AWARD NUMBER:
W81XWH-14-1-0237

TITLE:
Targeting Histone Abnormality in Triple-Negative Breast Cancer

PRINCIPAL INVESTIGATOR:
Yi Huang, M.D., Ph.D.

CONTRACTING ORGANIZATION:
University of Pittsburgh, Pittsburgh, PA  15213

REPORT DATE:
August 2015

TYPE OF REPORT:
Annual

PREPARED FOR:  U.S. Army Medical Research and Materiel Command
                  Fort Detrick, Maryland  21702-5012

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                        Distribution Unlimited

The views, opinions and/or findings contained in this report are those of the author(s) and should
not be construed as an official Department of the Army position, policy or decision unless so
designated by other documentation.
In the first funding year, we tested our hypothesis that silencing of key tumor suppressive genes by enhanced crosstalk between LSD1 and HDACs is a unique epigenetic mechanism promoting TNBC growth, and blockade of the LSD1/HDAC axis results in profound inhibition of TNBC growth and metastasis, mediated at least in part via induction of RGS16. We demonstrated that HDAC5 physically interacted with LSD1 complex through NLS domain, and promoted LSD1 protein stability through upregulating LSD1-specific deubiquitinase USP28. Increased cellular proliferation mediated by HDAC5 overexpression was diminished by LSD1-KD, suggesting a critical role of LSD1 in regulating oncogenic activity of HDAC5. By using MCF10A TNBC tumor progression model, we observed that HDAC5-LSD1 axis possesses a critical oncogenic function in driving breast cancer development. Moreover, teams of the two PIs collaborated to study the combinatorial effect of natural HDAC inhibitor sulforaphane and novel LSD1 inhibitor HCI-2509 on growth of MDA-MB-231 cells using xenograft model. These new findings provide solid evidence to suggest that crosstalk between LSD1 and HDACs represents a rational target for the development of drugs that can block their activity in TNBC cells.
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</table>
1. INTRODUCTION

Triple negative breast cancer (TNBC) is the most aggressive subtype of breast cancer and lack of specific targets for TNBC patients remains a major clinical challenge. Therefore, new targeted approaches are urgently needed to improve TNBC treatment and prevention. Our early published work has provided novel insights into molecular mechanisms of a unique alteration of gene expression pattern as a result of dysregulated interaction between HDAC5 and LSD1 that could promote the TNBC initiation and progression. This funded Breast Cancer Breakthrough Award is a partnership between Dr. Yi Huang (initiating PI) and Dr. Nancy E. Davidson (partner PI). In the first funding year, the two labs have been closely working together using multiple in vitro and in vivo models to decipher how to apply novel epigenetic agents in the most favorable combination strategy against TNBC and investigate how epigenetic changes might contribute directly to TNBC tumorigenesis. To study the role of LSD1/HDACs axis in promoting transformation of TNBC (Aim 1A), gain- and loss-of-function of MCF10A progression model was used. We observed that HDAC5 possessed a critical oncogenic function in driving TNBC development through blocking LSD1 protein degradation and re-shaping epigenetic landscape. Our studies also revealed that HDAC5 physically interacts with LSD1 and stabilizes LSD1 protein level through posttranslational modification in TNBC cells. In addition, we further elucidated the role of RGS16 signaling pathway in LSD1-mediated HDACi efficacy in TNBC (Aim 1B). By using quantitative ChIP analysis, we have demonstrated that shRNA-HDAC5 significantly decreased the occupancy of HDAC5/LSD1 complex and increased the levels of AcH3K9 and H34me2 at the promoter of RGS16. In the next funding year, the Huang and Davidson labs will continues to work together to explore the precise mechanisms of HDAC5-LSD1 pathway in TNBC development and evaluate the therapeutic effect of inhibition of HDAC5-LSD1 axis in prevention and therapy of TNBC.

2. KEYWORDS

Breast cancer, HDAC5, LSD1, USP28, sulforaphane, combination therapy

3. ACCOMPLISHMENTS

a. What were the major goals of the project?

The hypothesis for our work is that silencing of key tumor suppressive genes by enhanced crosstalk between LSD1 and HDACs is a unique epigenetic mechanism promoting TNBC growth and metastasis, and blockade of the LSD1/HDAC axis results in profound inhibition of TNBC growth and metastasis, mediated at least in part via induction of RGS16. This is to be addressed through three specific aims:
1. Delineate the molecular basis by which inhibition of LSD1 promotes HDACi-induced apoptosis through reactivation of aberrantly silenced tumor suppressor genes.
2. Elucidate the role of LSD1 in HDACi therapy and chemoprvention of TNBC in animal models.
3. Evaluate therapeutic effects of combination strategies in patient-derived xenografts (PDXs).

b. What was accomplished under these goals?

<table>
<thead>
<tr>
<th>Proposed Aims</th>
<th>Accomplishment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
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</tbody>
</table>

4
**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 Huang lab, in collaboration with Davidson lab, investigated whether LSD1/HDAC crosstalk promotes TNBC pathogenesis. Our studies provided solid evidence showing that an orchestrated interplay between HDAC5 and LSD1 is a fundamental epigenetic mechanism contributing to TNBC proliferation and metastasis.

<table>
<thead>
<tr>
<th>Major Task 1: Determine the role of LSD1/HDACs axis in promoting tumorigenic transformation of TNBC.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Subtask 1:</strong> Submit IRB approval for use of LSD1/HDAC expression plasmids. (Month 1-2)</td>
</tr>
<tr>
<td>The proposed work was approved by University of Pittsburgh Institutional Review Board (PRO14030148, 3/10/2014).</td>
</tr>
<tr>
<td><strong>Subtask 2:</strong> Establish MCF-10A cells with overexpression of LSD1, HDAC1, HDAC5 or combination. (Month 3-6)</td>
</tr>
<tr>
<td>We generated two MCF-10A cell lines stably overexpressing HDAC5 (MCF10A-HDAC5). Overexpression of HDAC5 in MCF10A cells increased LSD1 protein level and promoted cell proliferation of both HDAC5-KD clones (Fig. 1A &amp; B), indicating a growth-promoting role for HDAC5 in MCF10A cells.</td>
</tr>
<tr>
<td><strong>Subtask 3:</strong> Treat transfected MCF-10A cells for 6 months with mutagen ICR191 and test the potential transformation of transfected MCF-10A cells in 3D culture (Month 7-15).</td>
</tr>
<tr>
<td>Vector control and HDAC5 overexpressing MCF-10A cells were cultured for 7 months in growth medium containing ICR191. Soft agar colony formation study demonstrated that ICR191 treatment improved the ability of MCF10A cells to form growing colonies in soft agar, and overexpression of HDAC5 significantly promoted ICR191 induced colony formation in MCF10A cells, suggesting that HDAC5-LSD1 axis has the capacity to facilitate tumorigenic transformation induced by genomic instability in TNBC (Fig. 1C).</td>
</tr>
</tbody>
</table>

**Major Task 2:** Elucidate the role of RGS16 signaling pathway in LSD1-mediated HDACi efficacy in TNBC.

| **Subtask 1:** Stable knockdown of RGS16 expression in MCF-10A cells. |
| The generation of stable MCF-10A-RGS16-KD cell line is in progress. In addition, by using quantitative ChIP analysis, we have demonstrated that shRNA-HDAC5 significantly decreased the occupancy of HDAC5/LSD1 complex and increased the levels of AcH3K9 and H34me2 at the promoter of RGS16 (Fig 2). This result suggests that HDAC5/LSD1 complex plays an important role in governing the activities of key histone marks such as H3K4me and AcH3K9 at RGS16 promoter that may lead to the abnormal suppression of RGS16 transcription activity in breast cancer cells. |
| **Subtask 2:** Evaluate whether silencing of RGS16 promotes MCF-10A tumorigenesis (Month 5-8). |
| Once the stable MCF-10A-RGS16-KD cell line is successfully generated, we will test the effect of RGS16 inhibition on MCF-10A cell tumorigenesis. |
We have demonstrated that the interaction between LSD1 and HDAC5 stabilized LSD1 protein (Fig. 3A & 3B). Ubiquitination assays in MDA-MB-231 cells showed that HDAC5 overexpression significantly decreased LSD1 polyubiquitination (Fig. 3C). HDAC5 stabilizes LSD1 protein through upregulation of USP28, a specific deubiquitinase for LSD1 (Fig. 3D). These findings support the notion that interaction of HDAC5 and LSD1 stabilizes LSD1 protein via blockade of LSD1 proteasomal degradation. Simultaneous overexpression of USP28 prevented the destabilization of LSD1 by HDAC5 siRNA without altering HDAC5 protein expression (Fig. 3E). Together, these results suggested that HDAC5 acted as a positive LSD1 regulator through stabilization of USP28 protein expression and activity.

