BIOGRAPHICAL SKETCH

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NAME: Martinez, Elisabeth D.

eRA COMMONS USER NAME (credential, e.g., agency login): EMART4

POSITION TITLE: Associate Professor with tenure, Department of Pharmacology, UTSW

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Boston College, Boston, MA	B.S., *mcl*	05/94	Biochemistry
Georgetown University Medical Center, Washington, DC	Ph.D.	02/02	Biochemistry/Mol. Biol.
NCI, NIH; Bethesda, MD	Fellowship	03/02-06/05	Transcriptional/Epigenetics and Drug Discovery

A. Personal Statement My scientific program at UT Southwestern is built upon a combined approach of defining the function of epigenetic enzymes and developing chemical tools to modulate their function. This dual strategy gives us the great advantage of simultaneously advancing basic knowledge and generating chemical probes with therapeutic potential. We leverage the novel chemical biology tools we discover to query and modulate biological pathways in physiology and disease. Our main interest is to molecularly define and pharmacologically target the pathological epigenetic and transcriptional events that characterize transcriptional disorders, while uncovering new biology. For some years, our research has focused on Jumonji histone demethylase enzymes. We have discovered novel roles for Jumonji enzymes in transcriptional adaptation and reprogramming, in the development of chemotherapy resistance, in DNA repair pathways and in the response stress and subsequent adaptation in the heart and other organs. Our small molecule inhibitors have in vivo efficacy without toxicity and have been excellent tools for gaining mechanistic insights into the Jumonji-driven molecular events driving these processes. In addition to chemical biology and drug discovery, we use genetic, molecular and genomic approaches to understand the underlying biology and catalytic activity of these enzymes. My training in transcriptional regulation, epigenetic control of gene expression, enzyme biology and drug discovery has given me unique opportunities to comprehensively study enzyme mechanisms of action in a clinically relevant context with practical application to cancer. In my laboratory, I seek to empower trainees with conceptual, experimental and life-long skills and habits that will enable them to be responsible contributors to the scientific world and to society, while building a positive and inclusive environment that welcomes diversity and out-of-the-box career paths. I have been blessed with diverse teams which included URM trainees and junior faculty members who have enriched our work and our lives.

ONGOING RESEARCH PROJECTS

19TPA34910171
American Heart Association – OSC 7/1/19 – 6/30/22
"Mechanism of activation of histone lysine demethylase in pathological cardiac remodeling"
This application aims to understand the role of a Jumonji demethylases in maladaptive heart remodeling.

The WELCH Foundation, I-1878 6/1/18 – 5/30/25
Individual Investigator Award (Martinez) – PI
"Development of Epigenetic Inhibitors to Prevent Acquired Drug-Resistance"
This application aims at developing Jumonji inhibitors to prevent drug resistance.

NIH-NIAID R21AI19408 1/17/20 – 12/31/21
NIH – Exploratory/Developmental Research Grant (Martinez) – PI
"Epigenetic reprogramming of the malaria parasite"
This application seeks to define the role of malaria Jumonji enzymes and therapeutically target them.

NIH-NCI 5R01CA229487 8/1/20 – 1/31/24
R01 Research Grant (Kraus, PI Martinez co-investigator)
"Context – Dependent Effects of PARP Inhibitors on Breast Cancer Bone Metastasis"
This applicationt's goal is to define the roles of PARP enzymes and their substrates in cancer progression and metastasis.

Nolan Miller Lung Cancer Award (Martinez) – PI 5/1/07 – 5/30/27
"The anti-proliferative activity of novel compounds against lung cancer"
Support to complement studies on the anti-proliferative activity of novel compounds against lung cancer and to define the mechanism of action of the most effective drugs.

RECENTLY COMPLETED PROJECTS
RP160493 CPRIT 3/1/16 – 2/29/20
Individual Investigator Award (Martinez) – PI
"Defining the anti-cancer action of a new Jumonji demethylase inhibitor"
This application characterized the effects of a Jumonji inhibitor on cancer therapeutic response.

UTSW Lung Cancer SPORE Career 11/1/18 – 10/31/19
Enhancement Award (Martinez) – PI
This application determined how immunity is affected by epigenetic therapy.

NIH R33 AI116222-03
Indiv Investigator Award (D'Orso/Martinez) – coPIs 9/1/16 – 8/31/19
This application tested epigenetic compounds for their ability to reactivate HIV and thus make it susceptible to anti-viral therapy.

Department of Defense (Martinez) – PI 9/1/16 – 8/31/18
This application defined the role of epigenetic pathways in the response to radiation.

RELEVANT CITATIONS:

1. **Martinez, E.D.** and Danielsen, M. Loss of androgen receptor transcriptional activity at the G1/S transition: involvement of acetylation pathways (2002), Journal of Biological Chemistry 277(33):29719-29729. PMID: 12055183.
2. Wang, L. et al **and Martinez, E.D.** A small molecule modulates Jumonji histone demethylase activity and selectively inhibits cancer growth. (2013) Nature Communications 2013;4(2035). DOI:10.1038/ncomms3035. PMID:23792809. PMCID:PMC3724450.
3. Dalvi, M.P., Wang, L., Zhong, R., Kollipara, R.K., Park, H., Bayo, J., Yenerall, P., Zhou, Y., Timmons, B., Rodriquez-Canales, J., Behrens, C., Mino, B., Villalobos, P., Parra, E.R., Suraokar, M., Pataer, A., Swisher, S.G., Kalhor, N., Bhanu, N.V., Garcia, B.A., Heymach, J.V., Coomes, K., Xie, Y., Girard, L., Gazdar, A.F., Kittler, R., Wistuba, I.I., Minna, J.D., and **Martinez, E.D.** Taxane-Platin Resistant Lung Cancers Co-develop Hypersensitivity to JumonjiC Demethylase Inhibitors. Cell Reports (2017) doi.org/10.1016/j.celrep.2017.04.077.
4. Zhang, Q.J., Tran, T.A., Wang, M, Ranek, M.J., Kokkonen, K., Gao, J., Luo, X., Wei, T., Krychenko, V., Liao, L., Xu, J., Hill, J.A., Olson, E.N., Kass, D.A., **Martinez, E.D.*** and Liu, Z.P.* Histone lysine dimethyl-demethylase KDM3A controls pathological cardiac hypertrophy and fibrosis. Nature Communications, 2018, Vol 9, Article number: 5230 (2018). *co-corresponding authors
5. Bayo, J., Tran, T.A., Wang, L., Peña-Llopis S, Das, A.K and **Martinez, E.D.** Jumonji inhibitors radiosensitize cancers through changes in H3K4 methylation at double strand breaks. Cell Reports, 2018 doi.org/10.1016/j.celrep.2018.09.081.

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

6/2022-on Associate Director of Diversity, Equity and Inclusion, Simmons Comprehensive Cancer Center, University of Texas Southwestern Medical Center, Dallas, TX

9/2019-on Associate Professor, Department of Pharmacology, University of Texas Southwestern Medical Center, Dallas, TX (tenured 9/2019)

9/2009-2019 Assistant Professor, Department of Pharmacology, University of Texas Southwestern Medical Center, Dallas, TX (tenure-track from 9/2013)

2005-08/2009 Instructor, Department of Pharmacology, University of Texas Southwestern Medical Center, Dallas, TX

2002–2005 Postdoctoral Fellow, Laboratory of Receptor Biology and Gene Expression National Cancer Institute, NIH, Bethesda, MD. Supervisor: Gordon L. Hager, Ph.D.

1996–2002 Graduate Student Research Fellow, Department of Biochemistry and Molecular Biology, Georgetown University Medical Center, Washington, DC. Supervisor/mentor: Mark Danielsen, Ph.D.

1994–1996 Research Assistant, Department of Biochemistry and Molecular Biology, Georgetown University Medical Center, Washington DC. Supervisor: Mark Danielsen, Ph.D.

1993-1994 Undergraduate Research Assistant, Department of Chemistry Boston College, Newton, MA. Supervisor: Mary Roberts, Ph.D.

Honors

2019 UTSW John P. Perkins, Ph.D. Distinguished Professor in Biomedical Science

2016 UTSW Gilman Special Opportunities award

2014 UTSW Friends of Cancer Center award

2013 Early Investigator Abstract award and scholarship, Keystone Symposia

2013 UTSW LEAD program Dean's award

2007 Abstract Award, International Association for the Study of Lung Cancer, 7 annual Targeted Therapies for the Treatment of Lung Cancer Conference

2004 NIH Technology Transfer Award (Certificate and $1,000 unrestricted cash award)

2003 NIH FARE Research Excellence Award (Certificate and $1000 toward conference travel)

2000 Travel grants: Women in Endocrinology; Graduate Student Organization; Keystone Symposia and EMBO

1994 Phi Beta Kappa, induction

C. Contributions to Science

Development of cell based assay systems: Drug discovery strategies that yield cell permeable, biologically active small molecules with relevant mechanisms of action against a disease pathway are essential for effective development of chemical research tools and pharmacological therapeutics. I have designed, established and successfully utilized two cell-based assays for the discovery of nuclear receptor ligands or epigenetic modulators (*Martinez et al, Methods in Enzymology 2006; Martinez and Hager, Methods in Enzymology 2006; Martinez et al, J Steroid Biochem Mol Bio 2005; my role: first author*). These systems have yielded small molecules that alter transcriptional and epigenetic patters and interfere with disease pathways. Our assays have also been used in the establishment of high throughput screening centers by the NIH (*Auld et al, Methods in Enzymology 2006; my role: collaborator)*.

- **Martinez, E.D.**, Rayasam, G., Dull, A., Walker, D. and Hager, G.L. An Estrogen Receptor Chimera Senses Ligands by Nuclear Translocation (2005), J Steroid Biochem Mol Biol 97(4):307-321. PMID: 16162406.
- **Martinez, E.D**. and Hager, G.L. Development of assays for nuclear receptor ligands using fluorescently tagged proteins, (2006), Methods in Enzymol. 414:37-50. PMID: 17110185.
- **Martinez, E.D.**, Dull, A., McMahon, J., Beutler, J. and Hager, G.L., High content fluorescence-based screening for epigenetic modulators, (2006), Methods in Enzymol. 414:21-36. PMID: 17110184.
- Auld, D.S., Johnson, R.L., Zhang, Y., Veith, H., Jadhav, A., Yasgar, A., Simeonov, A., Zheng, W., **Martinez, E.D.**, Westwick, J.K., Austin, C.P., and Inglese, J. Fluorescent protein-based cellular assays analyzed by laser scanning microplate cytometry in 1536-well plate format, (2006), Methods in Enzymol. 414:566-589. PMID: 17110211.

Discovery and characterization of small molecule transcriptional and epigenetic modulators: Our cell based assays have led to the identification of compounds that alter histone modifications, normalize transcriptional

patterns, affect cell cycle progression and have anti-cancer properties in cell and animal models (*Johnson et al, Analytical Biochemistry, 2008; Best et al, Journal of Biomedicine and Biotechnology 2011; Wang et al, Nature Communications, 2013; Tran et al, ACS Chemical Biology, 2014; my role: PI and corresponding author for all four publications*). The need for new treatments for cancer and related proliferative disorders continues to grow, as therapeutic resistance develops and existing regimens fail. Small molecule inhibitors targeting enzymatic activities that drive oncogenesis or ligands that modulate receptor transcriptional activities are excellent potential drugs. Yet many times, compounds are identified with promising biochemical functions that end up having no cellular activity and thus must be abandoned in the drug discovery pipeline. By contrast, my approach has been to start from compounds that have biological activity in cells and desirable phenotypes in disease models, and work backwards towards mechanistic insight and target identification. My work has demonstrated that this approach is highly feasible and yields relevant small molecules with therapeutic activity. In particular, I would like to highlight my group's identification, mechanistic characterization and in vivo evaluation of JIB-04 *(Wang et al, Nature Communications 2013; my role: PI and corresponding author*), a first in class inhibitor of Jumonji histone demethylases, enzymes highly upregulated in many cancers. The compound has had significant impact in the field with over ten companies manufacturing it and selling it within a few months of publication and many laboratories around the globe using it as an investigational tool to elucidate new biology and as a therapeutic in multiple pre-clinical applications.

- Johnson, R.J., Huang, W., Jadhav, A., Austin, C.P., Inglese, J. **and Martinez, E.D.** A Quantitative High-Throughput Screen Identifies Potential Epigenetic Modulators of Gene Expression, (2008), Analytical Biochemistry 375(2):237-48. PMID: 18211814. PMCID: PMC2330280.
- Best, A., Chang, J., Dull, A., Beutler, J. **and Martinez, E.D.** Identification of four potential epigenetic modulators from the NCI structural diversity library using a cell based assay, (2011), Journal of Biomedicine and Biotechnology, 2011:868095. Epub 2010 Dec 22. PMCID: PMC3014726
- Wang, L. et al **and Martinez, E.D.** A small molecule modulates Jumonji histone demethylase activity and selectively inhibits cancer growth. (2013) Nature Communications 2013;4(2035). DOI:10.1038/ncomms3035. PMID:23792809. PMCID:PMC3724450
- Tran, A.T., Wichterman-Kouznetsova, J., Varghese, D., Huang, R., Huang, W., Becker, M., Austin, C.P., Inglese, J., Johnson, R.L., **and Martinez, E.D.** Identification of small molecule modulators of gene transcription with anti-cancer activity, (2014). ACS Chem. Biol., Article ASAP. doi: 10.1021/cb500532x.

Characterization of cellular responses to chemical perturbations: The heterogeneous response of cells to pharmacological treatments can lead to resistance or treatment failure. We have defined how both different cells within a tumor type respond differentially to compounds and how inhibitors of the same cellular target can have diverse biological effects. These studies have defined molecular determinants of therapeutic response and elucidated biological processes commonly or distinctly affected by enzyme inhibitors.

- Slack, M.D., **Martinez, E.D.**, Wu, L.F. and Altschuler, S.J. Characterizing heterogeneous cellular responses to perturbations (2008), PNAS 105 (49):19306-11. PMID: 19052231. PMCID: PMC2614757.
- Chang, J., Varghese, D.S., Gillam, M.C., Peyton, M., Modi, B., Schiltz, R.L., Girard, L., **and Martinez, E.D.** Differential response of cancer cells to HDAC inhibitors trichostatin A and depsipeptide,(2012), British Journal of Cancer, Jan 3;106(1):116-25. Epub 2011 Dec 8. PMCID: PMC3251870.
- Matthews KA, Senagbe KM, Nötzel C, Gonzales CA, Tong X, Rijo-Ferreira F, Bhanu NV, Miguel-Blanco C, Lafuente-Monasterio MJ, Garcia BA, Kafsack BFC, **and Martinez ED**. Disruption of the Plasmodium falciparum Life Cycle through Transcriptional Reprogramming by Inhibitors of Jumonji Demethylases. ACS Infect Dis. 2020 May 8;6(5):1058-1075. doi: 10.1021/acsinfecdis.9b00455. Epub 2020 Apr 24. PubMed PMID:32272012.
- Tran, T. A., Zhang, Q. J., Wang, L., Gonzales, C., Girard, L., May, H., Gillette, T., Liu, Z. P., & **Martinez, E. D.** (2022), Inhibition of Jumonji demethylases reprograms severe dilated cardiomyopathy and prolongs survival. The Journal of biological chemistry, 298(2), 101515. https://doi.org/10.1016/j.jbc.2021.101515

Identification of nuclear receptor expression patterns in human cancers: Nuclear receptors are ligand regulated transcription factors that control a wide range of transcriptional programs, including proliferative pathways. In two separate studies, we have defined the levels of expression of the full human family of 48

nuclear receptors and have elucidated gene-gene interactions, identified drugable targets and evaluated specific ligands to modulate growth in the first study, we profiled the receptors across the NCI-60 panel of tumor lines representing 9 different cancer types (*Holbeck et al, Molecular Endocrinology 2010; my role: PI and corresponding author*), we defined the nuclear receptors present in uveal melanomas that differentiate them from cutaneous melanomas and normal melanocytes (*Huffman et al, Frontiers in Endocrinology, 2015; my role: PI and corresponding author*) and identified epigenetic and transcriptional vulnerabilities in estrogen receptor positive vs. negative cancers *(Trost et al, Onctotarget 2016; Peña-Llopis et al, Oncotarget 2016; my role: PI and corresponding author).*

- Holbeck, S., Chang, J., Best, A.M., Bookout, A.L., Mangelsdorf, D.J. **and Martinez, E.D**. Expression Profiling of nuclear receptors in the NCI60 cancer cell panel reveals receptor-drug and receptor-gene interactions, (2010), Mol Endocrinol. 24(6):1287-96. PMID: 20375240. PMCID: PMC2875807.
- Huffman, K.E., Carstens, R., **and Martinez, E.D.** A subset of nuclear receptors are uniquely expressed in uveal melanoma cells, (2015) Frontiers in Endocrinology Jul 7, 6:93. doi: 10.3389/fendo.2015.00093. PubMed PMID: 2621730.
- Trost, N., Pena-Llopis, S., J., Potts, P.R., Fon Tacer, K. **and Martinez, E.D.** γKlotho is a Novel Marker and Cell Survival Factor in a Subset of Triple Negative Breast Cancers, (2016). Oncotarget. 2016 Jan 19;7(3):2611-28. doi: 10.18632/oncotarget.6006.
- Peña-Llopis, S., Wan, Y. and **Martinez E.D.** Unique epigenetic profiles define breast cancers with poor prognosis. Oncotarget. 2016 Dec 27;7(52):85819-85831. doi: 10.18632/oncotarget.13334. PubMed PMID: 27863398.

The role of Jumonji histone demetylase enzymes in physiology and disease: The pharmacological tools we have discovered and developed, especially JIB-04, have led us into mechanistic studies of Jumonji enzyme biology. We have elucidated the cancer-selective role of Jumonji enzymes in cancer through gain of function and loss of function studies (*Wang et al, Nature Communications, 2013; my role: PI and corresponding author; Duan et al, Chemistry and Biology, 2015; my role: collaborator and contributing author*), have elucidated the function of Jumonji enzymes as modulators of hedgehog signaling (*Schneider et al, Nature Communications, 2015; my role: collaborator and contributing author*) and have found that chemically related enzymes play a role in cancer metastasis (*Chen et al, Journal of Clinical Investigation, 2015; my role: collaborator and contributing author*). More recently, my group has discovered a role of Jumonji enzymes in therapy resistance. In chemotherapy resistance lung cancer, we reported upregulation of Jumonji enzymes and a consequent hypersensitivity to Jumonji inhibitors (*Dalvi et al, Cell Reports, 2017; my role: PI and corresponding author*). This has opened up the important possibility of preventing chemoresistance development by co-targeting Jumonji enzymes in tumors. We have also described a role for JARID1B in DNA repair and radiation resistance, and the ability of JARID inhibitors to radiosensitize cancer cells and tumors by the accumulation of histone methyl marks at sites of damage blocking DNA repair pathways. Finally, with the Liu lab we have shown Jumonjis are therapeutic targets in cardiac hypertrophy.

- Wang, L. et al **and Martinez, E.D.** A small molecule modulates Jumonji histone demethylase activity and selectively inhibits cancer growth. (2013) Nature Communications 2013;4(2035). DOI:10.1038/ncomms3035. PMID:23792809. PMCID:PMC3724450.
- Dalvi, M.P., Wang, L., Zhong, R., Kollipara, R.K., Park, H., Bayo, J., Yenerall, P., Zhou, Y., Timmons, B., Rodriquez-Canales, J., Behrens, C., Mino, B., Villalobos, P., Parra, E.R., Suraokar, M., Pataer, A., Swisher, S.G., Kalhor, N., Bhanu, N.V., Garcia, B.A., Heymach, J.V., Coomes, K., Xie, Y., Girard, L., Gazdar, A.F., Kittler, R., Wistuba, I.I., