW, Davidson NE, Egner PA, Guyton KZ, Groopman JD, Curphy TJ, Liu Y-L and Roebuck BD. Chemoprotection against aflatoxin-induced hepatocarcinogenesis by dithiolethiones, In: Mycotoxins, Cancer, and Health. Ed by Bray, G. and Ryan, D. LSU Press, Baton Rouge, LA, 1991, pp 238-252.

9. Davidson NE and Ableoff MD. Adjuvant systemic therapy for axillary node-negative breast cancer. In: Cancer Principles and Practice of Oncology PPO Update, Ed. by DeVita, Jr. VT, Hellman S, and Rosenberg SA. JB Lippincott, Philadelphia, 1992, Vol. 6, Number 7, pp 1-13.
10. Kensler TW, Davidson NE and Guyton KZ. Antioxidants and oncogenesis: roles in cancer causation and prevention. In: Atmospheric Oxidation and Antioxidants. Ed. by Scott G. Elsevier, Amsterdam, 1992, pp. 333-354.
11. Davidson NE. Breast cancer - molecular approaches and cell kinetics in assessing risk, In: Current Therapy in Oncology, Ed. by Niederhuber J, BC Decker Inc., Philadelphia, 1993, pp 304-308.
12. Kensler TW, Davidson NE, Groopman JD, Roebuck BD, Prochaska HJ and Talalay P. Chemoprotection by inducers of electrophile detoxication enzymes. In: Antimutagenesis and Anticarcinogenesis Mechanisms III, Ed. by Bronzetti G, DeFlora S, Waters MD, Hayatsu H and Shankel DE, Plenum Press, 1993, pp 127-136.
13. Davidson NE and Kennedy JM. Protein kinase C and breast cancer. In: Mammary Tumor Cell Cycle, Differentiation and Metastasis. Eds by Dickson RB and Lippman ME, Kluwer Academic Publishers, Boston, 1996, pp 91-105.
14. McCloskey DE, Armstrong DK, Jackisch C and Davidson NE. Programmed cell death in human breast cancer cells. In: Recent Progress in Hormone Research, Vol 51, Ed. by Conn, PM. The Endocrine Society, Baltimore, MD, 1996, pp 493-508.
15. Couzi RJ and Davidson NE. Breast cancer. In: Women's Health in Primary Care, Ed. by Rosenfeld JA, Williams & Wilkins, Baltimore, MD, 1996, pp 683-702.
16. Denmeade SR, McCloskey DE, Joseph IBJK, Hahm HA, Isaacs JT and Davidson NE. Apoptosis in hormone - responsive malignancies. In: Advances in Pharmacology, Ed. By Kaufmann, S.H., Academic Press, Inc., San Diego, 1997, pp 553-583.
17. Ferguson AT, Lapidus RG and Davidson NE. The regulation of estrogen receptor expression and function in breast cancer. In: Biological and Hormonal Therapies of Cancer. Ed. By Foon KA and Muss, HB, Kluwer Academic Publishers, Boston, 1998, pp 255-278.
18. Davidson NE. Treatment of breast cancer with autologous bone marrow transplantation. In: Current Surgical Therapy, Ed. by Cameron, J.L. Mosby, Inc., St. Louis, 1998, pp 640-643.
19. Davidson NE and Kennedy MJ. Dose-intensive chemotherapy for breast cancer. In: Diseases of the Breast Updates, Ed. by Harris, J.R. and Lippman, M.E. Lippincott-Raven, 1998, vol. 2, No. 3, pp 1-10.
20. Davidson NE and Valagussa P. Summary. In: Adjuvant Therapy of Primary Breast Cancer VI, Ed by Senn H-J, Gelber R, Goldhirsch A and Thurliman B. Springer-Verlag, Berlin, 1998, pp 368-370.
21. Davidson NE, Hahm HA and Armstrong DK. Apoptosis and breast cancer. In: Cancer Chemotherapy and Apoptosis, Ed. by Hickman, J.A. and Dive, C., Humana Press, 1999, pp 291-303.
22. Davidson NE. Breast Cancer. In: Scientific American Medicine, Ed. by Dale DC and Federman, DD, Scientific American, Inc., New York City, 1999, 12 ONCO VII 1-13.
23. Wolff AC, Lange JR and Davidson NE. Occult primary cancer with axillary node metastasis. In: Advanced Therapy of Breast Disease Ed. by Singletary, S.E. and Robb, G.L. BC Decker Inc., 2000, pp 191-195.

24. Emens LA, Davidson NE. Posoperative Endocrine Therapy in Invasive Breast Cancer, Steven T Rosen MD Series Editor. In: Cancer Treatment and Research, Ed by Monica Castiglione, Martine J. Piccart. Springer, 2009 pp 139-161.
25. Davidson NE, Kennedy MJ and Armstrong DK. Dose-intensive chemotherapy. In: Diseases of the Breast, Ed. by Harris JR, Lippman ME, Morrow M and Osborne CK. Lippincott Williams & Wilkins, Philadelphia. 2000, pp 633-644.
26. Kensler TW, Davidson NE, Groopman JD and Muñoz A. Biomarkers and surrogacy: relevance to chemoprevention. In: Biomarkers in Cancer Chemoprevention. Ed. by Miller AB, Bartsch H, Boffetta P, Dragsted L and Vainio H. IARC Scientific, International Agency for Research on Cancer. Lyon, 2001, pp 27-47.
27. Brewster A and Davidson N. Breast cancer screening. In: Handbook of Women's Health: An evidence-based approach. Ed. By Rosenfeld, J.A. Cambridge University Press, N.Y., N.Y., 2001, pp 383-398.
28. Wolff AC, Stearns V and Davidson NE. Adjuvant systemic therapy of breast cancer. In: The Breast Comprehensive Management of Benign and Malignant Disorders. Ed. By Bland KI, Copeland III EM, Davidson NE, Page DL, Recht A, and Unst MM. Saunders, Philadelphia, PA, 2004, pp 1189-1232.
29. Stearns V and Davidson NE. Adjuvant chemotherapy and chemoendocrine therapy for primary breast cancer. IN: Diseases of the Breast. Ed. By Harris JR, Lippman ME, Morrow M and Osborne CK. Lippincott Williams & Wilkins, Philadelphia, PA., 2004, pp 893-920.
30. Davidson NE and Osborne CK. Adjuvant systemic therapy treatment guidelines. IN: Diseases of the Breast. Ed. By Harris JR, Lippman ME, Morrow M and Osborne CK. Lippincott, William & Wilkins, Philadelphia, PA., 2004, pp 945-950.
31. Carraway H and Davidson NE. Adjuvant hormonal therapy in premenopausal women. VII. Systemic management of stage I and II breast cancer. In: Advanced Therapy of Breast Disease. Second Edition. Ed. By Singletary, E., Robb, Hortobagyi, G. BC Decker Inc., Hamilton, Ontario, 2004, pp 451-458.
32. Davidson NE. Breast Cancer IN: WebMD 12 VII Breast Cancer 1-15, 2004.
33. Prowell T, Davidson N. Metastatic breast cancer: Tailored endocrine therapy for premenopausal women. IN: Breast Cancer Management in the Era of Molecular Medicine—Towards Tailored Approaches. Ed. By Piccart M, Wood W, Hung M-C, Solin L, Cardoso F. Springer-Verlag, in press.
34. Visvanathan K and Davidson NE. Adjuvant endocrine therapy: controversies and perspectives. IN: Textbook of Breast Cancer: A Clinical Guide to Therapy, Third Edition. Ed. By Bonadonna G, Hortobagyi GN, Valagussa P. Taylor & Francis Group, 2006, pp 205-223.
35. Huang Y and Davidson NE. Breast cancer. IN: Principles of Molecular Medicine, Second Edition. Ed. By Runge, M.S. and Patterson, C. Humana Press, Inc., 2006, pp 728-735.
36. Stearns V, Zhou Q, and Davidson NE. Epigenetic regulation as a new target for breast cancer therapy. IN: Breast Cancer: Translational Therapeutic Strategies. Ed. by Lyman GH, Burstein H. Informa Healthcare USA, Inc. New York City, 2007, pp 285-295.
37. Davidson NE. Breast Cancer IN: WebMD 12 VII Breast Cancer 1-16, 2007.
38. Bao T and Davidson NE. Gene expression profiling of breast cancer. IN Advances in Surgery Volume 42 Ed. by Cameron JL, 2008, pp 249-60.

39. Stearns V, Davidson NE. Adjuvant Systemic Therapy: Chemoendocrine IN: Diseases of the Breast. Ed. by Harris JR, Lippman ME, Morrow M and Osborne CK. Lippincott, Williams & Wilkins, Philadelphia, PA 2009, pp 645-656.
40. Davidson NE, Winer EP, Osborne CK. Guidelines for Adjuvant Systemic Therapy IN: Diseases of the Breast. Ed. By Harris JR, Lippman ME, Morrow M and Osborne CK Lippincott, William & Wilkins, Philadelphia, PA., 2009, pp 711-713.
41. Emens LA, Davidson NE, Postoperative Endocrine Therapy for Invasive Breast Cancer IN: Adjuvant Therapy for Breast Cancer. Ed by Castiglione M, Piccart MJ. Springer, 2009, pp 139-161.
42. Reeder, JG, Lembersky BC, Davidson NE. Advances in Adjuvant and Neoadjuvant Therapy for Breast Cancer. IN: Current Surgical Therapy 10th Edition, Ed. by Cameron JL, Cameron AM. Elsevier Saunders, 2011, pp 547-552.
43. Davidson, NE. Breast Cancer and Benign Breast Disorders IN: Goldman's Cecil Medicine 24th Edition. Ed. by Goldman L, Schafer AI. , Elsevier Saunders, 2012, pp 1309-1316.
44. Jankowitz RC, Davidson NE. Adjuvant Hormonal Therapy in Premenopausal Women IN: Advanced Therapy of Breast Disease, Third Edition. Ed. by Babiera GV, Skoracki RJ, Esteva FJ, Peoples Medical Publishing, 2012, pp 799-811.
45. Wolff AC, Domchek SM, Davidson NE, Sacchini V, McCormick. Cancer of the Breast. IN: Abeloff's Clinical Oncology, 5th Edition. Ed. by Niederhuber JE, Armitage JO, Doroshow JH, Kastan MB, Tepper JE., Elsevier Churchill Livingstone, 2013. pp 1630-1692.
46. Stearns V, Davidson NE. Adjuvant Systemic Therapy: Chemoendocrine IN: Diseases of the Breast 5th Edition. Ed. by Harris JR, Lippman ME, Morrow M and Osborne CK, Lippincott Williams & Wilkins, 2014. pp 649-666.
47. Multiple authors including Davidson NE. The Health Consequences of Smoking—50 Years of Progress. A Report of the Surgeon General. US Department of Health and Human Service, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2014, pp 1-943.
48. Jankowitz RC, Davidson NE. Breast Cancer IN: Hematology-Oncology Therapy – Second Edition, Ed. by Boyiadzis MM, Frame JN, Kohler DR, Fojo T, McGraw Hill Education, 2014, pp 88-190.
49. Lee AV, Oesterreich S, Davidson NE. The Molecular Biology of Breast Cancer. IN: The Molecular Basis of Cancer 4th Edition. Ed. by Mendelsohn J, Gray JW, Howley PM, Israel MA, Thompson CB, Elsevier Saunders, 2015, pp 523-30.

PROFESSIONAL ACTIVITIES

Teaching:

1988-2005	Lecturer, Pathophysiology Course for 2 nd Year Medical Students
1991	Medical Student Advisor
1996-2009	Lecturer, Fundamentals of Clinical Oncology for Public Health Practitioners
1997-2009	Lecturer, Topics in Molecular Endocrinology, School of Public Health

2004-2009 Lecturer, Pathophysiology of Disease, Cellular and Molecular Medicine
 2010-present Lecturer, Cancer Biology and Therapy
 2013-present ILS Neoplasia & Neoplastic Diseases

Mentoring:

Postdoctoral Fellows – Laboratory

1988-1990	M. John Kennedy, MD	Consultant, St. James Hospital, Dublin, Ireland
1989-1992	Deborah K. Armstrong, MD	Professor of Oncology, Johns Hopkins
1991-1993	Yvonne L. Ottaviano, MD	Private Practice, Baltimore, MD
1993-1996	Diane McCloskey, PhD	Associate Professor of Cellular & Molecular Physiology, Penn State, Hershey, PA
1993-1997	Rena Lapidus, PhD	Director, Translational Core Laboratory Associate Professor, University of Maryland
1993-1998	Anne Ferguson, PhD	Non-profits, San Francisco, CA
1994-1995	Christian Jackisch, MD	Chief, Clinic for Gynecology and Obstetrics, Klinikum Offenbach, Offenbach, Germany
1996-1999	Hillary Hahm, MD, PhD	Private Practice, Atlanta, GA
1997-1999	Sharyl Nass, PhD	Director of the National Cancer Policy Forum Institute of Medicine, National Academy of Medicine, Washington, DC
1998-2001	Xiaowei Yang, MD, PhD	Staff Scientist, National Cancer Institute
1999-2001	Valerie Dunn, MD	Private Practice, Rochester, NY
2000-2001	Lan Yan, MD, PhD	Staff Scientist, Amgen, Thousand Oaks, CA
2001-2006	Yi Huang, MD, PhD	Assistant Professor, University of Pittsburgh, Pittsburgh, PA
2001-2004	Judith C. Keen, PhD	Director of Scientific Affairs at the American Society for Radiation Oncology (ASTRO)
2002-2003	Dipali Sharma, PhD	Associate Professor of Oncology, Johns Hopkins University School of Medicine, Baltimore, MD
2004-2008	Qun Zhou, MD, PhD	Associate Professor of Biochemistry and Molecular Biology, University of Maryland Medical School
2005-2006	Allison Tracy, PhD	Lecturer of Chemistry and Biochemistry, UMBC
2006-2009	Qingsong Zhu, PhD	Chief Operating Officer, InSilico Medicine, Inc., Baltimore, MD
2006-2009	Madhavi Billam, PhD	Senior Toxicologist, L'Oreal USA & RI
2011-2013	Tiffany Katz, PhD	Postdoctoral Research Associate, Texas A&M University
2014-present	Nilgun Tasdemir, PhD	Postdoctoral Fellow, University of Pittsburgh
2015-present	Lin Chen	Pre-doctoral Student

Doctoral Students

2000-2005	Julie Blum, PhD	Clinical Content Manager, MED-IQ
2001-2005	Allison Pledge, PhD	Senior Lecturer in Chemistry and Biochemistry at University of Maryland Baltimore County (UMBC)
2004-2010	Abigail Witt, PhD	Postdoctoral Fellow, University of Miami School of Medicine

2005-2010	Talmesha Richards, PhD	Chief Academic and Diversity Officer at STEMconnector
2006-2010	Patrick Shaw, PhD	Chief, Pathogen Detection Lab. USA Public Health Command Region-Pacific Camp Zama, Japan

Graduate Training Programs

1997-2011	Biochemistry and Molecular Biology, Hopkins Bloomberg School of Public Health (adjunct 2009-2011)
1999-2013	Cellular and Molecular Medicine, Hopkins School of Medicine (adjunct 2009-2013)

RESEARCH:

1. Current Grant Support

NIH P30CA047904 Davidson, PI	Cancer Center Support Grant	50%	2009-2020	\$3,330,944
BCRF 2016-2017 Davidson, PI	Investigating models and mechanisms of disease progression in invasive lobular carcinoma	10%	1998-2017	\$112,480
TBCRC-JHU PO2000667811 Davidson, PI	Translational Breast Cancer Research Consortium and the Komen Foundation.	2%	2009-2021	\$6,786
TBCRC- JHU 2000805196 Davidson, PI	Translational Breast Cancer Research Consortium and the Avon Foundation.	1%	2009-2021	\$6,080
BCRF 2016-2017 Davidson, PI	NABCG-BIG North American Breast Cancer Group/Breast International Group Collaboration	5%	2010-2017	\$208,333
DOD W81XWH-14-1-0237 Davidson, PI	Targeting Histone Abnormality in Triple-Negative Breast Cancer	10%	2014-2017	\$112,480
U10 CA180844 Davidson, Co-PI	NCI NCTN-Network Lead Academic Site at UPCI	5%	2014-2019	\$11,255

1a. Prior Grant Support

Grants Awarded as Principal Investigator

1986-1987	American Society of Clinical Oncology Young Investigator Award, "Isolation of estrogen-induced genes from human breast cancer."
1987-1988	American Cancer Society Institutional Grant, "The relationship between

epidermal growth factor receptor and estrogen receptor in breast cancer."

1987-1989 American Cancer Society Maryland Division. "The role of epidermal growth factor and its receptor in breast cancer."

1987-1988 Susan G. Komen Foundation. "The role of epidermal growth factor and its receptor in human breast cancer."

1988-1991 American Cancer Society Clinical Oncology Career Development Award.

1989-1995 NIH Grant R29 CA 49634. "Epidermal growth factor receptor in human breast cancer."

1989-1990 Phil N. Allen Charitable Trust Grant. "Novel approaches to hormone-unresponsive breast cancers."

1989-1990 Merck Clinician Scientist Award, Johns Hopkins University School of Medicine.

1990-1991 Johns Hopkins University School of Medicine Institutional Research Grant, "Elimination of breast cancer cells from human bone marrow by counterflow centrifugal elutriation".

1991-1993 Susan G. Komen Breast Cancer Foundation Fellowship.

1991-1992 Mildred Mindell Cancer Foundation, Inc. "Incidence of p53 mutations in the germ-line of young women with breast cancer".

1992-1994 NIH Grant R01 CA57545. "Programmed cell death in human breast cancer cells"

1992-1994 NIH Grant P30 CA06973 pilot. "DNA methylation and estrogen receptor expression in human breast cancer cells"

1995-1997 Susan G. Komen Breast Cancer Foundation Fellowship.

1994-1998 NIH Grant R21 CA/ES 66204 "Development of a breast cancer program at Johns Hopkins".

1994-1995 NIH Grant 5P50 CA-58236 pilot. "Effects of polyamine analogues on growth of human prostatic cancer cells"

1995-1999 NIH Grant 1 U01 CA66084. "New therapeutic approaches for breast cancer".

1995-1998 American Cancer Society BE-237 "Methylation of steroid receptors in human breast cancer".

1996-1997 Susan G. Komen Foundation, "Functional significance of DNA methylation of estrogen receptor in breast cancer."

1998-2004 NIH Grant R01 CA78352 "DNA methylation as a determinant of hormone resistant breast cancer."

1999-2003 DOD-USAMRDC DAMD 17-99-1-9242. "Therapeutic and chemopreventive actions of a novel polyamine analog against breast cancer"

1998-1999 NIH Grant P50 pilot. "Activity of a novel polyamine analog against breast cancer"

2001-2009 Avon Foundation

2001-2005 Susan G. Komen Foundation Postdoctoral Fellowship

2003-2005 Susan G. Komen Foundation Predoctoral Fellowship

2000-2009 American Breast Cancer Foundation

2006-2008 Susan G. Komen Foundation, BCTR 65706, "Polyamine analogues as novel anti-estrogen receptor alpha agents

2007-2009 Lee Jeans Translational Breast Cancer Research Program (with Entertainment Industry Foundation)

2008-2011 Susan G. Komen for the Cure, KG080923, Inhibition of lysine specific demethylase 1 (LSD1) as a strategy for re-expression of epigenetically silenced genes in breast cancer Robert Casero, Jr. and Nancy E. Davidson (Co-PIs)

- 2000-2013 NIH P50 CA88843. SPORC in Breast Cancer
(co-PI of University of Pittsburgh site 2009-2012)
- 2011-2013 Gynecologic Center of Excellence. Henry M. Jackson Foundation
- 2009-2013 Stand up to Cancer (AACR). Bringing epigenetic therapy to the forefront of cancer. (Dream Team Principal with Stephen Baylin and Peter Jones)

2. Seminars and Invited Lectureships

Invited Seminars

- 1985 Grand Rounds, Washington Veterans Administration Hospital, Washington, DC
- 1986 Medical Grand Rounds, Johns Hopkins Medical Institutions, Baltimore, MD
Symposium on Breast Cancer, Millville Hospital, Vineland, NJ
Department of Hematology-Oncology, University of Missouri, Kansas City, MO
Kansas City Round Table of Hematology/Oncology, Kansas City, MO
American Association of Osteopathic Internists, Washington, DC
Cincinnati Cancer Conference V, Cincinnati, OH
Advances in Oncology, Cherry Hill, NJ
- 1987 13th Annual Symposium on Diagnosis and Treatment of Neoplastic Disorders Course,
Johns Hopkins Medical Institutions, MD
Breast Cancer Session, Eastern Cooperative Oncology Group, Clearwater, FL
- 1988 Early Breast Cancer Conference, Memorial Hospital, Colorado Springs, CO
Grand Rounds, Liberty Medical Center, Baltimore, MD
Medical Grand Rounds, Johns Hopkins Medical Institutions, Baltimore, MD
Annual Hematology/Oncology Conference, The Medical Center of Delaware,
Wilmington, DE
Department of Medicine Professors Rounds, Johns Hopkins Medical Institutions,
Baltimore, MD
Medical Residents Journal Club, Johns Hopkins Medical Institutions, Baltimore, MD
Plastic Surgery Grand Rounds, Johns Hopkins Medical Institutions, Baltimore, MD
- 1989 Department of Medicine Bench to Bedside, Johns Hopkins Medical Institutions,
Baltimore, MD
Twelfth Annual Symposium on Current Concepts in Medicine and Surgery, Peninsula
General Hospital, Salisbury, MD
Topics in Internal Medicine Course, Johns Hopkins Medical Institutions, Baltimore, MD
15th Annual Symposium on Diagnosis and Treatment of Neoplastic Disorders, Johns
Hopkins Medical Institutions, Baltimore, MD
Eleventh Annual Cancer Symposium Selected Topics in Oncology, Raleigh, NC
Plastic Surgery Grand Rounds, Johns Hopkins Medical Institutions, Baltimore, MD
St. George's Society, Johns Hopkins Medical Institutions, Baltimore, MD
Hematology-Oncology Division Seminar, Indiana University School of Medicine,

Indianapolis, IN

- 1990 Grand Rounds, St. Agnes Hospital, Baltimore, MD
Department of Medicine Bench to Bedside, Johns Hopkins Medical Institutions, Baltimore, MD
American Cancer Society, Maryland Division, Baltimore, MD
Medical Grand Rounds, Johns Hopkins Medical Institutions, Baltimore, MD
16th Annual Symposium on Diagnosis and Treatment of Neoplastic Disorders, Johns Hopkins Medical Institutions, Baltimore, MD
NCI Strategy Meeting on High Dose Chemotherapy in Breast Cancer, National Cancer Institute, Bethesda, MD
Hematology-Oncology Division Seminar, University of Maryland School of Medicine, Baltimore, MD
- 1991 Hematology-Oncology Conference, Chester Hospital, West Chester, PA
Department of Medicine Professors Rounds, Johns Hopkins Medical Institutions, Baltimore, MD
Symposium on Early Breast Cancer, Montgomery General Hospital, Olney, MD
Hematology-Oncology Division Seminar, Northwestern University School of Medicine, Chicago, IL
Pennsylvania Oncology Society, Gettysburg, PA
Susan G. Komen Foundation Scientific Symposium, University of Texas - Southwestern Medical School. Dallas, TX
- 1992 Breast Cancer Symposium, Crozer-Chester Hospital, Upland, PA
Hematology-Oncology Grand Rounds, University of Maryland School of Medicine, Baltimore, MD
Department of Medicine Ambulatory Care Rounds, Johns Hopkins Medical Institutes, Baltimore, MD
Staff Conference, Roswell Park Cancer Institute, Buffalo, NY
Tumor Board, Anne Arundel Hospital, Annapolis, MD
18th Annual Symposium on the Diagnosis and Treatment of Neoplastic Disorders, Johns Hopkins Medical Institutions, Baltimore, MD
American Cancer Society, Teaneck, NJ
Australia - New Zealand Breast Cancer Trials Group, Surfers Paradise, Australia
Laboratory of Biologic Chemistry, National Cancer Institute, Bethesda, MD
Lederle Advisory Board, New York City, NY
Gordon Conference on Cancer, Newport, RI
American Society of Clinical Pathologists, Las Vegas, NV
The Cancer Center at Fairfax Hospital, Fairfax, VA
American Fertility Society, New Orleans, LA
Visiting Professor, Department of Medicine, Hahnemann University School of Medicine, Philadelphia, PA
- 1993 NCI Strategy Meeting on Breast Cancer in Young Women, National Institutes of Health, Bethesda, MD

- St. Georges Society, University of Maryland School of Medicine, Baltimore, MD
 US-Japanese Joint Scientific Meeting on New Breast Cancer Therapies, Oakland, CA
 Isaac Lewin Symposium, Baystate Medical Center, Springfield MA
 Discussant, Adjuvant Breast Cancer Session, American Society of Clinical Oncology,
 Orlando, FL
 Educational Session, National Cancer Institute Phase I Meeting, Bethesda, MD
 Working Group on the Pulmonary Complications Associated with Breast Cancer
 Therapy, National Heart, Lung, and Blood Institute, National Institutes of Health,
 Bethesda, MD
 Shanghai Cancer Institute, Shanghai, Peoples Republic of China
 Ethics and Politics in Clinical Trials, Johns Hopkins Medical Institutions, Baltimore, MD
 NCI Workshop on Prognostic and Predictive Factors in Breast Cancer, Bethesda, MD
- 1994 Hematology/Oncology Grand Rounds, Wayne State University School of Medicine,
 Detroit, MI
 Clinical Oncology Program Grand Rounds, National Cancer Institute, Bethesda, MD
 NCI Strategy Meeting on High Dose Chemotherapy for Breast Cancer, Bethesda, MD
 11th Annual Advances in Cancer Treatment Research, Albert Einstein College of
 Medicine, New York City, NY
 Recent Advances in the Biology of Breast, Colon, and Lung Cancer, American Society of
 Clinical Oncology, Dallas, TX
 Discussant, Plenary Session, American Society of Clinical Oncology, Dallas, TX
 Women's Health Seminar Series, Breast Cancer, National Institutes of Health,
 Bethesda, MD
 Chemotherapy Symposium, Berlex Oncology Foundation, Leesburg, VA
 The State of Breast Cancer 1994: An Interactive Symposium, University of California at
 San Francisco, San Francisco, CA
 Grand Rounds, Washington County Hospital, Hagerstown, MD
 Y-ME of the Cumberland Valley, Hagerstown, MD
- 1995 Department of Pharmacology and Toxicology, Robert C. Byrd Health Sciences Center of
 West Virginia University, Morgantown, WV
 12th Annual International Breast Cancer Conference, Miami, FL
 Controversy Session, American Association for Cancer Research, Toronto, Canada
 Department of Pharmacology, Mayo Clinic, Rochester, MN
 Susan G. Komen Foundation Congressional Breakfast, Washington, DC
 Commonwealth of Massachusetts Course on Breast Cancer, Boston, MA
 Law and Health Care Program, University of Maryland and Baltimore School of Law,
 Baltimore, MD
 Discussant, Breast Cancer Session, American Society of Clinical Oncology, Los Angeles,
 CA
 Topics in Clinical Medicine, Johns Hopkins University School of Medicine, Baltimore,
 MD
 Gordon Research Conference on Mammary Gland Biology, New London, NH
 The Endocrine Society's 51st Conference on Recent Progress in Hormone Research,
 Stevenson, WA

- Eighteenth Thomas W. Green Memorial Lecture, East Tennessee State University James
 H. Quillen College of Medicine, Bristol, TN
 Fifth International Congress on Hormones and Cancer, Quebec City, Canada
 Cancer Medicine, Harvard Medical School, Boston, MA
 Medical Oncology Board Review, George Washington University School of Medicine,
 Washington, DC
 The First Annual Kimmel-Slavin Memorial Lecture, George Washington University
 School of Medicine, Washington, DC
 Chemotherapy Symposium, Berlex Oncology Foundation, Leesburg, VA
 Meet the Professor, American Society of Clinical Oncology Fall Educational Conference,
 Washington, DC
 Grand Rounds, Department of Medicine, Johns Hopkins University School of Medicine,
 Baltimore, MD
 Division of Hematology/Oncology, Washington Hospital Center, Washington, DC
 18th Annual San Antonio Breast Cancer Symposium, San Antonio, TX
 Department of Medicine, St. Joseph Hospital, Baltimore, MD
 Dana-Farber Cancer Institute, Boston, MA
 22nd Annual Symposium on the Diagnosis and Treatment of Neoplastic Disorders, Johns
 Hopkins
- 1996 Department of Embryology, Carnegie Institute of Washington, Baltimore, MD
 Mayo Clinic Cancer Center, Rochester, MN
 New Approaches to Cancer Therapy, The Johns Hopkins Oncology Center,
 Baltimore, MD
 Topics in Clinical Medicine, Johns Hopkins University School of Medicine, Baltimore,
 MD
 University of Maryland Cancer Center, Baltimore, MD
 Discussant, Breast Cancer Session, American Society of Clinical Oncology, Philadelphia,
 PA
 Bowman Gray Comprehensive Cancer Center, Wake Forest University, Winston-Salem,
 N.C.
 American College of Surgeons, San Francisco, CA
 Session Chair, Gordon Conference on Cancer Chemotherapy, Oxford, UK
 Chemotherapy Symposium, Berlex Oncology Foundation, Leesburg, VA
 City of Hope National Medical Center, Duarte, CA
 Upstate New York Cancer Research and Education Foundation, Syracuse, NY
 Wendy and Emery Reeves International Breast Cancer Symposium, University of Texas
 Southwestern
 Medical Center, Dallas, TX 30th Anniversary Symposium, National Institute of
 Environmental Health Sciences, Research Triangle, NC
 Meet the Professor, American Society of Clinical Oncology Fall Educational
 Conference, Phoenix, AZ
 Maryland Cancer Control Symposium, Baltimore, MD
 Lombardi Cancer Center, Georgetown University Medical Center, Washington, DC
 Department of Biochemistry, Johns Hopkins School of Hygiene and Public Health,
 Baltimore, MD

- 1997 Breast Cancer Think Tank 7, St. Lucia
 4th Annual Breast Cancer Symposium of the New York Metropolitan Breast Cancer Group, New York City, NY
 2nd Annual Multidisciplinary Symposium on Breast Disease, Amelia Island, FL
 University of Colorado Cancer Center, Denver, CO
 Cambridge Symposium, Genetic Approaches to Breast and Prostate Cancer, Lake Tahoe, CA
 St. George's Society, University of Maryland Medical School, Baltimore, MD
 Issues in the Treatment of Breast Cancer, Greater Baltimore Medical Center, Baltimore, MD
 University of Chicago Cancer Center, Chicago, IL
 Conjoint Clinic, Johns Hopkins University School of Medicine, Baltimore, MD
 Breast Cancer Tumor Panel, American Society of Clinical Oncology, Denver, CO
 Pittsburgh Cancer Institute, University of Pittsburgh Medical School, Pittsburgh, PA
 International Cancer Alliance, Washington, DC
 Perspectives in Breast Cancer, Emory University, Atlanta, GA
 US Public Health Services Office on Women's Health Healthy Women 2000, Washington, DC
 Chemotherapy Symposium, Berlex Oncology Foundation, Leesburg, VA
 American College of Surgeons, Chicago, IL
 Susan G. Komen Foundation Breast Cancer Symposium, Dallas, TX
 Medical Oncology Board Review, George Washington University School of Medicine, Washington, DC
 Case Western Reserve University/Ireland Cancer Center, Cleveland, OH
 Holy Cross Hospital, Silver Spring, MD
 Department of Medicine and Cancer Center, University of California at San Francisco, San Francisco, CA
 American Society of Clinical Oncology Fall Education Conference, Orlando, FL
 14th Annual American College of Physicians/Army Regional Meeting, Reston, VA
 Fallston Hospital, Fallston, MD
- 1998 Breast Cancer Think Tank 8, Tobago
 Session Co-Chair, 6th International Conference on Adjuvant Therapy of Primary Breast Cancer, St. Gallen, Switzerland
 Controversy Session Chair, American Association for Cancer Research, New Orleans, LA
 24th Annual Symposium on Diagnosis and Treatment of Neoplastic Diseases, Johns Hopkins Medical Institutions, Baltimore, MD
 Breast Cancer Symposium, Inova Fairfax Hospital, Fairfax, VA
 Discussant, Plenary Session, American Society of Clinical Oncology, Los Angeles, CA
 Department of Pathology, Vanderbilt School of Medicine, Nashville, TN
 Suburban Hospital, Bethesda, MD
 Department of Medicine, Columbia-Presbyterian Medical Center, New York City, NY
 Gordon Conference on Cancer, Newport, RI

- Current Topics in Breast Cancer Research III: Cell Death in Breast Cancer, Cambridge, UK
 Chemotherapy Symposium, Berlex Oncology Foundation, Leesburg, VA
 2nd Annual Advances in Cancer Therapy, VCU/MCV, Richmond, VA
 Kent and Queen Anne's Hospital, Chestertown, MD
 Breast Cancer Awareness Month, The White House Washington, DC
 Medical Oncology Board Review, George Washington University School of Medicine, Washington, DC
 21st Annual San Antonio Breast Cancer Symposium, San Antonio, TX
- 1999 Breast Cancer Think Tank 9, St. Thomas, Virgin Islands
 Joint Cancer Conference of the Florida Universities, Orlando, FL
 Grand Rounds, Department of Medicine, Johns Hopkins Medical Institutions, Baltimore, MD
 Congressionally Directed Medical Research Programs, Frederick, MD
 Topics in Internal Medicine, Department of Medicine, Johns Hopkins, Baltimore, MD
 American Society of Clinical Oncology, Atlanta, GA
 1st Milan Breast Cancer Conference, Milan, Italy
 Johns Hopkins Singapore, Singapore
 Grand Rounds, Department of Surgery, Northwest Hospital, Baltimore, MD
 6th Nottingham International Breast Cancer Conference, Nottingham, England
 Seeking Excellence in Breast Cancer Care: Best Practices in Diagnosis and Treatment, Johns Hopkins University School of Medicine, Baltimore, MD
 First Annual Lynn Sage Breast Cancer Symposium, Robert H. Lurie Comprehensive Cancer Center of Northwestern University, Chicago, IL
 Chemotherapy Symposium, Berlex Oncology Foundation, Leesburg, VA
 Cancer Medicine, Harvard Medical School, Boston, MA
 41st Annual Meeting of the American Society of Therapeutic and Radiation Oncology, San Antonio, TX
 SERMs - Implication for Prevention and Treatment of Cancer, Philadelphia, PA
 American Society of Clinical Oncology Fall Education Conference, San Francisco, CA
 Genetics Program, University of Missouri, Columbia, MO
 22nd Annual San Antonio Breast Cancer Symposium, San Antonio, TX
- 2000 Sibley Hospital, Washington, DC
 Franklin Square Hospital, Baltimore, MD
 Molecular Biology of Breast Cancer, Lillehammer, Norway
 Keystone Symposium in Advances in Human Breast and Prostate Cancer, Lake Tahoe, NV
 NIH Workshop on Selective Estrogen Receptor Modulators (SERMs), Bethesda, MD
 Topics in Internal Medicine, Johns Hopkins University School of Medicine, Baltimore, MD
 National Breast Cancer Coalition Eighteenth Annual Advocacy Training Conference
 2nd Milan Breast Cancer Conference, Milan, Italy
 Australia - New Zealand Breast Cancer Trials Group, Queenstown, New Zealand
 Suburban Hospital, Bethesda, MD

- 15th Annual Excalibur Round Table, American Cancer Society, Baltimore, MD
 Susan G. Komen Breast Cancer Foundation National Symposium - Reaching for the
 Cure..... Making a Difference, Washington, DC
 WellStar Kennestone Hospital, Marietta, GA
 WellStar Cobb Hospital, Marietta, GA
 Hematology-Oncology Board Review, George Washington University School of
 Medicine, Arlington, VA
 Berlex Oncology Foundation Clinical Pharmacology of Anticancer Drugs, Leesburg, VA
 42nd Annual Meeting of the American Society of Therapeutic and Radiation Oncology,
 Boston, MA
 National Institutes of Health Consensus Development Conference on Adjuvant Therapy
 of Breast Cancer, Bethesda, MD
 Seeking Excellence in Breast Cancer Care, Johns Hopkins University School of Nursing
 and School of Medicine, Baltimore, MD
- 2001 Breast Cancer Think Tank 11, Punta Cana, Dominican Republic Potential Clinical
 Applications for GnRH Agonists, National Institutes of Health, Bethesda, MD
 7th International Conference on Adjuvant Therapy of Primary Breast Cancer, St. Gallen,
 Switzerland
 8th Annual Miami Breast Cancer Conference, Miami, FL
 Central Pennsylvania Oncology Group, Harrisburg, PA
 Mary E. Humphreys Biology Lecture, Mary Baldwin College, Staunton, VA
 Department of Medicine Grand Rounds, Johns Hopkins Bayview, Baltimore, MD
 Discussant, American Society of Clinical Oncology, San Francisco, CA
 Anne Arundel Medical Center, Annapolis, MD
 Lombardi Comprehensive Cancer Center, Georgetown University, Washington, DC
 Women's Malignancy Group, MD Anderson Cancer Center, Houston, TX
 3rd Milan Breast Conference, Milan, Italy
 Gordon Conference on Polyamines, New London, CT
 Australian Society for Breast Diseases, Surfers Paradise, Australia (by video conference)
 White House/Komen Breast Cancer Summit, Washington, DC
 3rd Annual Lynn Sage Breast Cancer Symposium, Northwestern University, Chicago, IL
 Hematology-Oncology Board Review, George Washington University School of
 Medicine, Arlington, VA
 Berlex Oncology Foundation Clinical Pharmacology of Anticancer Drugs, Leesburg, VA
 Tumor Board, Greater Baltimore Medical Center, Baltimore, MD
 Hematology Grand Rounds, Johns Hopkins, Baltimore, MD
 William L. McGuire Memorial Lecture, 24th Annual San Antonio Breast Cancer
 Symposium, San Antonio, TX
- 2002 Breast Cancer Symposium Think Tank 12, St. Maarten, The Netherlands Antilles
 Grand Rounds Department of Medicine, Johns Hopkins University, Baltimore, MD
 Current Trends in Breast Cancer, Philadelphia, PA
 3rd European Breast Cancer Conference, Barcelona, Spain
 The Third North American Symposium on Skeletal Complications of Malignancy,
 National Institutes of Health, Bethesda, MD

- Educational Symposium, American Society for Clinical Oncology, Orlando, FL
 4th Milan Breast Cancer Conference, Milan, Italy
 Second International Conference on Recent Advances and Future Directions in Endocrine Manipulation of Breast Cancer. Cambridge, MA
 Breast Cancer: Current Controversies and New Horizons, Dana Farber Cancer Institute, Boston, MA
 Center for Cancer Research Grand Rounds, National Cancer Institute, Bethesda, MD
 2nd Annual Karmanos Cancer Institute Breast Cancer Symposium, Detroit, MI
 Era of Hope, Department of Defense Breast Cancer Research Program, Orlando, FL
 Fox Chase Cancer Center, Philadelphia, PA
 IX Congresso Nacional de Oncologia, Lisbon, Portugal
- 2003 NCI – Hopkins Workshop on Clinical Translation of Gene Re-expression in Cancer, Baltimore, MD
 Breast Cancer Think Tank 13, Aruba
 20th Annual Miami Breast Cancer Conference, Miami, FL
 8th International Conference on Primary Therapy of Early Breast Cancer, St. Gallen, Switzerland
 American Society for Breast Disease, Dallas, TX
 Upper Chesapeake Medical Center, Fallston, MD
 American Society of Clinical Oncology, Chicago, IL
 Gordon Conference on Cancer Chemotherapy, Oxford, UK
 National Cancer Institute Workshop on Ductal Lavage, Bethesda, MD
 9th Annual Perspectives in Breast Cancer, Boston, MA
 Cancer Education Consortium Clinical Pharmacology of Anticancer Agents, Leesburg, VA
 Indiana University Cancer Center, Indianapolis, IN
 4th Annual Hampton Roads Fall Cancer Conference, Portsmouth, VA
 Friends of Cancer Research, Woodrow Wilson International Center for Scholars, Washington, DC
 Astrazeneca Breast Cancer Symposium, Waltham, MA
- 2004 Breast Cancer Think Tank 14, St Kitts
 Translational Conference, Johns Hopkins Oncology Center, Baltimore, MD
 Current Trends in Breast Cancer: Updates from the 2003 San Antonio Breast Cancer Symposium, Washington, DC
 Breast Cancer—Bench to Bedside, Loyola University, Chicago, IL
 Massachusetts General Hospital, Boston, MA
 4th European Breast Cancer Conference, Hamburg, Germany
 American Association for Cancer Research, Orlando, FL
 The Philip A. Tumulty Topics in Clinical Medicine at Johns Hopkins, Baltimore, MD
 Medical Grand Rounds, University of Florida—Shands Medical School, Gainesville, FL
 Henry Lemon Memorial Lecture, University of Nebraska—Eppley Cancer Center, Omaha, NE
 Discussant, Best of Oncology Symposium, American Society of Clinical Oncology, New Orleans, LA

6th Milan Breast Cancer Symposium, Milan, Italy
 Gordon Conference on Molecular Therapeutics of Cancer, New London, NH
 7th Annual Mission Conference of the Susan G. Komen Breast Cancer Foundation,
 Washington, DC
 George Washington University Hematology-Oncology Board Review Course,
 Alexandria, VA
 Cancer Education Consortium Clinical Pharmacology of Anticancer Agents, Leesburg,
 VA
 6th Lynn Sage Breast Cancer Symposium of Northwestern University, Chicago, IL
 Alta Bates Summit Medical Center, Berkeley, CA
 Association of Northern California Oncologists, San Francisco, CA
 4th American Association for Cancer Research Prevention Meeting, Seattle, WA
 Project LEAD, National Breast Cancer Coalition, Washington, DC
 Mayo Clinic Oncology Society, Rochester, MN
 Department of Molecular Pharmacology and Experimental Therapeutics, Mayo Clinic,
 Rochester, MN
 Career Day, Baltimore Polytechnic Institute, Baltimore, MD
 2nd Breast Cancer Inter-SPORE Meeting, Chapel Hill, NC
 27th Annual San Antonio Breast Cancer Symposium, San Antonio, TX

2005 Greenebaum Cancer Center, University of Maryland Medical School, Baltimore, MD
 Breast Cancer Think Tank 15, Curacao
 22nd Miami Breast Cancer Symposium, Miami, FL
 Lorne Cancer Conference, Phillip Island, Australia
 Delaware Oncology Society, Wilmington, DE
 New Strategies in Breast Cancer Conference, Philadelphia, PA
 Educational Symposium, American Society of Clinical Oncology, Orlando, FL
 Highlights of the Day Symposium, American Society of Clinical Oncology, Orlando, FL
 National Breast Cancer Coalition Fund Annual Advocacy Conference, Washington, DC
 Third International Symposium on the Molecular Biology of Breast Cancer, Molde,
 Norway
 Breast Cancer: Current Controversies and New Horizons, Harvard Medical School,
 Boston, MA
 New England Journal of Medicine Clinical Pathologic Conference, Harvard Medical
 School, Boston, MA
 Hematology-Oncology Board Review, George Washington University Medical Center,
 Washington, DC
 Frances Bull Lecture, University of Michigan, Ann Arbor, MI
 University of Minnesota Cancer Center, Minneapolis, MN
 50th Anniversary Avon Foundation Symposium, New York City, NY
 Cancer Education Consortium Clinical Pharmacology of Anticancer Agents, Leesburg,
 VA
 100 Women Professors Symposium, Johns Hopkins, Baltimore, MD
 Working Group on Translational Epigenetics in Cancer, National Cancer Institute,
 Bethesda, MD

- 2006 Mayo Clinic, Rochester, MD
Helen Padykula Lecture, Wellesley College, Wellesley, MA
Lynne Abraham Symposium, Susan G. Komen Foundation, New York City, NY
Third Current Concepts in the Multidisciplinary Management of Breast Cancer, Johns Hopkins, Baltimore, DC
Forum on Breast Cancer Prevention. American Association of Cancer Research, Washington, DC
Vth Santiago Breast Cancer Symposium, Santiago, Chile
8th Milan Breast Cancer Symposium, Milan, Italy
International Union Against Cancer (UICC) World Cancer Congress, Washington, DC
8th Lynn Sage Breast Cancer Symposium, Chicago, IL
Hematology-Oncology Board Review, George Washington University Medical Center, Washington, DC
Cancer Education Consortium Clinical Pharmacology of Anti-Cancer Agents, Leesburg, VA
44th Meeting of the Japan Society of Clinical Oncology, Tokyo, Japan
National Comprehensive Cancer Network Adjuvant Therapy in Breast Cancer Symposium, Baltimore, MD
Women's Board, Johns Hopkins Hospital, Baltimore, MD
National Cancer Institute-Ft. Detrick Distinguished Scientist Seminar, Frederick, MD
Science Lecture Series 2006-7 Radcliffe Institute for Advanced Study, Cambridge, MA
- 2007 Johns Hopkins Workshop on Clinical Targeting of Epigenetic Changes in Cancer Treatment, Phoenix, Arizona
24th Annual Miami Breast Cancer Conference, Miami, FL
6th Annual Mid-Atlantic Oncology Update, St Agnes Hospital, Baltimore, MD
10th International Conference on Primary Therapy of Early Breast Cancer, St. Gallen, Switzerland
Breast Cancer Think Tank 17, Playa del Carmen, Mexico
Annual Advances in Basic Science Symposium, Northwestern University Cancer Center, Chicago, IL
American Society of Clinical Oncology Education Symposium, Chicago, IL
10th Komen Mission Conference, Washington, DC
St Joseph's Hospital, Baltimore, MD
Australia-New Zealand Breast Cancer Clinical Trials Annual Meeting, Alice Springs, Australia
National Cancer Advisory Board, Bethesda, MD
Hematology-Oncology Board Review, George Washington University Medical Center, Washington, DC
CR-UK Cambridge Research Institute Plenary Lecture, 3rd National Cancer Research Institute Cancer Conference, Birmingham, UK
President's Cancer Panel, San Diego, CA
Scientific Symposium, Breast Cancer Research Foundation, New York City, NY
Florida Oncology Society, Orlando, FL
Collaborative Summit on Breast Cancer Research, Foundation for the NIH, Lansdowne, VA

- American Association of Cancer Research Prevention Symposium, Philadelphia, PA
- 2008 7th Rosalind E. Franklin Award for Women in Science, National Cancer Institute, Bethesda, MD
 Breast Cancer Think Tank 18, Waikaloa, HI
 Cancer Institute of New Jersey, New Brunswick, NJ
 5th Early Detection Research Network Scientific Workshop, National Cancer Institute, Bethesda, MD
 Vanderbilt-Ingram Comprehensive Cancer Center, Nashville, TN
 11th American Association for Cancer Research-Women in Cancer Research Charlotte Friend Award, San Diego, CA
 14th Annual Educational Symposium, Susan G. Komen for the Cure Maryland, Baltimore, MD
 4th Current Concepts in the Multidisciplinary Management of Breast Cancer, Johns Hopkins University, Baltimore, MD
 Department of Medicine, University of Pennsylvania School of Medicine, Philadelphia, PA
 Best of ASCO, Boston, MA
 Annual Meeting of the American Association for Clinical Chemistry, Washington, DC
 Seventh International Congress on the Future of Breast Cancer, Kauai, HI
 Nuclear Hormone Receptors, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY
 Hematology-Oncology Board Review, George Washington University, Washington, DC
 Fourth Annual Oncology Congress, San Francisco, CA
 Oberstar Lecture, George Washington University, Washington, DC
- 2009 Breast Cancer Think Tank 19, Costa Rica
 Bernard Fisher Lecture, University of Pittsburgh, Pittsburgh PA
 11th International Congress Oncology Conference on Primary Therapy of Early Breast Cancer, Saint Gallen, Switzerland
 Grand Rounds, MD Anderson Cancer Center – Houston TX
 Women Leading the Way, MD Anderson Cancer Center, Houston, TX
 Jean Sindab Lecture, Emory Winship Cancer Institute, Atlanta, GA
 Oncology Grand Rounds, Ohio State University, Columbus, OH
 16th Annual Pennsylvania Bar Association Women in the Profession, Pittsburgh, PA
 American Society of Clinical Oncology Educational Symposium, Orlando, FL
 24th Annual Aspen Cancer Conference, Aspen, CO
 Harvard Breast Cancer Conference, Boston, MA
 Medical Grand Rounds, UPMC Shadyside Hospital, Pittsburgh, PA
 University of Pittsburgh Postdoctoral Association Data and Dine Lecture, Pittsburgh, PA
 Women's Studies and the Provost's Advisory Committee on Women's Concerns New Faculty Lecture, University of Pittsburgh, Pittsburgh, PA
 Pancreasfest 2009, University of Pittsburgh, Pittsburgh, PA
 AACR Advances in Breast Cancer Research, San Diego, CA
 Cincinnati Cancer Symposium, Jensen Symposium on Nuclear Receptors, Cincinnati, Ohio
 Translating Scientific Advances into Clinical Care Cancer, Lineberger Comprehensive

- Cancer Center, Chapel Hill, NC
 New Options in Breast Cancer Treatment, UPMC Cancer Centers, Johnstown, PA
- 2010 University of Pittsburgh Winter Academy, Naples, FL
 Achievement Rewards for College Scientists, Pittsburgh, PA
 Medical Grand Rounds, UPMC Montefiore University Hospital, Pittsburgh, PA
 Katz Lecture, Magee Womens Hospital of Pittsburgh, Pittsburgh, PA
 NYU Cancer Institute Seminar Series, New York, NY
 The Regional Cancer Center, Erie, PA
 Leses Visiting Professor, Medical Grand Rounds, Beth Israel Deaconess Medical Center, Boston, MA
 Hematology-Oncology Grand Rounds, Beth Israel Deaconess Medical Center, Boston, MA
 University of Maryland Marlene and Stewart Greenebaum Cancer Center, Hormone Responsive Cancer Program Retreat, Baltimore, MD
 Lois O'Grady Breast Cancer Lecture, University of California Davis Cancer Center, Sacramento, CA
 11th Annual Advances in Oncology, University of California Davis Cancer Center, Sacramento, CA
 American Society of Clinical Oncology Breast Cancer Symposium - Gianni Bonadonna Award, Washington, DC
 Advances in Oncology, Keynote speaker, UPMC Beacon Hospital, Ireland
 Oncology Grand Rounds, Thomas Jefferson University Kimmel Cancer Center, Philadelphia, PA
- 2011 Dept of Environmental & Occupational Health, University of Pittsburgh, Pittsburgh, PA
 Department of Pharmaceutical Sciences, University of Pittsburgh, Pittsburgh, PA
 Breast Cancer Program Retreat, UCSF Cancer Center, San Francisco, CA
 Lineberger Cancer Center, UNC Chapel Hill, Chapel Hill, NC
 XI Michelangelo Foundation Seminar, Milan Italy
 Georgetown University, Undergraduate Research Conference Keynote Speaker, Washington, DC
 City of Hope Cancer Center Grand Rounds, Duarte, CA
 Cleveland Clinic Grand Rounds, Taussig Cancer Center, Cleveland, Ohio
 McArdle Laboratory Seminar, University of Wisconsin, Madison, WI
 13th Milan Breast Cancer Conference, Milan, Italy
 Annual Meeting, American Society of Clinical Oncology, Chicago, IL
 International Cancer Conference, Trinity Medical School, Dublin, Ireland
 Fifth Annual Ri.MED Scientific Symposium, Palermo, Italy
 Medical Oncology Board Review, George Washington University, Washington, DC
 Department of Epidemiology, University of Pittsburgh, Pittsburgh, PA
 Department of Pharmacology and Chemical Biology, University of Pittsburgh, Pgh, PA
 San Antonio Breast Cancer Symposium, San Antonio, TX
- 2012 Breast Cancer Think Tank 22, Mexico

- Siteman Cancer Center at Washington University, Saint Louis, MO
 Miami Breast Cancer Conference, Miami, FL
 University of Pittsburgh Department of Pathology, Pittsburgh, PA
 American Society of Preventive Oncology, Washington, DC
 Tsinghua University, Beijing, China
 University of Pittsburgh, Chancellors Inaugural Lecture - Hillman Professor of Oncology, Pittsburgh, PA
 University of Chicago Cancer Biology Seminar Series, Chicago, IL
 Johns Hopkins University School of Medicine, Baltimore, MD
 American Society of Clinical Oncology, Chicago, IL
 34th Annual Scientific Meeting, Australia-New Zealand Breast Cancer Trials Group, Hobart, Australia
 Medical Oncology Board Review, George Washington University, Washington, DC
 University of Texas Southwestern, Pamela Hearn Isom Lecture, Medicine Grand Rounds, Dallas Texas
 Potamkin Lecture, PA Breast Cancer Coalition Conference, Harrisburg, PA
 Northwestern University Feinberg School of Medicine's 16th Annual Department of Pathology Joseph C. Calandra Lecture, Chicago, IL
 The Shanghai Breast Cancer Symposium, Shanghai, China
- 2013 Bay City Capital Scientific Advisory Board Meeting
 13th International Congress Oncology Conference on Primary Therapy of Early Breast Cancer, St. Gallen, Switzerland
 Annual Meeting, American Association of Cancer Research, Washington, DC
 Case Western Reserve Comprehensive Cancer Center, Cleveland, Ohio
 Medical Oncology Board Review, George Washington University, Washington, DC
 The Hong Kong University of Science and Technology, Tetralateral Symposium, Hong Kong
 PA Cancer Planning Summit, Pittsburgh, PA
 Breast Cancer Symposium, San Francisco, CA
 Cancer Caucus, House of Representatives, Harrisburg, PA
 Science 2013, Pittsburgh, PA
 Global Breast Cancer Conference, Seoul, South Korea
- 2014 Annual Meeting, American Association for Cancer Research, San Diego, CA
 American Society of Clinical Oncology, Chicago, IL
 German Cancer Research Center (DKFZ), Heidelberg, Germany
 Medical Oncology Board Review, George Washington University, Washington, DC
 National Cancer Advisory Board, Bethesda, MD
 International Oncology Symposium, Astana, Kazakhstan
 University of Chicago Simon M. Shubitz Lecture, Chicago, IL
 Congressional Briefing, Alliance for Health Reform, Washington, DC
 San Antonio Breast Cancer Conference, San Antonio, TX
- 2015 14th St. Gallen International Breast Cancer Conference, Primary Therapy of Early Breast Cancer, Vienna, Austria

Pediatric Hematology/Oncology Pediatric Hematology/Oncology BMT & CT
 Conference, Childrens Hospital of Pittsburgh, Pittsburgh, PA
 University of Pittsburgh, Winter Academy, Palm Beach, Florida
 The Wistar Institute, Distinguished Lecture, Philadelphia, PA
 Annual Meeting, American Association for Cancer Research, Philadelphia, PA
 Inaugural Lecture as Distinguished Professor of Medicine, University of Pittsburgh,
 Pittsburgh PA
 Stephen D Williams, MD Lectureship, Indiana University Simon Cancer Center,
 Indianapolis, IN
 Medical Oncology Board Review, George Washington University, Washington, DC
 ASCO 2015 Breast Cancer Symposium, San Francisco, CA
 Taipei Medical University, Taipei, Taiwan
 Eighth Annual Robert B. Dickson Memorial Lectureship, Georgetown University
 Lombardi Cancer Center, Washington DC
 First Gabriel Hortobagyi Lecture, MD Anderson Cancer Center, Houston, TX
 Lynn Sage Distinguished Lecture, Robert H. Curie Comprehensive Cancer Center of
 Northwestern University, Chicago, IL

- 2016 University of Pittsburgh, Winter Academy, Palm Beach, Florida
 American Association for Cancer Research (AACR), 2016 Annual Meeting,
 New Orleans, LA
 American Society of Clinical Oncology (ASCO), 2016 Annual Meeting, Chicago, IL
 Maryland Breast Cancer Consortium, Baltimore, MD
 AACR High Tech Strategic Business Meeting, Sunnyvale, CA
 Medical Oncology Board Review, George Washington University, Washington, DC
 Great Lakes Breast Cancer Symposium, University of Pittsburgh, Pittsburgh, PA
 Seattle Cancer Care Alliance, Anchorage, Alaska
 2016 Cooper Lecture, University of Pittsburgh, Pittsburgh, PA

3. Other Research Related Activities

PATENTS GRANTED:

US Patent 7,858,317 B2 Aberrantly methylated genes as markers of breast malignancy (Sukumar S, Evron E, Dooley WC, Sacchi N, Davidson N, Fackler MJ). Issued December 28, 2010

EDITORIAL BOARDS:

1993-1995, 2006-9	Journal of Clinical Oncology
1995-2005	Cancer Research
1995-2009	The Breast Journal
1996-2011	The Breast
1997-2005	American Journal of Medicine
1999-2005	Clinical Cancer Research

2007-2014	Hem/Onc Today
2008-present	Oncology
2008-present	Cancer Prevention Research
2012-present	Journal of the National Cancer Institute
2012-present	Breast Cancer Research and Treatment

STUDY SECTION MEMBERSHIPS:

1988	Member, Ad Hoc Technical Review Section, National Cancer Institute, Bethesda, MD
1990, 1991, 1992	Ad Hoc Member, Reproductive Endocrinology Study Section, National Institutes of Health, Bethesda, MD
1992-1993	Member, Awards Committee, Susan G. Komen Foundation, Dallas, TX
1993-1997	Member, Reproductive Endocrinology Study Section, National Institutes of Health, Bethesda, MD
1994	Member, Walt Disney – American Cancer Society Breast Cancer Professorship Selection Committee, Atlanta, GA
1997-1998	Co-Chair, Progress Review Group for Breast Cancer Research, National Cancer Institute, Bethesda, MD
1996-1998	Chair, Pre-clinical and Clinical Studies Study Section, California Breast Cancer Research Program, San Francisco, CA
1999-present	Medical Advisory Board, Breast Cancer Research Foundation, New York City, NY
2001	Member, Breast and Prostate SPORE Review Group, National Cancer Institute
2002	Co-chair, Breast Cancer SPORE Review Group, National Cancer Institute
2003-2008	Vice-Chair, National Cancer Institute Breast Cancer Intergroup Correlative Science Committee
2002-2005	Member, Charles Kettering Prize Selection Committee, General Motors Cancer Research Foundation, Chair, 2005
2003	Chair, Innovator Award Review Committee, Department of Defense Breast Cancer Program
2005	Member, Lung and Bladder Cancer SPORE Review Group, National Cancer Institute
2005-2006	Ad hoc member, Kimmel Scholars Award Committee
2006-present	Member, Kimmel Scholars Award Committee
2006-2010	Member, Subcommittee A – Cancer Centers, National Cancer Institute
2008	Co-chair, Lung Cancer and Lymphoma SPORE Review Group, National Cancer Institute
2008-present	Member, Scientific Advisory Board, V Foundation for Cancer Research
2008	Chair, Therapeutic Targets I Review Committee, Susan G Komen for the Cure
2012-present	Member, Damon Runyon Cancer Research Foundation Clinical Investigator Award Committee
2012-2013	Chair of the Cancer Program Review, Helmholtz Senate Commission, Helmholtz Association of German Research Centers, Berlin, Germany
2014	Member, Scientific Advisory Committee, Breakthrough Breast Cancer, London, UK

2014-	Chair, CTAC SPORE Program Evaluation Working Group, NCI
2015	Chair, Stand Up To Cancer Canada-Canadian Breast Cancer Foundation Breast Cancer Dream Review Team Committee

EXTRA-MURAL GRANT REVIEWING:

Ad hoc grant reviewer for: National Institutes of Health, American Cancer Society, Veterans Administration, Manitoba (Canada) Health Council, Health Research Council of New Zealand, National Cancer Institute - Canada, Medical Research Council - Canada, Department of Defense Breast Cancer Program, many others

ADVISORY BOARD MEMBERSHIPS:

2000-present	Member, External Advisory Board, Vanderbilt-Ingram Cancer Center, Nashville, TN
2001-2006	Member, External Advisory Board, Fox Chase Cancer Center, Philadelphia, PA
2001-2011	Member, External Advisory Board, Bay Area UCSF Breast Cancer SPORE, San Francisco, SF
2003-present	Member, External Advisory Board, Karmanos Cancer Center, Detroit, MI
2003-2008	Member, External Advisory Board, Indiana University Cancer Center, Indianapolis, IN
2005-2016	Member, External Advisory Board, University of Maryland Cancer Center, Baltimore, MD
2008-present	Member, Board of Scientific Consultants, Memorial Sloan Kettering Cancer Center, New York City, NY
2008-present	Member, External Advisory Board, Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, Chapel Hill, NC, Chair 2014-
2009-present	Member, External Advisory Board, MD Anderson Cancer Center, Houston, TX Chair 2014-
2010-present	Member, External Advisory Board, University of Michigan Comprehensive Cancer Center
2010-present	Member, External Advisory Board, Washington University Siteman Cancer Center, St. Louis, MO
2010-present	Member, External Advisory Board Breast Cancer SPORE, Mayo Clinic, Rochester, MN
2010-present	Member, External Advisory Board, Institut National du Cancer, Paris, France
2011-present	Member, External Advisory Board, Fred Hutchinson Cancer Research Center University of Washington Cancer Consortium, Seattle, Washington
2011-present	Member, Scientific Advisory Board, CTSA, Case Western Reserve University School of Medicine, Cleveland, Ohio
2012-present	Member, Scientific Advisory Board, Cologne Center for Integrated Oncology, Cologne, Germany
2013-present	Member, External Advisory Board, Baylor College of Medicine Breast Cancer SPORE
2014-present	Member, External Advisory Board, University of Chicago Comprehensive Cancer Center, Chicago, IL

2014-2015	Member, Scientific Advisory Board, A. Alfred Taubman Medical Research Institute, University of Michigan, Ann Arbor, MI
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LIST OF CURRENT RESEARCH INTERESTS

Cancer biology and treatment, especially breast cancer

SERVICE

1. UNIVERSITY AND MEDICAL SCHOOL:

Committees - Johns Hopkins

1987	Co-Director, Oncology Multidisciplinary Conference
1987-1997	Member, Oncology Fellowship Selection Committee
1993-1995	Department Representative, Medical School Council
1999-2003	Departmental Appointments and Promotions Committee
2000-2005	Member, School of Medicine Professorial Promotion Committee
2001-2009	Member, MD-PhD Admissions Committee
2003-2005	Member, Search Committee for Director of Biophysics and Biophysical Chemistry

Committees – University of Pittsburgh, University of Pittsburgh Physicians (UPP), UPMC

2009-present	Member, Chair Management Committee
2009-present	Member, UPP Clinical Chairs Committee
2009-present	Member, Breast Cancer Steering Committee
2009-present	Member, Clinical Research Oversight Committee
2009-2012	Member, ReSet Steering Committee
2009-present	Member, Adolescent and Young Adult Cancer Committee
2010-2011	Member, Search Committee for Department of Medicine Chairman
2011-2012	Member, Search Committee for the Institute of Personalized Medicine
2012-present	Member, UPMC Presbyterian Shadyside Hillman Cancer Committee
2012-present	Member, School of Medicine Financial Oversight Committee
2014-present	Member, Internal Advisory Board Gynecologic SPORE
2015-present	Member, Internal Advisory Board for the Center for Causal Discovery
2015-present	Member, Internal Advisory Board of the Center for Medical Counter Measures Against Radiation (CMCR)

2. EXTERNAL ORGANIZATIONS:

1993-1995	Member, Medical Advisory Committee, Maryland Cancer Consortium
1994-1996	Executive Committee, American Cancer Society – Maryland Division Chair, Research Committee
1995-1998	Member, Medical Knowledge Self Assessment Program 11-Oncology, American College of Physicians

1999-2000	Planning Committee, National Institutes of Health Consensus Development Conference on Adjuvant Therapy for Breast Cancer, Bethesda, MD
1998-2001	Data Monitoring Committee, Southwest Oncology Group
1999-2006	Data Monitoring Committee, RUTH Trial, Lilly
2000-2006	Data Monitoring Committee, Breast Cancer International Research Group (BCIRG)
2003, 2005, 2007, 2009, 2011, 2013, 2015	Member, St. Gallen Consensus Panel, St. Gallen, Switzerland
2006-2011	Member, Data and Safety Monitoring Committee, TEACH Trial, Glaxo Smith Kline
2009-2012	NMR Center Advisory Committee, Carnegie Mellon University
2010-2016	Co-Chair, Breast Cancer Steering Committee, National Cancer Institute
2011-present	Member, Clinical Trials and Translational Research Advisory Committee (CTAC), National Cancer Institute, Chair 2015-present
2013-present	Board of Trustees, Phipps Conservatory, Pittsburgh, PA
2015-	Member, Search Committee for the Scientific Director (SD), Center for Cancer Research (CCR), National Cancer Institute
2015-	Member, Breast Cancer Now's Science Strategy Committee

ORIGINAL ARTICLE

Functional interaction of histone deacetylase 5 (HDAC5) and lysine-specific demethylase 1 (LSD1) promotes breast cancer progression

C Cao^{1,2,3}, SN Vasilatos^{1,3}, R Bhargava^{1,3,4}, JL Fine^{1,4}, S Oesterreich^{1,2,3}, NE Davidson^{1,2,3} and Y Huang^{1,2,3}

We have previously demonstrated that crosstalk between lysine-specific demethylase 1 (LSD1) and histone deacetylases (HDACs) facilitates breast cancer proliferation. However, the underlying mechanisms are largely unknown. Here, we report that expression of HDAC5 and LSD1 proteins were positively correlated in human breast cancer cell lines and tissue specimens of primary breast tumors. Protein expression of HDAC5 and LSD1 was significantly increased in primary breast cancer specimens in comparison with matched-normal adjacent tissues. Using HDAC5 deletion mutants and co-immunoprecipitation studies, we showed that HDAC5 physically interacted with the LSD1 complex through its domain containing nuclear localization sequence and phosphorylation sites. Although the *in vitro* acetylation assays revealed that HDAC5 decreased LSD1 protein acetylation, small interfering RNA (siRNA)-mediated HDAC5 knockdown did not alter the acetylation level of LSD1 in MDA-MB-231 cells. Overexpression of HDAC5 stabilized LSD1 protein and decreased the nuclear level of H3K4me1/me2 in MDA-MB-231 cells, whereas loss of HDAC5 by siRNA diminished LSD1 protein stability and demethylation activity. We further demonstrated that HDAC5 promoted the protein stability of USP28, a bona fide deubiquitinase of LSD1. Overexpression of USP28 largely reversed HDAC5-KD-induced LSD1 protein degradation, suggesting a role of HDAC5 as a positive regulator of LSD1 through upregulation of USP28 protein. Depletion of HDAC5 by shRNA hindered cellular proliferation, induced G1 cell cycle arrest, and attenuated migration and colony formation of breast cancer cells. A rescue study showed that increased growth of MDA-MB-231 cells by HDAC5 overexpression was reversed by concurrent LSD1 depletion, indicating that tumor-promoting activity of HDAC5 is an LSD1 dependent function. Moreover, overexpression of HDAC5 accelerated cellular proliferation and promoted acridine mutagen ICR191-induced transformation of MCF10A cells. Taken together, these results suggest that HDAC5 is critical in regulating LSD1 protein stability through post-translational modification, and the HDAC5–LSD1 axis has an important role in promoting breast cancer development and progression.

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INTRODUCTION

Lysine-specific demethylase 1 (LSD1) is the first identified FAD-dependent histone demethylase that has been typically found in association with a transcriptional repressor complex that includes CoREST, HDAC1/2, BHC80 and others.^{1–4} A role for elevated expression of LSD1 has been implicated in tumorigenesis in various cancers including breast cancer.^{3,5–9} Studies from our and other laboratories consistently showed that inhibition of LSD1 hindered proliferation of breast cancer cells.^{6,8,10} Lim *et al.*⁶ reported that LSD1 is highly expressed in estrogen receptor-negative breast cancers. A recent study found that LSD1 is significantly overexpressed in high-grade ductal carcinoma *in situ* or invasive ductal carcinoma versus low/intermediate ductal carcinoma *in situ*.¹¹ These studies point to a tumor-promoting role for LSD1 in breast cancer. We were among the first to report the use of small-molecule compounds and preclinical treatment strategies that have promise to work through this target in cancer.^{8,9,12} The development of novel LSD1 inhibitors is progressing rapidly. For example, a new generation of (bis)urea/(bis)thiourea LSD1 inhibitors displayed improved potency against LSD1 in cancer cells.¹³ A newly reported

GSK-LSD1 inhibitor exhibited interesting cell type-specific inhibition against small-cell lung cancer cells in preclinical models.¹⁴

However, how LSD1 is upregulated in breast cancer and the precise role of LSD1 in breast cancer development are still unclear. Our most recent work showed that small interfering RNA (siRNA)-mediated inhibition of HDAC5 led to a significant increase of H3K4me2, a known substrate of LSD1, suggesting a potential role of HDAC5 in regulating LSD1 activity.¹⁰ However, little is known about the precise role of HDAC5 and mechanisms underlying its regulation on LSD1 activity in breast cancer. HDAC5 is an important member of class IIa histone deacetylase (HDAC) isozymes with important functions in transcriptional regulation, cell proliferation, cell cycle progression and cellular developmental activities.^{15,16} HDAC5 has been shown to have important roles in many diseases including cancer.^{17,18} In this study, we addressed the following clinically relevant issues that have been understudied: (1) Is elevation of LSD1 expression associated with HDAC5 overexpression during breast cancer development? (2) How is LSD1 regulated by HDAC5 in breast cancer? (3) What is the role of the HDAC5–LSD1 axis in breast cancer initiation, proliferation and metastasis? To answer these questions, we delineated the

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mechanisms underlying the functional link between LSD1 and HDAC5 in chromatin remodeling and demonstrated that these two important chromatin modifiers closely cooperate to mediate proliferation, cell cycle and metastasis of breast cancer cells.

RESULTS

HDAC5 and LSD1 proteins are coordinately expressed in human breast cancer

To study the potential association of HDAC5 and LSD1 in breast cancer, we first examined mRNA levels of HDAC5 and LSD1 in human immortalized normal mammary epithelial MCF10A cells, fully malignant MCF10A-CA1a cells transformed from MCF10A cells with transfection of *HRAS*,¹⁹ and several human breast cancer cell lines. Quantitative PCR (qPCR) studies showed that there was no clear association of mRNA expression between HDAC5 and LSD1 in breast cancer cell lines (Figure 1a). The Oncomine-TCGA database showed moderate change of the mRNA level of LSD1 and HDAC5 in IBC (Supplementary Figures 1a and b). mRNA levels of both HDAC5 and LSD1 are altered in ~6% of breast cancer patients (www.cbioportal.org) without an apparent association with specific subtypes (Supplementary Figures 1c and d). However, protein expression of both HDAC5 and LSD1 was significantly elevated in malignant breast cell lines compared with MCF10A (Figure 1b), and protein levels of HDAC5 and LSD1 were positively correlated (Figure 1c). The correlation of HDAC5 and LSD1 protein expression was further validated in 50 primary breast cancers using immunohistochemical staining with validated antibodies (Supplementary Figures 2a and b). The χ^2 analysis showed a statistically significant correlation between HDAC5 and LSD1 protein expression in these tumors (Figure 1d). Furthermore, the immunohistochemistry (IHC) analysis showed that breast cancer tissues ($n=18$) expressed significantly higher level of HDAC5 and LSD1 than matched-normal adjacent tissues ($n=18$) (Figure 1e). The mean H-score for HDAC5 staining in stage 3 breast tumors ($n=25$) was statistically significantly higher than stage 2 counterparts ($n=25$). The mean H-score of LSD1 staining for stage 3 tumors was also higher than that of stage 2 tumors with a P -value of 0.07 (Figure 1f). These results were further validated with independent manual H-score evaluations by two breast cancer pathologists with moderate interobserver concordance (Supplementary Figures 3a and b). Taken together, these findings suggest that HDAC5 and LSD1 proteins are coordinately over-expressed in breast cancer cell lines and tissue specimens.

Physical interaction of LSD1 and HDAC5 in breast cancer cells

To address whether LSD1 and HDAC5 physically interact, a co-immunoprecipitation study was carried out in MDA-MB-231 and MCF10A-CA1a cells transiently transfected with pcDNA3.1 or pcDNA3.1-FLAG-HDAC5 plasmids. After immunoprecipitation (IP) with LSD1 antibody, we found that both endogenous and exogenous HDAC5 proteins were co-immunoprecipitated with LSD1 protein (Figure 2a). The interaction between native LSD1 and HDAC5 was further validated in additional breast cancer cell lines (Figure 2b). A similar result was obtained in the reciprocal immunoprecipitation using anti-FLAG antibody to confirm that

LSD1 was co-immunoprecipitated with FLAG-HDAC5 (Figure 2c). To precisely map the HDAC5 domain(s) responsible for interaction with LSD1, we expressed a series of HDAC5 deletion mutants engineered in pcDNA3.1-FLAG plasmids in MDA-MB-231 cells (Figure 2d). Immunoprecipitation assays of cells transfected with full-length HDAC5 complementary DNA (cDNA) confirmed the HDAC5–LSD1 interaction and deletion of an N-terminal myocyte enhancer factor-2 (MEF2) binding domain (HDAC5- Δ 1) alone had no impact on HDAC5–LSD1 interaction. However, removal of both the MEF2 domain and nuclear localization sequence (NLS) (HDAC5- Δ 2) completely abolished HDAC5–LSD1 interaction. Further deletion of an N-terminal HDAC and nuclear export sequence (HDAC5- Δ 3) and MEF2 domain (HDAC5- Δ 4) did not adversely alter LSD1 binding with HDAC5 fragments (Figure 2e). Immunofluorescence studies showed nuclear localization of full-length HDAC5, HDAC5- Δ 1, HDAC5- Δ 3 and HDAC5- Δ 4. Depletion of the NLS-containing domain (HDAC5- Δ 2) completely blocked HDAC5 nuclear translocation (Figure 2f). *In vitro* pull-down assays by using His-tag recombinant LSD1 protein incubating with HDAC5 full-length or deletion mutants validated that HDAC5 domain containing NLS element is essential for interaction with LSD1 (Supplementary Figure 4).

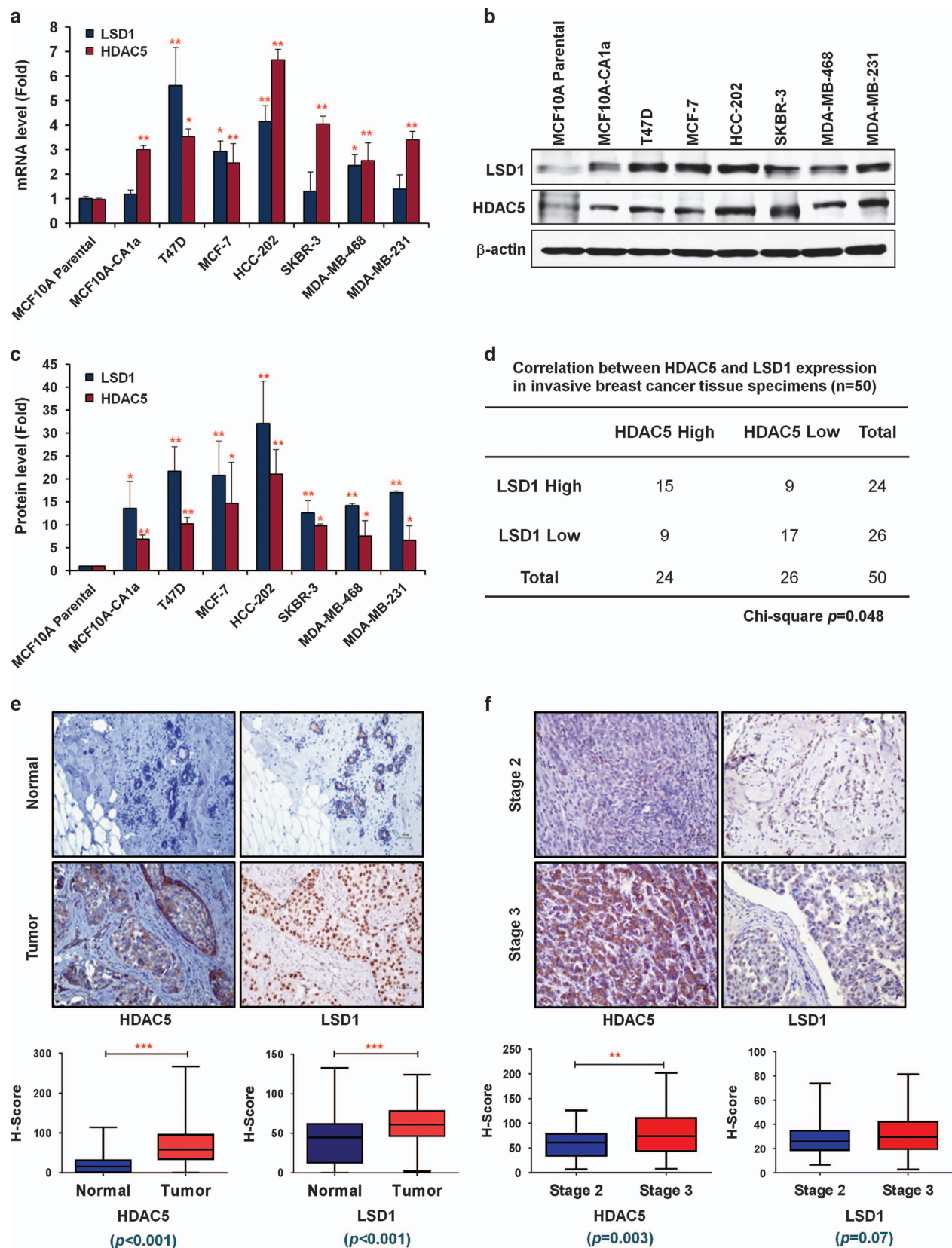
HDAC5 promotes LSD1 protein stability and activity

Next, we examined whether the mRNA or protein levels of HDAC5 and LSD1 were affected by their interaction with each other. Overexpression of HDAC5 in MDA-MB-231 cells failed to alter LSD1 mRNA expression, but led to a significant increase of LSD1 protein expression (Figures 3a and b). HDAC5 knockdown by siRNA attenuated LSD1 protein expression without affecting its mRNA level (Figures 3c and d). The effect of LSD1 on HDAC5 expression was subsequently assessed using our previously established MDA-MB-231-LSD1-KD cells.¹⁰ Depletion of LSD1 exerted no effect on HDAC5 mRNA or protein levels (Figures 3e and f). Simultaneous overexpression of pcDNA3.1-HDAC5 with HDAC5 siRNA significantly reversed the decrease of LSD1 (Supplementary Figure 5a). These results suggest that HDAC5 functions as an upstream regulator that governs LSD1 protein stability via post-translational regulation. Quantitative immunoblots showed that levels of H3K4me1/2 and AcH3K9, the substrates for LSD1 and HDAC5, respectively, were downregulated by HDAC5 overexpression, whereas loss of HDAC5 exerted the opposite effect (Figure 3g; Supplementary Figure 5b), suggesting a critical role of HDAC5 in governing chromatin modifying activity of LSD1. The cycloheximide chase assay showed that overexpression of HDAC5 significantly extended LSD1 protein half-life, whereas depletion of HDAC5 by siRNA decreased LSD1 protein half-life in MDA-MB-231 cells (Figures 3h and i; Supplementary Figure 5c). To determine whether other recognized LSD1 cofactors or HDACs exert similar effects on LSD1 protein stability, MDA-MB-231 cells were treated with siRNA against several LSD1 complex cofactors (CoREST, HDAC1 and HDAC2) or other class II HDAC isozymes (HDAC 4, 6, 7, 9, 10), respectively. Transfection with siRNA probes effectively knocked down mRNA expression of target genes without affecting LSD1 protein level (Figure 3j; Supplementary Figure 6a). To confirm the qPCR results, quantitative immunoblotting (IB) was performed and showed depletion of

Figure 1. Correlated overexpression of HDAC5 and LSD1 protein in breast cancer. **(a)** The levels of mRNA expression of HDAC5 and LSD1 in breast cancer cell lines versus MCF10A cells (set as fold 1) using real-time qPCR with β -actin as an internal control. **(b)** Immunoblots with anti-HDAC5 and LSD1 antibodies in indicated cell lines. β -actin protein was blotted as a loading control. **(c)** Histograms represent the mean protein levels of HDAC5 or LSD1 in three determinations relative to β -actin $\pm$ s.d. as determined by quantitative immunoblots. **(d)** 50 primary human invasive breast tumor samples were immunostained with antibodies against HDAC5 or LSD1. The χ^2 study was performed by using median H-scores as the cutoff for high- versus low-protein expression. **(e)** Representative HDAC5 and LSD1 staining (200 $\times$) in invasive breast carcinoma and adjacent normal tissue specimens from one representative patient. H-scores represent average staining intensity in breast tumors ($n=18$) versus adjacent normal breast tissue ($n=18$). **(f)** Representative HDAC5 and LSD1 staining (200 $\times$) in stage 2 and 3 invasive breast carcinoma specimens. H-scores represent average staining intensity in stage 3 breast tumors ($n=25$) versus stage 2 breast tumors ($n=25$). * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, Student's t -test.

CoREST led to insignificant change of LSD1 protein stability (Supplementary Figure 6b and 6c). Together, these results strengthen the conclusion that HDAC5 functions as a positive regulator of LSD1 protein in breast cancer cells.

HDAC5 regulates LSD1 protein stability through modulation of the LSD1-associated ubiquitination system
Protein ubiquitination assays indicated that HDAC5 overexpression significantly attenuated LSD1 polyubiquitination (Figure 4a),



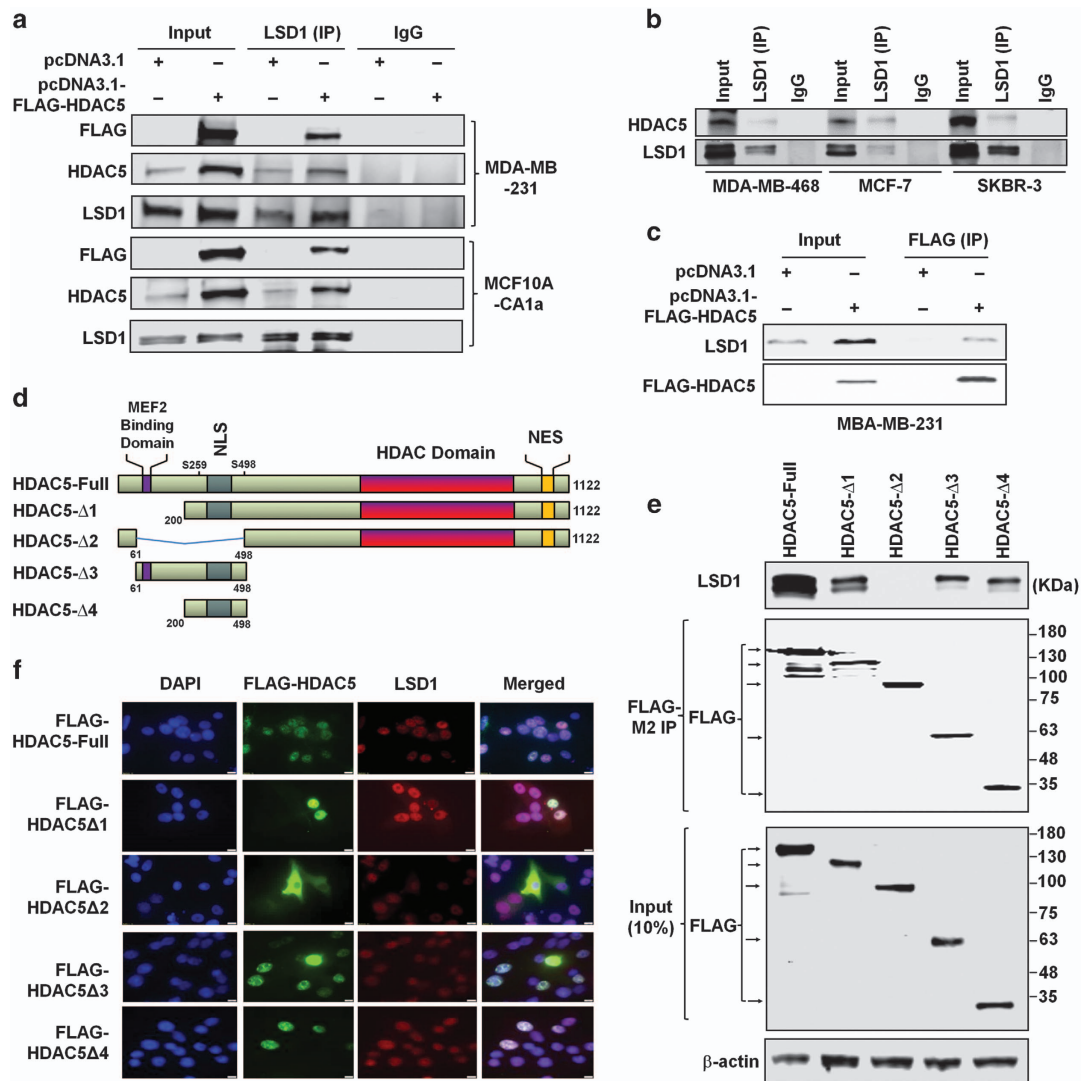


Figure 2. HDAC5 and LSD1 physically interact in breast cancer cells. **(a)** MDA-MB-231 or MCF10A-CA1a cells were transfected with control vector pcDNA3.1 or pcDNA3.1-HDAC5 plasmids. IP was performed with anti-LSD1 antibody followed by immunoblotting (IB) with anti-LSD1, anti-FLAG or anti-HDAC5 antibodies, respectively. **(b)** Whole-cell lysates were immunoprecipitated with anti-LSD1 antibody followed by IB with anti-HDAC5 and LSD1 antibodies in indicated breast cancer cell lines. IgG was used as negative control. **(c)** MDA-MB-231 cells were transfected with control vector pcDNA3.1 or pcDNA3.1-HDAC5-FLAG plasmids, and IP was performed with anti-FLAG followed by IB with anti-LSD1 and anti-FLAG antibodies, respectively. **(d)** Schematic representation of full-length and deletion mutants of HDAC5-FLAG constructs. **(e)** FLAG-tagged full-length or deletion mutants of HDAC5 were expressed in MDA-MB-231 cells. Extracts were immunoprecipitated with anti-FLAG antibody, and bound LSD1 was examined by IB using anti-LSD1 antibody. IB with anti-FLAG was used to detect the levels of FLAG-tagged HDAC5 full-length or deletion mutants in IP and input (10%) samples. **(f)** MDA-MB-231 cells were transfected with plasmids expressing FLAG-tagged full-length or deletion mutants of HDAC5 proteins. Immunofluorescence study was performed using anti-FLAG antibody. 4,6-Diamidino-2-phenylindole was used as a control for nuclear staining. All the experiments were performed three times with similar results.

whereas depletion of HDAC5 by siRNA facilitated LSD1 polyubiquitination (Supplementary Figure 7a). Recently, Jade-2 and USP28 were identified as specific E3 ubiquitin ligase and deubiquitinase for LSD1, respectively.^{20,21} Our study showing that increase of LSD1 protein expression by Jade-2 siRNA and decrease of LSD1 protein expression by USP28 siRNA in MDA-MB-231 cells confirmed the roles of Jade-2/USP28 as LSD1 ubiquitin ligase/deubiquitinase in breast cancer cells (Figure 4b; Supplementary Figure 7b). qPCR studies demonstrated that mRNA level of either Jade-2 or USP28 was not altered by HDAC5 knockdown or overexpression (Figure 4c). The regulation of HDAC5 on protein expression of Jade-2 or USP28 was subsequently assessed. Due to the lack of highly specific antibody against Jade-2, plasmids expressing Jade-2-FLAG fusion protein were transfected into cells as an alternative approach. MDA-MB-231 and MCF10A-CA1a cells

expressing Jade-2-FLAG protein were simultaneously treated with HDAC5 siRNA to evaluate the effect of HDAC5 on Jade-2 protein expression. Immunoblot showed that depletion of HDAC5 did not change the protein level of Jade-2 (Figure 4d). However, overexpression of HDAC5 led to significant increase of USP28 protein expression in both cell lines (Figure 4e). *In vitro* pull-down assay using His-tag recombinant LSD1 protein incubated with USP28-FLAG protein indicated a direct interaction of LSD1 and USP28 (Supplementary Figure 4), and HDAC5 overexpression significantly attenuated USP28 polyubiquitination (Supplementary Figure 7c). To understand whether HDAC5 may stabilize LSD1 protein through upregulation of USP28 protein stability, a rescue study was carried out in MDA-MB-231 and MCF10A-CA1a cells using concurrent transfection of HDAC5 siRNA and USP28 expression plasmids, and showed that overexpression of USP28

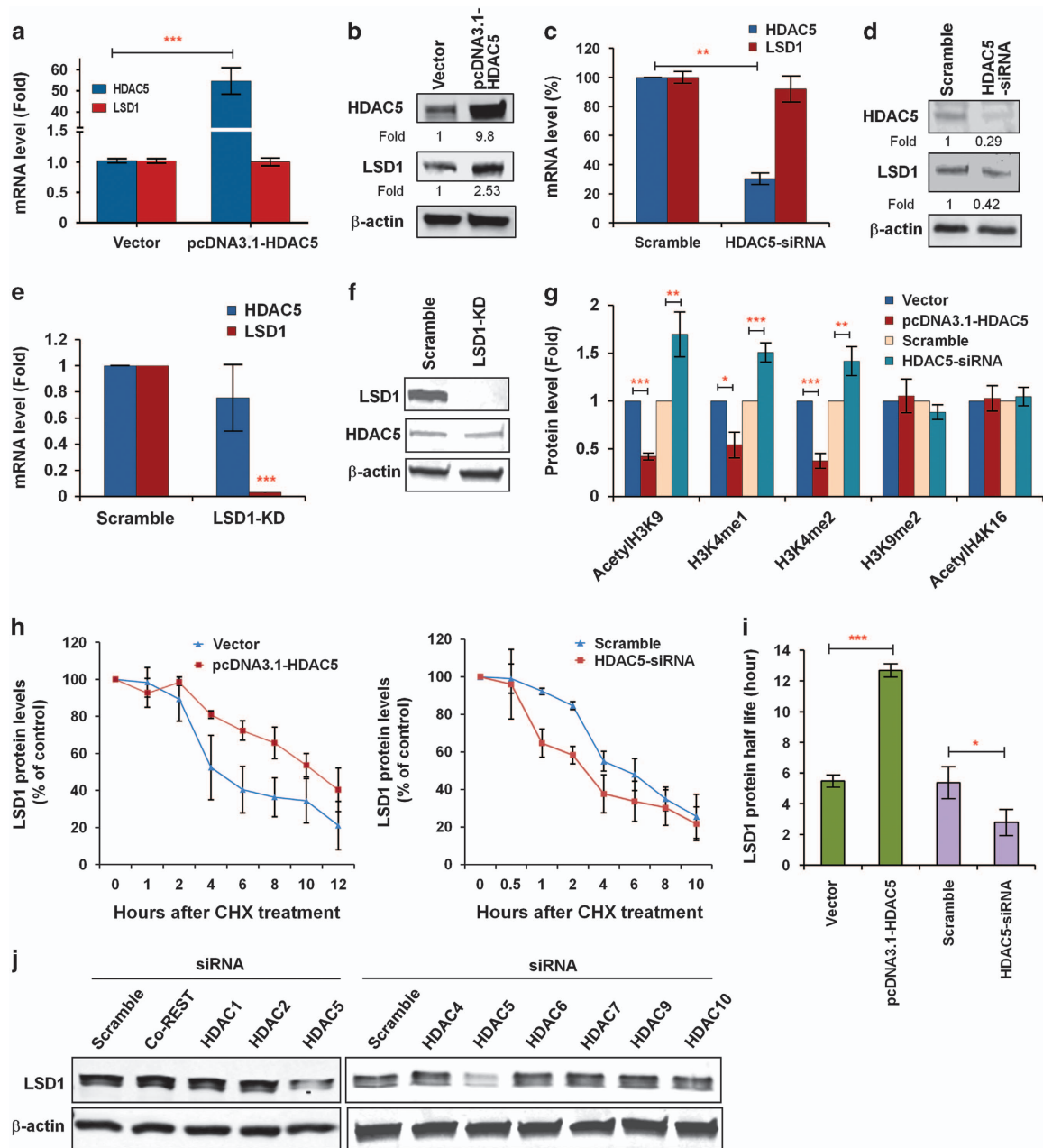


Figure 3. HDAC5 stabilizes LSD1 protein in breast cancer cells. **(a)** MDA-MB-231 cells were transfected with control vector pcDNA3.1 or pcDNA3.1-HDAC5 for 48 h. mRNA expression of HDAC5 and LSD1 was measured by quantitative real-time PCR with β -actin as an internal control. **(b)** MDA-MB-231 cells were transfected with control vector pcDNA3.1 or pcDNA3.1-HDAC5 plasmids for 48 h. Effect of HDAC5 overexpression on LSD1 protein expression in MDA-MB-231 cells was evaluated by immunoblots with anti-LSD1 and anti-HDAC5 antibodies. **(c)** MDA-MB-231 cells were transfected with scramble siRNA or HDAC5 siRNA for 48 h. Effect of HDAC5 knockdown on LSD1 mRNA expression was examined by quantitative real-time PCR with β -actin as internal control. **(d)** Effect of HDAC5 siRNA on LSD1 protein expression in MDA-MB-231 cells. **(e)** Effect of depletion of LSD1 on mRNA expression of HDAC5 in MDA-MB-231-Scramble or MDA-MB-231-LSD1-KD cells. **(f)** Effect of LSD1-KD on protein expression of HDAC5 in MDA-MB-231-scramble or MDA-MB-231-LSD1-KD cells. **(g)** MDA-MB-231 cells were transfected with control vector pcDNA3.1, pcDNA3.1-HDAC5, scramble siRNA or HDAC5 siRNA for 48 h and analyzed by immunoblots for nuclear expression of indicated histone marks. Proliferating cell nuclear antigen was used as loading control. **(h)** Effect of HDAC5 overexpression or siRNA on LSD1 protein half-life in cycloheximide chase study. **(i)** Measurement of LSD1 half-life using the CalcuSyn program. **(j)** Effect of siRNA knockdown of LSD1 cofactors or class II HDACs on LSD1 protein level. All the experiments were performed three times. Bars represent the mean of three independent experiments $\pm$ s.d. * P < 0.05, ** P < 0.01, *** P < 0.001, Student's t -test.

completely blocked the destabilization of LSD1 by HDAC5 depletion (Figure 4f; Supplementary Figure 7d). In an additional rescue experiment, overexpression of HDAC5 failed to promote LSD1 protein expression when cells were simultaneously treated with USP28 by siRNA (Supplementary Figure 7e). All these data

support the notion that HDAC5 stabilizes LSD1 protein by enhancing protein expression of its deubiquitinase.

To examine whether interaction of HDAC5 with the LSD1/USP28 complex deacetylates LSD1 or USP28, *in vitro* protein acetylation assays was first carried out by incubating GST-tagged recombinant

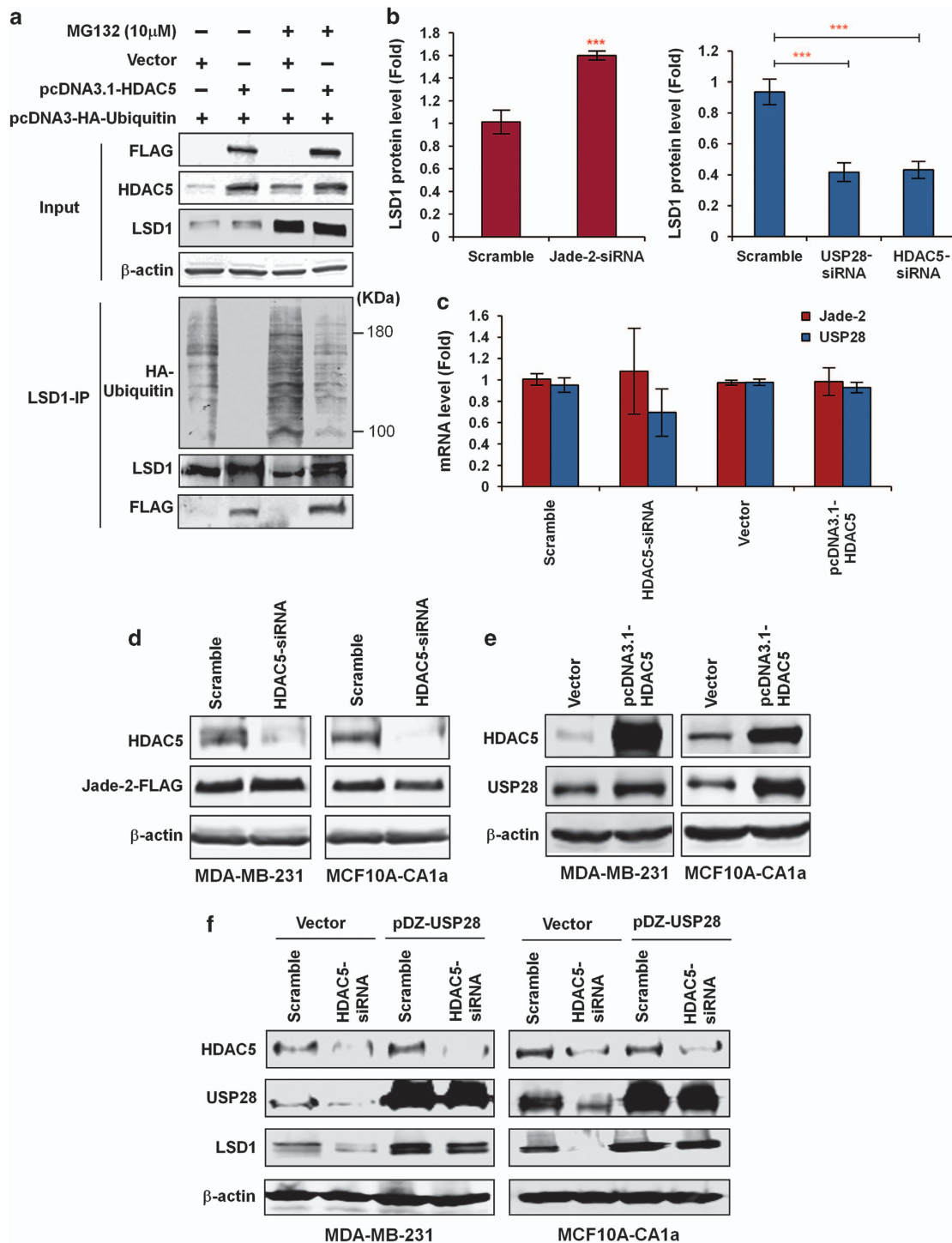


Figure 4. HDAC5 regulates LSD1 by altering USP28 stability. **(a)** MDA-MB-231 cells transfected with pcDNA3.1-FLAG, pcDNA3.1-FLAG-HDAC5 or pcDNA3-HA-ubiquitin plasmids were treated with or without proteasome inhibitor 10 μ M MG132 for 10 h followed by IP using LSD1 antibody and immunoblots with anti-HA, LSD1 or HDAC5 antibodies. **(b)** Effect of siRNA of Jade-2, USP28 and HDAC5 on LSD1 protein expression in MDA-MB-231 cells. Results represent the mean of three independent experiments $\pm$ s.d. *** P < 0.001, Student's t -test. **(c)** MDA-MB-231 cells were transfected with scramble siRNA, HDAC5 siRNA, control vector pcDNA3.1 or pcDNA3.1-HDAC5 plasmids for 48 h. mRNA expression of Jade-2 and USP28 was measured by qPCR. β -actin was used as an internal control. **(d)** MDA-MB-231 or MCF10A-CA1a cells were simultaneously transfected with pcDNA3.1-FLAG-Jade-2 and HDAC5 siRNA for 48 h and subjected to immunoblots with anti-HDAC5 or Jade-2 antibodies. β -actin was used as loading control to normalize target protein levels. **(e)** After MDA-MB-231 or MCF10A-CA1a cells were transfected with control vector pcDNA3.1 or pcDNA3.1-HDAC5 plasmids for 48 h, IB was performed for expression of HDAC5 and USP28. **(f)** MDA-MB-231 or MCF10A-CA1a cells were transfected with scramble or HDAC5 siRNA alone, or in combination with pDZ-USP28 for 48 h. Whole-cell lysates were analyzed for protein levels of HDAC5, USP28 and LSD1. β -actin was used as loading control to normalize target protein levels. The experiments were performed three times with similar results.

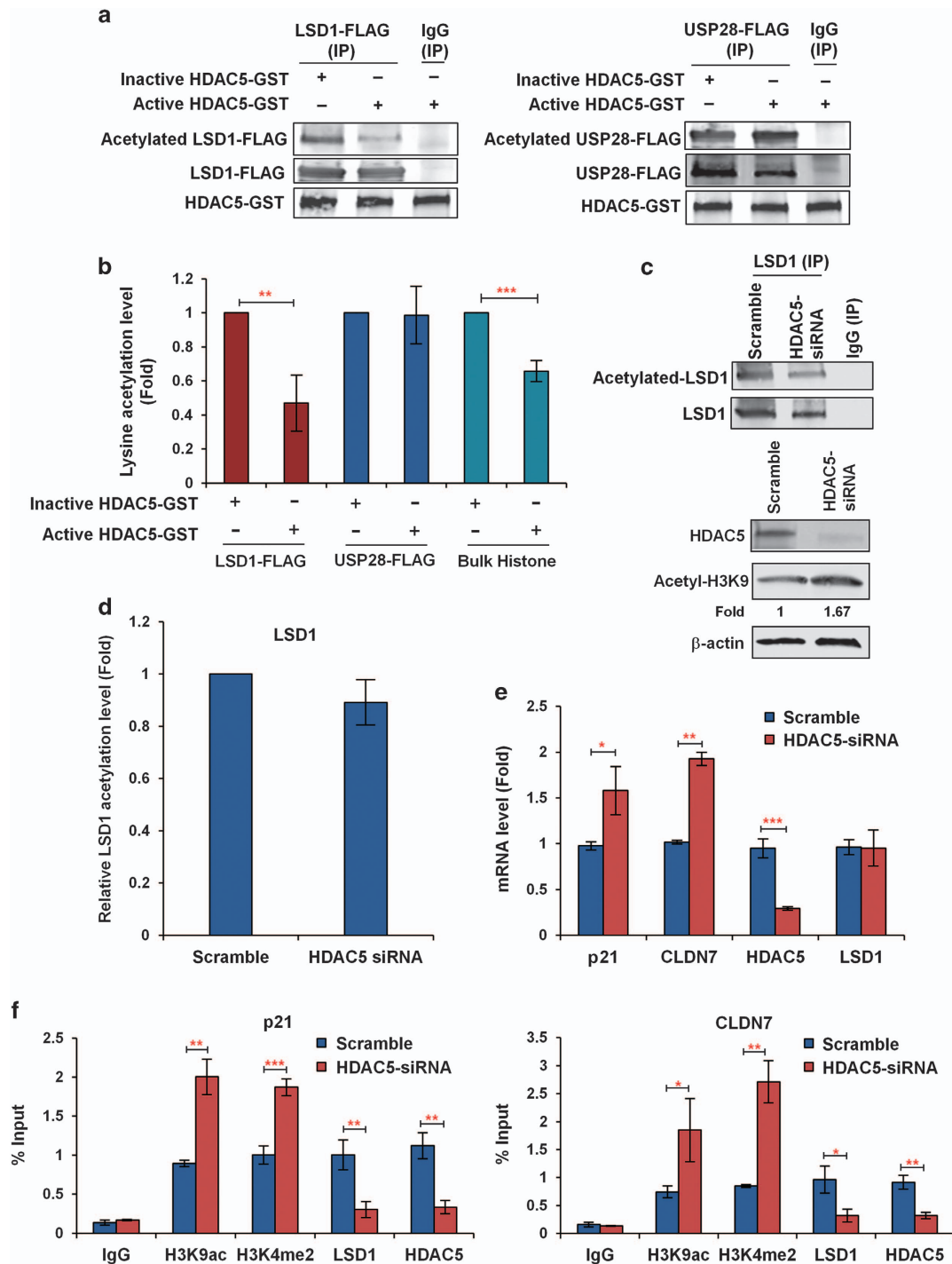
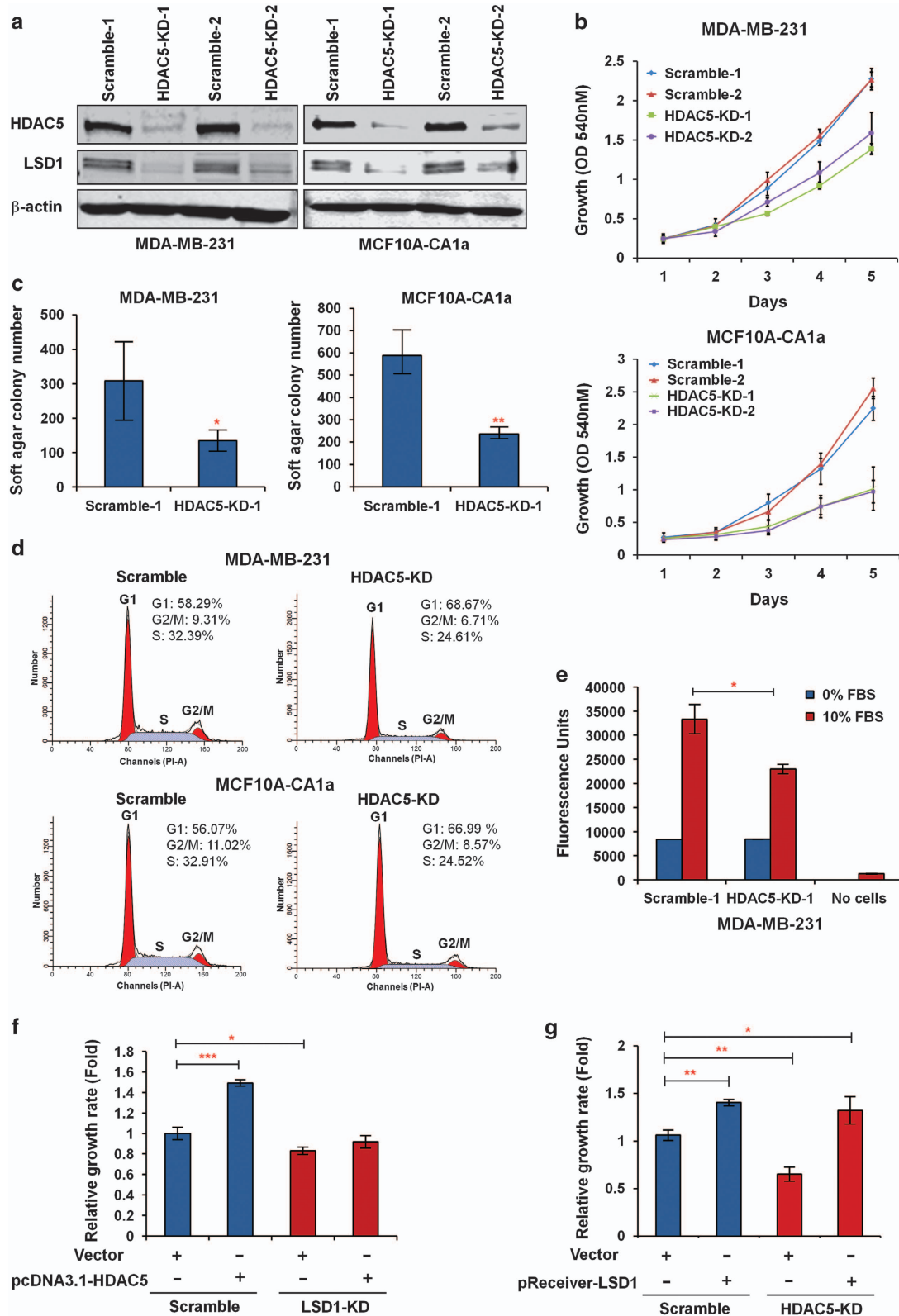


Figure 5. Effect of HDAC5 on protein acetylation of LSD1/USP28 and transcription of LSD1 target genes. **(a)** The immunoprecipitates of FLAG using FLAG-M2 agarose from MDA-MB-231 cells overexpressing FLAG-tagged USP28 or FLAG-tagged LSD1 were used as substrates for protein deacetylation assay. IgG was used as negative control. Active or heat inactivated recombinant human GST-tagged HDAC5 protein were mixed with immunoprecipitates and incubated at 37 °C for 6 h as described in 'Materials and Methods'. The reactions were then subjected to immunoblots with anti-acetyl lysine antibody. FLAG-tagged USP28 or LSD1 proteins were probed with anti-FLAG antibody. HDAC5-GST protein was probed with anti-HDAC5 antibody. **(b)** Histograms represent the means of levels of acetyl-LSD1, acetyl-USP28 and acetyl-histone determined by quantitative IB using infrared IB detection and analysis. **(c)** MDA-MB-231 cell transfected with scramble or HDAC5 siRNAs for 48 h. LSD1 or IgG antibodies were added to cell lysate. IP was performed with anti-LSD1 antibody followed by IB with anti-acetyl lysine and anti-LSD1 antibodies, respectively. Effect of HDAC5 siRNA on AcetylH3K9 protein expression in MDA-MB-231 cells was examined by IB with anti-acetyl-H3K9 antibody. **(d)** Histograms represent the means of relative levels of acetyl-LSD1 determined by quantitative IB using infrared IB detection and analysis. **(e)** mRNA expression of indicated genes in MDA-MB-231 cells transfected with scramble siRNA or HDAC5 siRNA. Data are means $\pm$ s.d. of three independent experiments. **(f)** Quantitative chromatin immunoprecipitation (ChIP) analysis was used to determine the occupancy by acetyl-H3K9, H3K4me2, LSD1 and HDAC5 at promoters of p21 or CLDN7 in MDA-MB-231 cells transfected with scramble or HDAC5 siRNA. * P < 0.05, ** P < 0.01, *** P < 0.001, Student's *t*-test.

HDAC5 protein with cellular pull-down of LSD1-FLAG or USP28-FLAG by IP, and immunoprecipitates of IgG was incubated with recombinant HDAC5 protein as negative control of assays (Figure 5a). Bulk histone was used as control substrate (Supplementary Figure 8). Quantitative immunoblots using antibody against pan-acetylated lysine showed that HDAC5 reduced

acetylation level of LSD1 without altering the acetylation status of USP28 (Figures 5a and b). Next, the *in vivo* effect of HDAC5 depletion on LSD1 acetylation was investigated in MDA-MB-231 cells transfected with scramble or HDAC5 siRNAs. After immunoprecipitation with LSD1 antibody or IgG (negative control), IB was performed and the results showed that expression levels of both



total LSD1 protein and acetylated LSD1 protein were decreased by HDAC5 depletion (Figure 5c). Quantitative immunoblots indicated that the relative acetylation level of LSD1 was not statistically altered by HDAC5 siRNA in MDA-MB-231 cells (Figure 5d). Acetyl-H3K9 was used as control of substrate and its expression was increased by HDAC5 siRNA (Figure 5c). These results suggest that inhibition of HDAC5 alone is not sufficient enough to increase LSD1 acetylation in breast cancer cells.

Inhibition of HDAC5 reactivates expression of LSD1 target genes. In cancer cells, amplified LSD1 expression is frequently associated with abnormal suppression of key tumor suppressor genes.^{3,22} We next examined whether expression of LSD1 target tumor suppressor genes could be reactivated following HDAC5 inhibition. Loss of expression of cyclin-dependent kinase inhibitor p21 and epithelial marker claudin-7 (CLDN7) has been reported to be associated with an aggressive phenotype of breast cancer.^{23,24} The transcription activity of p21 and CLDN7 has been found to be suppressed by enhanced activity of LSD1 in breast cancer.^{6,25} Transfection of HDAC5 siRNA resulted in significantly increased mRNA expression of p21 and CLDN7 in MDA-MB-231 cells (Figure 5e). Quantitative chromatin immunoprecipitation assays revealed that depletion of HDAC5 decreased occupancy of both HDAC5 and LSD1, and increased enrichment of H3K4me2 and acetyl-H3K9 at the promoters of both genes (Figure 5f). These data suggest that transcriptional de-repression of these genes lies largely in the cooperation between HDAC5 and LSD1 at key active histone marks.

Inhibition of HDAC5–LSD1 axis hinders breast cancer proliferation and invasion

To explore the functional role of the HDAC5–LSD1 axis in regulating breast cancer development, stable knockdown of HDAC5 mRNA (HDAC5-KD) was generated in MDA-MB-231 and MCF10A-CA1a cells by infection with short hairpin RNA (shRNA) lentiviral particles. Similar to the effect of transient inhibition of HDAC5 by siRNA, stable knockdown of HDAC5 expression significantly reduced LSD1 protein expression in two independent HDAC5-KD clones (Figure 6a). Loss of HDAC5 in both clones hindered cell proliferation and colony formation in soft agar (Figures 6b and c). The flow cytometry analysis showed that inhibition of HDAC5 resulted in a greater fraction of cells accumulated at G1 phase and reduction of the S-phase cell fraction (Figure 6d; Supplementary Figure 9). Moreover, loss of HDAC5 attenuated motility and invasion of MDA-MB-231 cells in a Boyden chamber assay (Figure 6e). A rescue experiment indicated that HDAC5 overexpression promoted growth of MDA-MB-231-Scramble cells, but failed to alter the growth of MDA-MB-231-LSD1-KD cells (Figure 6f). An additional rescue study revealed that LSD1 overexpression rescued growth inhibition by HDAC5 depletion in MDA-MB-231-HDAC5-KD cells (Figure 6g). Taken together, these results demonstrate that tumor-promoting activity of HDAC5 is dependent on LSD1 activity in breast cancer cells.

Overexpression of HDAC5 promotes mutagen-induced tumorigenic development in MCF10A cells

To address whether enhanced interaction between HDAC5 and LSD1 is a critical epigenetic alteration driving tumorigenic transformation of breast cancer, we generated two MCF10A cell lines overexpressing HDAC5 (MCF10A-HDAC5). Stable overexpression of HDAC5 in MCF10A cells increased LSD1 protein level and promoted cell proliferation of both clones (Figures 7a and b), indicating a growth-promoting role for HDAC5 in MCF10A cells. Inhibition of LSD1 by shRNA significantly hindered MCF10A growth and reversed the growth promotion mediated by HDAC5 overexpression, suggesting that HDAC5 promotes MCF10A growth in an LSD1 dependent manner (Figure 7c; Supplementary Figure 10). To evaluate if MCF10A-HDAC5 cells have altered susceptibility to tumorigenesis, MCF10A-Vector and MCF10A-HDAC5 cells were cultured for 7 months in medium containing 500 ng/ml ICR191. ICR191 generates genomic instability and genetic variability, and has been successfully used to induce epithelial cell transformation in several models including MCF10A.^{26,27} MCF10A-HDAC5 cells were subsequently tested for the capacity of anchorage-independent growth in soft agar for 4 weeks. The soft agar colony formation study demonstrated that ICR191 treatment improved the ability of MCF10A cells to form growing colonies, and overexpression of HDAC5 significantly promoted ICR191-induced colony formation in MCF10A cells (Figure 7d). To determine the role of LSD1 in HDAC5 enhanced tumorigenic transformation induced by ICR191, scramble control and LSD1 shRNA lentivirus particles were infected into MCF10A-Vector or MCF10A-HDAC5 cells, which had been treated with ICR191 for 7 months, and the soft agar growth assays showed that loss of LSD1 in MCF10A-HDAC5 cells significantly abolished cellular ability in colony formation (Figure 7e). A model illustrating the role of HDAC5–LSD1 axis in breast cancer development is proposed based on the above findings (Figure 7f).

DISCUSSION

High levels of HDAC5 have been found to be associated with poor survival in multiple cancer types.^{28,29} LSD1 overexpression has been reported to be a poor prognostic factor in basal-like breast cancer, a subtype with aggressive clinical characteristics.^{6,30} In this study, the IHC analysis showed that breast cancers expressed higher levels of HDAC5 compared to the matched-normal adjacent breast tissue. Importantly, our study found a positive correlation between HDAC5 and LSD1 proteins in breast tumor cell lines and patient tissue specimens. Increased expression of HDAC5 and LSD1 is correlated with higher stage of breast cancer in our exploratory study. These findings suggest that the coordinated overexpression of HDAC5 and LSD1 may serve as potential novel prognostic markers as well as possible therapeutic targets for breast cancer. More robust studies will be necessary to understand the precise role of elevated protein expression levels of HDAC5 and LSD1 in the risk stratification of breast cancer patients.

Figure 6. HDAC5–LSD1 axis is implicated in breast cancer progression. **(a)** Depletion of HDAC5 by shRNA lentivirus infection downregulated LSD1 protein expression in MDA-MB-231 and MCF10A-CA1a cells. **(b)** Scramble shRNA and HDAC5-KD cells were analyzed for growth and viability by crystal violet assays. **(c)** Soft agar colony formation for HDAC5-KD and scramble control of MDA-MB-231 and MCF10A-CA1a cells. **(d)** Scramble shRNA and HDAC5-KD cells were harvested and stained for DNA with propidium iodide for the flow cytometric analysis. The fractions corresponding to G1, S and G2/M phases of the cell cycle are indicated. **(e)** The Boyden Chamber transwell migration assays for cell invasion for MDA-MB-231-Scramble or MDA-MB-231-HDAC5-KD-1 cells. **(f)** MDA-MB-231-Scramble or MDA-MB-231-LSD1-KD cells were transfected with control vector pcDNA3.1 or pcDNA3.1-HDAC5 for 5 days and crystal violet assays for growth were carried out. **(g)** MDA-MB-231-Scramble or MDA-MB-231-HDAC5-KD cells were transfected with empty or pReceiver-LSD1 expression plasmids for 5 days and crystal violet assays for growth were carried out. Bars represent the means of three independent experiments $\pm$ s.d. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, Student's *t*-test.

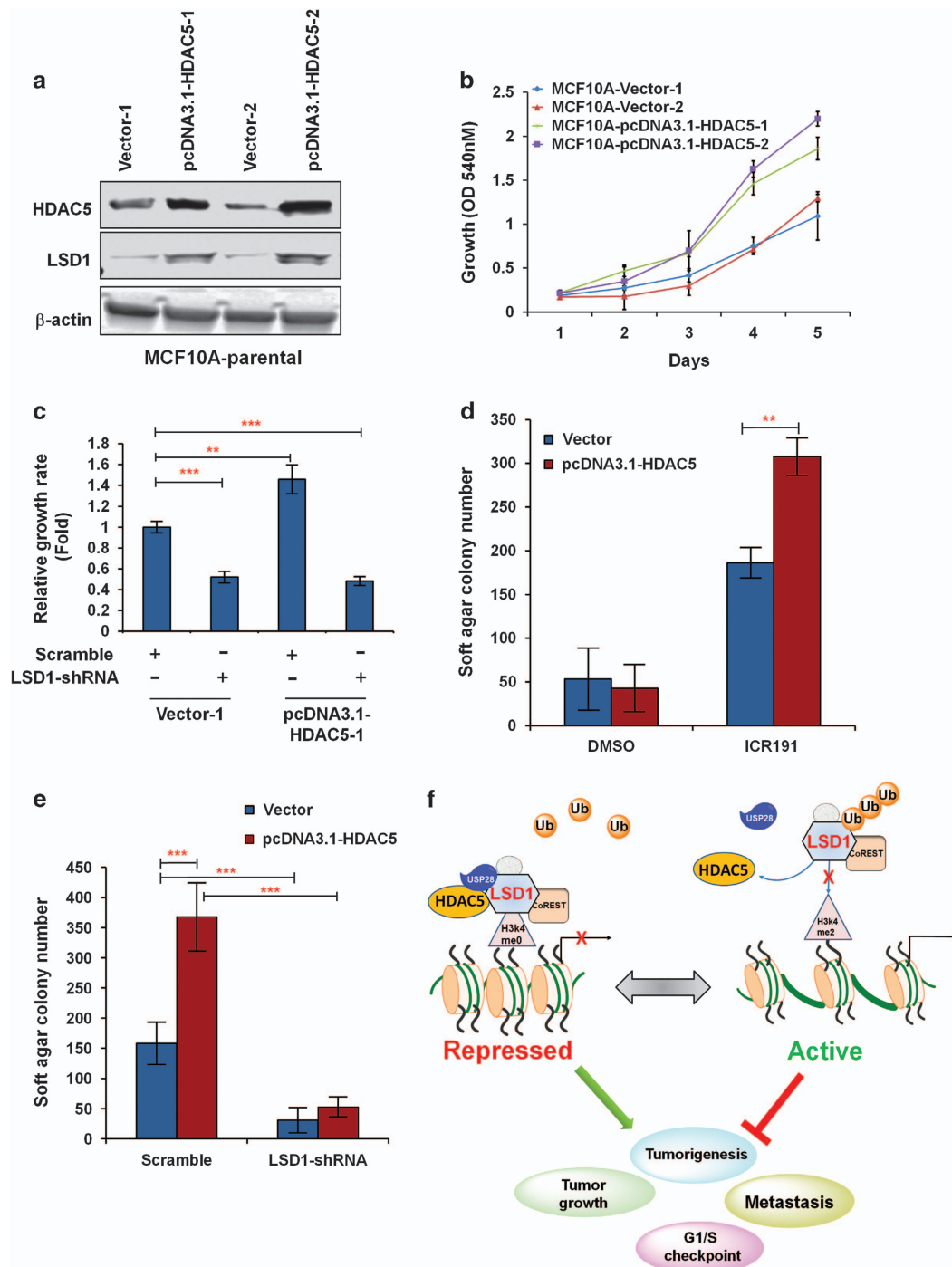


Figure 7. Effect of HDAC5 on growth and mutagen-induced tumorigenic transformation in MCF10A cells. **(a)** pcDNA3.1 or pcDNA3.1-HDAC5 transfected MCF10A cells (clone 1 and 2) were analyzed for protein levels of HDAC5 and LSD1 by immunoblots with anti-HDAC5 and anti-LSD1 antibodies. **(b)** The crystal violet assay for growth of MCF10A stably transfected with control vector or pcDNA3.1-HDAC5 plasmids. **(c)** MCF10A-Vector-1 or MCF10A-HDAC5-1 cells were infected with scramble or LSD1 shRNA lentivirus particles for 5 days followed by crystal violet assays for growth. **(d)** MCF10A cells transfected with pcDNA3.1 or pcDNA3.1-HDAC5 plasmids were treated with dimethyl sulfoxide or 500 ng/ml ICR191 for 7 months followed by soft agar colony formation assays. **(e)** After treatment with 500 ng/ml ICR191 for 7 months, MCF10A-HDAC5 cells were infected with scramble control or LSD1 shRNA lentivirus particles and soft agar colony formation assay was carried out. **(f)** Proposed model of the role of HDAC5–LSD1 axis in breast cancer development. Bars represent the means of three independent experiments $\pm$ s.d. ** $P < 0.01$, *** $P < 0.001$, Student's *t*-test.

LSD1 protein stability is controlled by several post-translational modifications such as ubiquitination and methylation.^{20,21,31} However, the precise mechanism of how LSD1 protein stability is regulated is still not understood. A previous study reported that stable depletion of CoREST facilitated LSD1 degradation in HeLa

cells.³² However, siRNA-mediated knockdown of CoREST alone in breast cancer cells failed to destabilize LSD1 protein, suggesting additional layers of control of LSD1 protein stability are required in breast cancer. In this study, we observed for the first time that LSD1 protein stability is promoted by HDAC5. We further found

that the HDAC5 domain containing NLS is essential for LSD1–HDAC5 interaction. The NLS element provides docking sites for 14–3–3 chaperone binding and has been shown to be critical for HDAC5 import into the nucleus and the regulation of its repressor activity.^{17,33} Although an *in vitro* assay demonstrated that HDAC5 reduced LSD1 acetylation, HDAC5 siRNA treatment in breast cancer cells failed to alter acetylation of LSD1 protein. Our *in vivo* results suggest that LSD1 acetylation is likely regulated by a large complex that may involve additional protein deacetylases or cofactors. Further studies are needed to identify the regulatory complex and clarify the precise role of HDAC5 in regulation of LSD1 acetylation in breast cancer cells.

Our studies revealed that HDAC5 regulates LSD1 via enhancement of the protein stability of deubiquitinase USP28. High expression of USP28 has been found to promote the progression of breast and colon cancers.^{20,34} Importantly, USP28 has been reported to deubiquitinate important tumor growth regulators such as c-Myc and TP53BP1 that are involved in MYC proto-oncogene stability and DNA damage response checkpoint regulation, respectively.^{35,36} Our pilot microarray study revealed that inhibition of the HDAC5–LSD1 axis down-regulates c-Myc expression (data not shown). Sen *et al.*³⁷ recently reported that HDAC5 is a key component in the temporal regulation of p53-mediated transactivation. All of these findings imply an interaction of HDAC5/LSD1 axis and USP28-associated ubiquitin–proteasome system in regulating downstream targets involved in tumor development. USP28 has been well-characterized for its role in promoting tumorigenesis, and thus is a potential candidate target in cancer therapy. Given the current inability to use drugs to directly target USP28-driven cancer proliferation, our study suggests a novel alternative approach of targeting USP28 stability by development of HDAC5-specific inhibitors in cancer.

Our findings provide supportive evidence showing that HDAC5 control of cell proliferation is largely dependent on LSD1 stabilization. Furthermore, in this study, we showed that non-transformed MCF10A cells overexpressing HDAC5 significantly promoted ICR191-induced transformation of MCF10A cells. The overexpressed HDAC5 is consistently associated with upregulated LSD1 protein expression over the entire course of transformation induction. These data indicate that enhanced crosstalk between HDAC5 and LSD1 may represent a critical mechanism contributing to breast tumorigenesis. HDAC inhibitors hold great promise for cancer therapy. Despite the promising clinical results produced by the HDAC inhibitors in treatment of hematological cancers such as T-cell lymphoma, no apparent clinical evidence indicates that HDAC inhibitors work effectively as a monotherapy against solid tumors including breast tumors.^{38–41} From a clinical perspective, our novel findings have significance for design and development of novel combination strategies targeting HDAC5–LSD1 axis as an alternative approach for improvement of therapeutic efficacy of HDAC inhibitors in breast cancer.

As summarized in Figure 7f, we show for the first time that LSD1 protein stability is promoted by HDAC5 through the LSD1 associated ubiquitin–proteasome system, confirming that the regulation of LSD1 by HDAC5 is a post-translational event. Our novel findings also provide supportive evidence that an orchestrated interaction between HDAC5 and LSD1 is a critical epigenetic mechanism to suppress transcriptional activities of important tumor suppressor genes that may contribute to breast cancer development.

MATERIALS AND METHODS

Reagents and cell culture conditions

MDA-MB-231, MDA-MB-468, MCF-7, T47D, HCC-202 and SK-BR-3 cell lines were obtained from the ATCC/NCI Breast Cancer SPORC program. MCF10A-parental and MCF10A-CA1a cells were gifts from Dr Saraswati Sukumar

(Johns Hopkins University). Cells were cultured in growth medium as described previously.^{10,42}

Tissue microarrays and immunohistochemistry

Tissue microarrays (US Biomax, Rockville, MD, USA) were stained using LSD1 or HDAC5 antibodies. Standard staining procedure for paraffin sections was used for IHC according to manufacturer's recommendations (Vector Labs Inc., Burlingame, CA, USA). Monoclonal antibodies were used for detection of LSD1 (1:800; Cell Signaling, Danvers, MA, USA) and HDAC5 (1:100; Santa Cruz, CA, USA). The staining was visualized using diaminobenzidine, and quantitated using IHC Profiler, an ImageJ plugin (National Institutes of Health, Bethesda, MD, USA).⁴³ H-scores were calculated as previously described.⁴⁴ The manual scoring of H-scores was also carried out by two breast cancer pathologists.

Plasmid construction and stable transfection

Plasmids pcDNA3.1(+)-FLAG, pcDNA3.1(+)-FLAG-HDAC5 and pDZ-FLAG-USP28 were purchased from Addgene (Cambridge, MA, USA). pReceiver-FLAG-LSD1 was obtained from Gene Copoeia (Rockville, MD, USA). A FLAG-tagged ORF cDNA clone for Jade-2 was purchased from GenScript (Piscataway, NJ, USA). pcDNA3-HA-ubiquitin was obtained from Dr Yong Wan (University of Pittsburgh). HDAC5 deletion mutants were engineered into pcDNA3.1(+)-FLAG-HDAC5 by PCR with primers shown in Table S1. HDAC5-Δ2 was constructed by digesting full-length plasmids with SacII from amino acid 61 to 489. Stable transfection was carried out using Lipofectamine 3000 transfection reagent (Life Technologies, Grand Island, NY, USA), and colonies were selected with 800 μg/ml G418.

siRNA and shRNA treatment and stable cell line generation

Pre-designed siRNA and non-targeting scramble siRNA (Santa Cruz) were transfected into cells following the manufacturer's protocol. Cells were collected 48 h post-transfection for further analysis. Scramble control, LSD1-specific or HDAC5-specific shRNA lentiviral particles (Santa Cruz) were infected into cells according to manufacturer's protocol. Cells were treated with 10 μg/ml puromycin 72 h after infection. Single colonies were analyzed for expression of LSD1 or HDAC5 via immunoblots.

RNA extraction and qPCR

Total RNA extraction and cDNA synthesis used the methods described previously.¹⁰ Quantitative real-time PCR was performed on the StepOne real-time PCR system (Life Technologies). All of the TaqMan gene expression assays were pre-designed and obtained from Life Technologies.

Western blotting

Western blotting was performed as previously described.^{12,45,46} Antibodies used in this study were shown in Supplementary Table S2. Membranes were scanned with Li-Cor BioScience Odyssey Infrared Imaging System (Lincoln, NE, USA).

Crystal violet and cell invasion assays

The crystal violet proliferation assays were performed as described in our previous study.⁴⁷ The invasive capability of breast carcinoma cells was tested with Millipore QCM 24-well invasion assay kit (Merck KGaA, Germany) according to manufacturer's protocol.

Soft agar colony formation assay

A total of 1.2% Bacto-agar (BD Biosciences, Franklin Lakes, NJ, USA) was autoclaved and mixed with growth medium to produce 0.6% agar. The mixture was quickly plated and solidified for 45 min. Cells were suspended in 0.6 ml 2× growth medium and mixed gently with 0.6 ml 0.8% agar/medium. Overall 1 ml of cells with 0.4% agar/medium mixture was added onto plate for solidification. Colony formation was examined using stereo microscopy and analyzed (CellSens Dimension, Olympus, Shinjuku, Tokyo, Japan).

Flow cytometry analysis

Cells were collected and fixed with 70% ethanol. The cell pellet was then treated with 1% TritonX-100. Cells were subsequently resuspended in 50 μg/ml propidium iodide (Sigma, St Louis, MO, USA) containing RNaseI (Roche, Indianapolis, IN, USA) followed by analysis on the LSR II XW4400 workstation (BD Biosciences).

Immunofluorescence

After 48 h of transfection, cells were fixed with 4% paraformaldehyde and incubated with primary antibodies (1:250) overnight at 4 °C. After washing, cells were incubated with fluorescence-labeled secondary antibody (1:100). After washing, coverslips were placed on a glass slide using UltraCruz mounting medium (Santa Cruz) before fluorescence microscope examination.

Immunoprecipitation, ubiquitination and protein half-life assays

The cell lysate was obtained by using immunoprecipitation lysis buffer as described previously.⁴⁸ LSD1 or IgG antibodies were added to cell lysate. Protein G-plus agarose beads (Santa Cruz) or Flag-M2 affinity gel were collected and subjected to IB. HA-Ubiquitin, pcDNA3.1-Flag-HDAC5 or empty vector plasmids were co-transfected into cells for 38 h. Cells were then treated with 10 μ M MG132 for 10 h and collected for immunoprecipitation assay with protein G-plus agarose beads. For half-life studies 48 h after transfection with pcDNA3.1-HDAC5 or HDAC5 siRNA, cells were treated with 100 μ g/ml cycloheximide and then collected at indicated times for IB.

Protein acetylation assay

The immunoprecipitates of FLAG-M2 agarose from MDA-MB-231 cells overexpressing FLAG-tag USP28 or FLAG-tag LSD1 were used as substrates for the protein deacetylation assay. Pull-down of IgG was used as negative control. A total of 0.25 μ g of recombinant human GST-tagged HDAC5 protein (Creative BioMart, NY, NY) was mixed with 30 μ l immunoprecipitates or 1.5 μ g bulk histone at 37 °C for 6 h in a buffer containing 40 mM Tris–HCl (pH 8.0), 2.5 mM MgCl₂, 50 mM NaCl, 2 mM KCl, 0.5 mM DTT, 1 mM EDTA and protease inhibitor. The reactions were then subjected to immunoblots with anti-acetyl lysine antibody (EMD Millipore, Billerica, MA, USA). FLAG-tagged USP28 or LSD1 and bulk histone were probed with anti-FLAG antibody or H3 antibody as loading control. Inactive HDAC5–GST protein was used as negative control by heating recombinant protein at 95 °C for 5 min. *In vivo* protein acetylation assay was performed using cell lysate of MDA-MB-231 cell transfected with scramble and HDAC5 siRNAs. LSD1 or IgG antibodies were added to cell lysate. Protein G-plus agarose beads (Santa Cruz) were collected and subjected to IB with anti-acetyl lysine or LSD1 antibodies.

Chromatin immunoprecipitation

Chromatin immunoprecipitation assay was performed as described previously.¹² Primary antibodies against HDAC5, LSD1, H3K4me2 and acetyl-H3K9 were used as indicated for immunoprecipitation of the protein–DNA complexes. PCR primer sets used for amplification of precipitated fragments were shown in Supplementary Table S1. Input DNA was used for normalization.

Statistical analysis

Data were represented as the mean $\pm$ s.d of three independent experiments. The quantitative variables were analyzed by the two-tailed Student's *t*-test. The χ^2 study was used to assess the correlation between HDAC5 and LSD1 protein expression by using median H-scores as the cutoff for high- versus low-protein expression. *P*-value < 0.05 was considered statistically significant for all tests. Statistical analyses were performed using GraphPad Prism 6 (GraphPad Software Inc., La Jolla, CA, USA).

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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REFERENCES

- Shi Y, Lan F, Matson C, Mulligan P, Whetstone JR, Cole PA et al. Histone demethylation mediated by the nuclear amine oxidase homolog LSD1. *Cell* 2004; **119**: 941–953.
- Lee MG, Wynder C, Cooch N, Shiekhatair R. An essential role for CoREST in nucleosomal histone 3 lysine 4 demethylation. *Nature* 2005; **437**: 432–435.
- Huang Y, Marton LJ, Woster PM, Casero RA. Polyamine analogues targeting epigenetic gene regulation. *Essays Biochem.* 2009; **46**: 95–110.
- Lee M, Wynder C, Cooch N, Shiekhatair R. An essential role for CoREST in nucleosomal histone 3 lysine 4 demethylation. *Nature* 2005; **437**: 432–435.
- Garcia-Bassets I, Kwon YS, Telese F, Prefontaine GG, Hutt KR, Cheng CS et al. Histone methylation-dependent mechanisms impose ligand dependency for gene activation by nuclear receptors. *Cell* 2007; **128**: 505–518.
- Lim S, Janzer A, Becker A, Zimmer A, Schule R, Buettner R et al. Lysine-specific demethylase 1 (LSD1) is highly expressed in ER-negative breast cancers and a biomarker predicting aggressive biology. *Carcinogenesis* 2010; **31**: 512–520.
- Metzger E, Wissmann M, Yin N, Muller J, Schneider R, Peters A et al. LSD1 demethylates repressive histone marks to promote androgen-receptor-dependent transcription. *Nature* 2005; **437**: 436–439.
- Zhu Q, Huang Y, Marton LJ, Woster PM, Davidson NE, Casero RA Jr. Polyamine analogs modulate gene expression by inhibiting lysine-specific demethylase 1 (LSD1) and altering chromatin structure in human breast cancer cells. *Amino Acids* 2012; **42**: 887–898.
- Huang Y, Greene E, Murray Stewart T, Goodwin AC, Baylin SB, Woster PM et al. Inhibition of lysine-specific demethylase 1 by polyamine analogues results in reexpression of aberrantly silenced genes. *Proc Natl Acad Sci U S A* 2007; **104**: 8023–8028.
- Vasilatos SN, Katz TA, Oesterreich S, Wan Y, Davidson NE, Huang Y. Crosstalk between lysine-specific demethylase 1 (LSD1) and histone deacetylases mediates antineoplastic efficacy of HDAC inhibitors in human breast cancer cells. *Carcinogenesis* 2013; **34**: 1196–1207.
- Serce N, Gnatzy A, Steiner S, Lorenzen H, Kirfel J, Buettner R. Elevated expression of LSD1 (Lysine-specific demethylase 1) during tumour progression from pre-invasive to invasive ductal carcinoma of the breast. *BMC Clin Pathol* 2012; **12**: 13.
- Huang Y, Stewart TM, Wu Y, Baylin SB, Marton LJ, Perkins B et al. Novel oligoamine analogues inhibit lysine-specific demethylase 1 and induce reexpression of epigenetically silenced genes. *Clin Cancer Res* 2009; **15**: 7217–7228.
- Nowotarski SL, Pachaiyappan B, Holshouser SL, Kutz CJ, Li Y, Huang Y et al. Structure-activity study for (bis)ureidopropyl- and (bis)thioureidopropylamine LSD1 inhibitors with 3-5-3 and 3-6-3 carbon backbone architectures. *Bioorg Med Chem* 2015; **23**: 1601–1612.
- Mohammad HP, Smitheman KN, Kamat CD, Soong D, Federowicz KE, Van Aller GS et al. A DNA hypomethylation signature predicts antitumor activity of LSD1 inhibitors in SCLC. *Cancer Cell* 2015; **28**: 57–69.
- Yang XJ, Gregoire S. Class II histone deacetylases: from sequence to function, regulation, and clinical implication. *Mol Cell Biol* 2005; **25**: 2873–2884.
- Martin M, Kettmann R, Dequiedt F. Class Ila histone deacetylases: regulating the regulators. *Oncogene* 2007; **26**: 5450–5467.
- McKinsey TA, Zhang CL, Lu J, Olson EN. Signal-dependent nuclear export of a histone deacetylase regulates muscle differentiation. *Nature* 2000; **408**: 106–111.
- Martin M, Kettmann R, Dequiedt F. Class Ila histone deacetylases: conducting development and differentiation. *Int J Dev Biol* 2009; **53**: 291–301.
- Santner SJ, Dawson PJ, Tait L, Soule HD, Eliason J, Mohamed AN et al. Malignant MCF10CA1 cell lines derived from premalignant human breast epithelial MCF10 AT cells. *Breast Cancer Res Treat* 2001; **65**: 101–110.
- Wu Y, Wang Y, Yang XH, Kang T, Zhao Y, Wang C et al. The deubiquitinase USP28 stabilizes LSD1 and confers stem-cell-like traits to breast cancer cells. *Cell Rep* 2013; **5**: 224–236.
- Han X, Gui B, Xiong C, Zhao L, Liang J, Sun L et al. Destabilizing LSD1 by Jade-2 promotes neurogenesis: an antibreast system in neural development. *Mol Cell* 2014; **55**: 482–494.
- Huang Y, Nayak S, Jankowitz R, Davidson NE, Oesterreich S. Epigenetics in breast cancer: what's new? *Breast Cancer Res* 2011; **13**: 225.
- Abukhdeir AM, Park BH. P21 and p27: roles in carcinogenesis and drug resistance. *Expert Rev Mol Med* 2008; **10**: e19.
- Kominsky SL, Argani P, Korz D, Evron E, Raman V, Garrett E et al. Loss of the tight junction protein claudin-7 correlates with histological grade in both ductal carcinoma in situ and invasive ductal carcinoma of the breast. *Oncogene* 2003; **22**: 2021–2033.
- Lin T, Ponn A, Hu X, Law BK, Lu J. Requirement of the histone demethylase LSD1 in Snai1-mediated transcriptional repression during epithelial-mesenchymal transition. *Oncogene* 2010; **29**: 4896–4904.
- Chen WD, Eshleman JR, Aminoshariae MR, Ma AH, Veloso N, Markowitz SD et al. Cytotoxicity and mutagenicity of frameshift-inducing agent ICR191 in mismatch repair-deficient colon cancer cells. *J Natl Cancer Inst* 2000; **92**: 480–485.

- 27 Zientek-Targosz H, Kunnev D, Hawthorn L, Venkov M, Matsui S, Cheney RT *et al*. Transformation of MCF-10A cells by random mutagenesis with frameshift mutagen ICR191: a model for identifying candidate breast-tumor suppressors. *Mol Cancer* 2008; **7**: 51.
- 28 Milde T, Oehme I, Korshunov A, Kopp-Schneider A, Remke M, Northcott P *et al*. HDAC5 and HDAC9 in medulloblastoma: novel markers for risk stratification and role in tumor cell growth. *Clin Cancer Res* 2010; **16**: 3240–3252.
- 29 He P, Liang J, Shao T, Guo Y, Hou Y, Li Y. HDAC5 promotes colorectal cancer cell proliferation by up-regulating DLL4 expression. *Int J. Clin Exp Med* 2015; **8**: 6510–6516.
- 30 Nagasawa S, Sedukhina AS, Nakagawa Y, Maeda I, Kubota M, Ohnuma S *et al*. LSD1 overexpression is associated with poor prognosis in basal-like breast cancer, and sensitivity to PARP inhibition. *PLoS One* 2015; **10**: e0118002.
- 31 Piao L, Suzuki T, Dohmae N, Nakamura Y, Hamamoto R. SUV39H2 methylates and stabilizes LSD1 by inhibiting polyubiquitination in human cancer cells. *Oncotarget* 2015; **6**: 16939–16950.
- 32 Shi YJ, Matson C, Lan F, Iwase S, Baba T, Shi Y. Regulation of LSD1 histone demethylase activity by its associated factors. *Mol Cell*. 2005; **19**: 857–864.
- 33 Greco TM, Yu F, Guise AJ, Cristea IM. Nuclear import of histone deacetylase 5 by requisite nuclear localization signal phosphorylation. *Mol Cell Proteom* 2011; **10**: M110.004317.
- 34 Diefenbacher ME, Popov N, Blake SM, Schulein-Volk C, Nye E, Spencer-Dene B *et al*. The deubiquitinase USP28 controls intestinal homeostasis and promotes colorectal cancer. *J Clin Invest* 2014; **124**: 3407–3418.
- 35 Popov N, Wanzel M, Madiredjo M, Zhang D, Beijersbergen R, Bernards R *et al*. The ubiquitin-specific protease USP28 is required for MYC stability. *Nat Cell Biol* 2007; **9**: 765–774.
- 36 Zhang D, Zaugg K, Mak TW, Elledge SJ. A role for the deubiquitinating enzyme USP28 in control of the DNA-damage response. *Cell* 2006; **126**: 529–542.
- 37 Sen N, Kumari R, Singh MI, Das S. HDAC5, a key component in temporal regulation of p53-mediated transactivation in response to genotoxic stress. *Mol Cell* 2013; **52**: 406–420.
- 38 Traynor AM, Dubey S, Eickhoff JC, Kolesar JM, Schell K, Huie MS *et al*. Vorinostat (NSC# 701852) in patients with relapsed non-small cell lung cancer: a Wisconsin Oncology Network phase II study. *J Thorac Oncol* 2009; **4**: 522–526.
- 39 Luu TH, Morgan RJ, Leong L, Lim D, McNamara M, Portnow J *et al*. A phase II trial of vorinostat (suberoylanilide hydroxamic acid) in metastatic breast cancer: a California Cancer Consortium study. *Clin Cancer Res* 2008; **14**: 7138–7142.
- 40 Modesitt SC, Sill M, Hoffman JS, Bender DP. A phase II study of vorinostat in the treatment of persistent or recurrent epithelial ovarian or primary peritoneal carcinoma: a Gynecologic Oncology Group study. *Gynecol Oncol* 2008; **109**: 182–186.
- 41 Blumenschein Jr GR, Kies MS, Papadimitrakopoulou VA, Lu C, Kumar AJ, Ricker JL *et al*. Phase II trial of the histone deacetylase inhibitor vorinostat (Zolinza, suberoylanilide hydroxamic acid, SAHA) in patients with recurrent and/or metastatic head and neck cancer. *Invest New Drugs* 2008; **26**: 81–87.
- 42 Shaw PG, Chaerkady R, Wang T, Vasilatos S, Huang Y, Van Houten B *et al*. Integrated proteomic and metabolic analysis of breast cancer progression. *PLoS ONE* 2013; **8**: e76220.
- 43 Varghese F, Bukhari AB, Malhotra R, De A. IHC Profiler: an open source plugin for the quantitative evaluation and automated scoring of immunohistochemistry images of human tissue samples. *PLoS ONE* 2014; **9**: e96801.
- 44 Ishibashi H, Suzuki T, Suzuki S, Moriya T, Kaneko C, Takizawa T *et al*. Sex steroid hormone receptors in human thymoma. *J Clin Endocrinol Metab* 2003; **88**: 2309–2317.
- 45 Huang Y, Hager ER, Phillips DL, Dunn VR, Hacker A, Frydman B *et al*. A novel polyamine analog inhibits growth and induces apoptosis in human breast cancer cells. *Clin Cancer Res* 2003; **9**: 2769–2777.
- 46 Huang Y, Keen J, Pledgie A, Marton L, Zhu T, Sukumar S *et al*. Polyamine analogues down-regulate estrogen receptor alpha expression in human breast cancer cells. *J Biol Chem* 2006; **281**: 19055–19063.
- 47 Katz TA, Vasilatos SN, Harrington E, Oesterreich S, Davidson NE, Huang Y. Inhibition of histone demethylase, LSD2 (KDM1B), attenuates DNA methylation and increases sensitivity to DNMT inhibitor-induced apoptosis in breast cancer cells. *Breast Cancer Res Treat* 2014; **146**: 99–108.
- 48 Huang Y, Vasilatos SN, Boric L, Shaw PG, Davidson NE. Inhibitors of histone demethylation and histone deacetylation cooperate in regulating gene expression and inhibiting growth in human breast cancer cells. *Breast Cancer Res Treat* 2012; **131**: 777–789.

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