Figure 1. Effect of HDAC5 on growth and mutagen-induced tumorigenic transformation in MCF10A cells. (A) MCF10A cells were transfected with pcDNA3.1-HDAC5 plasmid followed by immunoblots with anti-HDAC5 and anti-LSD1. (B) Crystal violet assay for growth of MCF10-A stably transfected with empty or pcDNA3.1-HDAC5 plasmids. (C) MCF10A cells transfected with pcDNA3.1 or pcDNA3.1-HDAC5 plasmids were treated with 500ng/ml ICR191 for 7 months followed by soft agar colony formation assays. Bars represent the means of three independent experiments ± SD. ** p<0.01, ***p<0.001 (Student’s t-test).

Figure 2. Stable knockdown of HDAC5 decreases the occupancy of HDAC5/LSD1 complex and increased the levels of AcH3K9 and H34me2 at the promoter of RGS16. Quantitative ChIP analysis was used to determine the occupancy of the RGS16 promoters by HDAC5, LSD1, H3K4me2 and acetyl-H3K9. IgG was used as a negative control.
Specific Aim 2: Elucidate the role of LSD1 in HDACi therapy and chemoprevention of TNBC in animal models.

Major Task 4: Evaluate in vivo therapeutic effects of combination strategies using LSD1 inhibitors and HDACi in different subtypes of breast tumors.

Subtask 1: Submit documents for local IACUC review (Month 6-8).

Proposed Aims | Accomplishment
---|---
Specific Aim 2: Elucidate the role of LSD1 in HDACi therapy and chemoprevention of TNBC in animal models. | Dr. Huang’s team assisted Dr. Davidson’s team in designing and performing the animal studies.
Major Task 4: Evaluate in vivo therapeutic effects of combination strategies using LSD1 inhibitors and HDACi in different subtypes of breast tumors. | The research proposal has been approved by The University of Pittsburgh’s Institutional Animal Care and Use Committee (Protocol #: 14033448, 3/24/2014, PI: Davidson).
<table>
<thead>
<tr>
<th>Subtask 2: Examine the <em>in vivo</em> effects of LSD1/HDAC signaling on tumorigenic transformation of MCF-10A cells (Month 8-16).</th>
<th>We are currently evaluating the role HDAC5/LSD1 in breast tumorigenesis using MCF10A-HDAC5-KD cell line model. If the results obtained from these studies suggest that overexpression of LSD1/HDAC5 promotes tumorigenic transformation of MCF-10A cells, we will validate the <em>in vitro</em> results in MCF-10A xenograft-bearing mice.</th>
</tr>
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<tbody>
<tr>
<td><strong>Subtask 3:</strong> Evaluate combination strategies using LSD1i and HDACi in different subtypes of breast tumors (Month 10-26).</td>
<td>We investigated the potential effect of HDAC inhibitors on activity of HDAC5-LSD1 axis. We first tested a panel of HDAC inhibitors for their ability to affect HDAC5-USP28-LSD1 signaling pathway, and found that sulforaphane, a natural HDAC inhibitor found in cruciferous vegetables, significantly inhibited mRNA expression of HDAC5 without changing mRNA levels of LSD1 and UPS28 in MDA-MB-231 cells (Fig. 4A). Immunoblot studies indicated that sulforaphane, but not other HDACis, significantly downregulated protein expression of HDAC5 and LSD1 (Fig. 4B), and ubiquitination assays showed that treatment with sulforaphane in MDA-MB-231 cells increased LSD1 polyubiquitination (Fig. 4C), suggesting that sulforaphane might destabilize LSD1 through inhibition of HDAC5 expression. To confirm this hypothesis, we performed a rescue expression of HDAC5 cDNA in MDA-MB-231 cells through transfection of CMV promoter driven pCDNA3.1 vector that lacked any 5’-HDAC5 promoter sequence. QPCR test indicated that sulforaphane failed to suppress exogenous HDAC5 mRNA expressed driven by CMV promoter (Fig. 4D). This result thereby validated that sulforaphane downregulated HDAC5 mRNA level through repression of transcriptional activities at the native HDAC5 promoter. Immunoblot results indicated that sulforaphane exerted no effect on overexpressed HDAC5 protein and drug-mediated downregulation of USP28 and LSD1 protein was obviously reversed (Fig. 4E). We further studied whether overexpression of HDAC5 impeded cellular response to growth inhibition by sulforaphane. We demonstrated that MDA-MB-231 cells transfected with HDAC5 expression plasmid were more resistant to sulforaphane mediated growth inhibition which was evidenced by significantly increased IC₅₀ value in both cell lines (Fig. 4F). Taken together, these results clearly suggest that HDAC5 acts as a critical regulator of antineoplastic activity of sulforaphane.</td>
</tr>
<tr>
<td>We assisted the Davidson lab to test the <em>in vivo</em> effect of sulforaphane alone or in combination with the LSD1 inhibitor, HCI-2509, using MDA-MB-231 xenografts in athymic nude mice. Treatment with either sulforaphane or HCI-2509 alone significantly inhibited growth of MDA-MB-231 xenografts, and the combination was even more effective. (See Dr. Davidson’s report).</td>
<td></td>
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</table>
c. What opportunities for training and professional development has the project provided?

This award provides an excellent vehicle for a postdoctoral fellow, Chunyu Cao, Ph.D., working on this project to advance his breast cancer research career and transition to an independent position.

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


This work was also presented in at the annual retreats of the University of Pittsburgh Cancer Institute and Women’s Cancer Research Center at the University of Pittsburgh.

One manuscript has been submitted to *Oncogene* for publication and it is currently under revision.

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

During the next reporting period, we plan to: (1) continue to elucidate the role of HDAC5 and LSD1 in regulation of TNBC initiation and transformation (*Aim 1A*). We will investigate whether synchronized gain-of-function of HDAC5 and LSD1 facilitates TMBC tumorigenesis. (2) explore the mechanism by which RGS16 reactivation enhances HDACi-induced apoptosis (*Aim
(3) continue to study how HDAC5 stabilizes LSD1 protein and promotes LSD1 activity in TNBC cells. We will define the mechanisms underlying the regulation of HDAC5 on posttranslational modification of LSD1 protein. We will further characterize how the interplay between HDAC5 and USP28 regulates LSD1 protein stability. (4) characterize the biological function of newly identified genes regulated by crosstalk between HDAC5 and LSD1 (Aim 1C).

4. IMPACT

(a) What was the impact on the development of the principal discipline(s) of the project? Our new findings in the first funding year have opened a new avenue for the potential utility of crosstalk between HDAC5 and LSD1 as a novel epigenetic target for poorly differentiated and aggressive TNBC, which is an important research area that has been understudied in invasive breast cancer. The information derived from these studies will likely validate whether the new subset of aberrantly silenced tumor suppressor genes governed by HDAC5-LSD1 axis has potential to serve as a novel panel of therapeutic biomarkers to predict or indicate the response to epigenetic therapy in TNBC patients. Targeted HDAC5 inhibition with the natural product, sulforaphane, in combination with a newly developed potent LSD1 inhibitor HCI-2509 showed superior antineoplastic activity both in vitro and in vivo. The ongoing study will seek 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

The natural HDAC inhibitor sulforaphane and novel LSD1 inhibitor HCI-2509 have been added as new agents to study their ability in targeting HDAC5-LSD1 axis in breast cancer.

6. PRODUCTS

(a) Publications, conference papers, and presentations

One manuscript has been submitted to *Oncogene* for publication and it is currently under revision.

(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 who have worked on the project

<table>
<thead>
<tr>
<th>Name</th>
<th>Yi Huang</th>
<th>Nancy Davidson</th>
<th>Shauna Vasilatos</th>
<th>Chunyu Cao</th>
</tr>
</thead>
<tbody>
<tr>
<td>Project Role</td>
<td>Co-PI</td>
<td>Co-PI</td>
<td>Technician</td>
<td>Postdoc Fellow</td>
</tr>
<tr>
<td>Researcher Identifier</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
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<tr>
<td>Contribution to</td>
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<td>Oversaw IHC</td>
<td>Performed IHC</td>
<td>Studied molecular</td>
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<td>Project:</td>
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<td>and animal</td>
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<td>breast cancer</td>
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#### Funding Support:

- CDMRP Breast Cancer Breakthrough Award, Breast Cancer Research Foundation
- CDMRP Breast Cancer Breakthrough Award, Breast Cancer Research Foundation
- 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. Tiffany Katz completed her postdoctoral fellow training, and Dr. Chunyu Cao joined the laboratory to carry out the work as a postdoctoral fellow.

c) What other organizations were involved as partners?

Nothing to Report

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: Partnering PI, Dr. Nancy E. Davidson, will submit her annual report separately.

QUAD CHARTS: N/A

9. APPENDICES: updated curriculum vitae is attached
CURRICULUM VITAE
University of Pittsburgh
School of Medicine

BIOGRAPHICAL

Name: Yi Huang

Office Address: Magee Womens Research Institute, Room A406, 204 Craft Avenue, Pittsburgh, PA 15213
Email: huangy2@upmc.edu, yih26@pitt.edu

Office Phone: 412-641-3589
Office Fax: 412-641-2458

Web: http://www.pharmacology.us/Faculty/YiHuang
http://upci.upmc.edu/bocp/Yi-Huang.cfm?member=397

EDUCATION and TRAINING

<table>
<thead>
<tr>
<th>Date Attended</th>
<th>Name and Location of Institution</th>
<th>Degree Received and Year</th>
<th>Major Subject</th>
</tr>
</thead>
<tbody>
<tr>
<td>Undergraduate</td>
<td>Nanjing Medical University, Nanjing, China</td>
<td>M.D., 1991</td>
<td>Clinical Medicine</td>
</tr>
<tr>
<td>Graduate</td>
<td>Medical University of South Carolina, Charleston, SC</td>
<td>Ph.D., 2001</td>
<td>Pathology and Lab Medicine</td>
</tr>
<tr>
<td>Postgraduate</td>
<td>Affiliated Hospital of Medical College of Nanjing University, Nanjing, China</td>
<td>Residency</td>
<td>Surgery</td>
</tr>
<tr>
<td></td>
<td>Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University, Baltimore, MD</td>
<td>Postdoctoral fellow</td>
<td>Oncology</td>
</tr>
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</table>
APPOINTMENTS and POSITIONS

ACADEMIC:

<table>
<thead>
<tr>
<th>Years Inclusive</th>
<th>Name and Location of Institution or Organization</th>
<th>Rank/Title</th>
</tr>
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<tbody>
<tr>
<td>2006-2009</td>
<td>Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University School of Medicine, Baltimore, MD</td>
<td>Research Associate (Faculty)</td>
</tr>
<tr>
<td>2009-2015</td>
<td>Department of Pharmacology and Chemical Biology, School of Medicine, University of Pittsburgh, Pittsburgh, PA</td>
<td>Research Assistant Professor</td>
</tr>
<tr>
<td>2010-2012</td>
<td>Cancer Therapeutics Program, University of Pittsburgh Cancer Institute, Pittsburgh, PA</td>
<td>Member</td>
</tr>
<tr>
<td>2012-2015</td>
<td>Mens Cancer Research Center, Breast and Ovarian Cancer Program, University of Pittsburgh Cancer Institute, Pittsburgh, PA</td>
<td>Member</td>
</tr>
<tr>
<td>2015-</td>
<td>Department of Pharmacology and Chemical Biology, School of Medicine, University of Pittsburgh, Pittsburgh, PA</td>
<td>Assistant Professor (tenure track)</td>
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MEMBERSHIP in PROFESSIONAL and SCIENTIFIC SOCIETIES

<table>
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<tr>
<th>Organization</th>
<th>Year</th>
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<tr>
<td>The American Association for Cancer Research (Active Member).</td>
<td>1998-</td>
</tr>
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</table>

HONORS

<table>
<thead>
<tr>
<th>Honors and Awards</th>
<th>Year</th>
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<tbody>
<tr>
<td>1st Prize of 32nd Annual Research Day, Medical University of South Carolina.</td>
<td>1997</td>
</tr>
<tr>
<td>Young scholar award for the 8th International Symposium of SCBA in Hong Kong.</td>
<td>1999</td>
</tr>
<tr>
<td>DOD breast Cancer Postdoctoral Fellowship Award</td>
<td>2002</td>
</tr>
<tr>
<td>Hodson Young Investigator in Oncology, Johns Hopkins Sidney Kimmel Comprehensive Cancer Center.</td>
<td>2007</td>
</tr>
<tr>
<td>Invited lecturer of Gordon Research Conference on Polyamines</td>
<td>2009</td>
</tr>
<tr>
<td>Samuel and Winters Foundation award for Medical Research</td>
<td>2011</td>
</tr>
</tbody>
</table>
PUBLICATIONS

I. Research Articles


9. Huang Y, Keen JC, Pledgie A, Marton LJ, Zhu T, Sukumar S, Park BH, Blair BG, Brenner K, Casero RA, Davidson NE. Polyamine analogues down-regulate estrogen receptor α expression in


II. Peer-Reviewed Review Articles


**III. Book Chapters**


**IV. Published Meeting Abstracts (partial list)**


24. Katz TA, Vasilatos SV, Oesterreich S, Chandran U Davidson, NE, **Huang Y**. Inhibition of histone demethylase, LSD2, and DNA methyltransferase cooperates in reducing growth and modulating ERα expression in human breast cancer cells. Keystone meeting on Epigenetic Marks and Cancer Drugs, New Mexico, 2013.


27. Cao C, Vasilatos S, Oesterreich S, Davidson NE, **Huang Y**. Functional crosstalk between histone deacetylase 5 (HDAC5) and lysine-specific demethylase 1 (LSD1) as a novel therapeutic target in triple-negative breast cancer cells. The 106th AACR annual meeting; Philadelphia, PA; Cancer Res; 75(15 Suppl): 3838, 2015.

*Total citations: 1694 (Google scholar) *Total journal impact factors: 163.90 *H-index: 22 *i10-index 29 (as of 12/30/2015)

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**PROFESSIONAL ACTIVITIES**

**TEACHING**

**Mentoring**

Postdoctoral fellows

<table>
<thead>
<tr>
<th>Year</th>
<th>Name</th>
<th>Position</th>
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<tr>
<td>2014-2016</td>
<td>Chunyu Cao, Ph.D.</td>
<td>Postdoc fellow, University of Pittsburgh</td>
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</tbody>
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**Doctoral Students**

<table>
<thead>
<tr>
<th>Year</th>
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<tbody>
<tr>
<td>2015-</td>
<td>Julia C. Woodcock, Pharmacology &amp; Chemical Biology, University of Pittsburgh</td>
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**Undergraduate Students**

<table>
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<tr>
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<tr>
<td>2010</td>
<td>Emily Platz</td>
</tr>
<tr>
<td>2015-2017</td>
<td>Lin Chen</td>
</tr>
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**High School Students**
2013 Jennifer Han, UPCI Summer Academy
2015 Jeewon Lee, UPCI Summer Academy

Ph.D. Candidacy Exam Committee
2013 Courtney Anderson, Pharmacology & Chemical Biology, University of Pittsburgh
2013 Kyle Knickelbein, Pharmacology & Chemical Biology, University of Pittsburgh
2015 Nolan Priedigkeit, Pharmacology & Chemical Biology, University of Pittsburgh
2015 Alison Nagle, Pharmacology & Chemical Biology, University of Pittsburgh

Ph.D. Dissertation Committee
2013-present Julia C. Woodcock, Pharmacology & Chemical Biology, University of Pittsburgh

RESEARCH

1. Research Supports

Active Grant Support

<table>
<thead>
<tr>
<th>Project number</th>
<th>Title: Targeting histone abnormality in triple negative breast cancer</th>
<th>Role in project: PI (Partnering PI: Davidson)</th>
<th>Year Inclusive: 8/1/2014-7/31/2017</th>
<th>Source: Department of Defense – Breast Cancer Program Breakthrough</th>
<th>Amount: $565,048</th>
</tr>
</thead>
</table>

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<thead>
<tr>
<th>Project number</th>
<th>Title: Role of LSD2 in epigenetic gene silencing in breast cancer</th>
<th>Role in project: PI</th>
<th>Year Inclusive: 2013-2014</th>
<th>Source: UPCI Pilot Grant</th>
<th>Amount: $5,000</th>
</tr>
</thead>
</table>

| Project number | Title: Role of histone demethylase in epigenetic regulation of gene expression in breast cancer | Role in project: Co-I, PI: Davidson | Year Inclusive: 2014-2015 | Source: Breast Cancer Research Foundation | Amount: $200,000/yr ($70,279 supports Dr. Huang’s research) |

Prior Grant Support

<table>
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<tr>
<th>Project number</th>
<th>Title: Targeting crosstalk between LSD1 and HDAC in triple negative breast cancer</th>
<th>Role in project: PI</th>
<th>Year Inclusive: 2012-2013</th>
</tr>
</thead>
</table>
Source: UPMC Competitive Medical Research Fund
Amount: $25,000

Project number: P50 CA88843-08 (JHU PO#2009 12087) (Davidson)
Project number: BCRF0016554
Title: Role of histone demethylase in epigenetic regulation of gene expression in breast cancer
Role in project: Co-I, PI: Davidson
Year Inclusive: 2009-2014
Source: Breast Cancer Research Foundation
Amount: $89,418/yr

Title: Specialized Program in Research Excellence (SPORE in Breast Cancer)
Role in project: Co-I, PI of Project 2-2
Year Inclusive: 2009-2012
Source: NCI
Amount: $43,163/yr

Title: Crosstalk between histone demethylase and histone deacetylase: a novel epigenetic target for breast cancer
Role in project: PI
Year Inclusive: 2011-2012
Source: Samuel and Emma Winters Foundation
Annual direct cost: $9,000

Title: Antineoplastic efficacy of novel polyamine analogues in human breast cancer
Role in project: PI
Year Inclusive: 2003-2006
Source: DOD Breast Cancer Research Program
Amount: $170,000

Title: The role of histone deacetylase and DNA methylation in estrogen receptor expression in breast cancer
Role in project: PI
Year Inclusive: 2002-2003
Source: DOD Breast Cancer Research Program
Amount: $96,000

Pending Grant Support

NCI RO1 Targeting HDAC5-LSD1 axis in triple negative breast cancer
2. Invited Seminars and Lectureships

2008.5. AACR special conference-Cancer Epigenetics, Boston, MA, “Novel oligoamine analogues inhibit lysine specific demethylase 1 and activate silenced gene re-expression in colon cancer cells.”


2011.9. The 1st Annual Retreat of Women’s Cancer Research Center, University of Pittsburgh, “Epigenetics and breast cancer: exploding the box, or unraveling the chromatin”


3. Invited Journal Peer Review Activities

♦ Amino Acids
♦ Breast Cancer Research
♦ Breast Cancer Research & Treatment
♦ BBA - Molecular Cell Research
♦ BMC Cancer
♦ Cancer Biology & Therapy
♦ Cancer Investigation
♦ Cancer Research
♦ Carcinogenesis
♦ Cell Death and Differentiation
♦ Clinical Cancer Research
♦ Clinical & Experimental Metastasis
♦ Cancer Letters
♦ Cell Biochemistry and Biophysics
♦ Frontiers of Epigenomics
♦ Hormones and Cancer
♦ Journal of National Cancer Institute
♦ Life Science
♦ Medicinal Chemistry Communications
♦ Molecular and Cellular Endocrinology
4. Editorial Boards

2011- present  Frontiers in Epigenomics
2013-2015  Cancer and Clinical Research

5. Study Section or Scientific Review Services

2015  Reviewer, Israel Science Foundation

SERVICE

University and Medical School Service

2000-01  President, International Association of Medical University of South Carolina
2013  Poster judge, 3rd Annual WCRC retreat, UPCI
2013  Poster judge, 24th Annual Vascular Biology and Hypertension Symposium, University of Alabama at Birmingham
2014  WCRC retreat planning committee
2014  UPCI retreat judge
2015  UPCI retreat organization committee member
2015-  UPCI Summer Academy, WCRC site director
2015  WCRC retreat judge
2016  2nd Great Lakes Breast Cancer Symposium organizing committee

Community Service

2000-01  Vice President, Association of Chinese Scholar and students of Charleston SC
2015.11.  Speaker, 2nd UPCI breast cancer advocacy boot camp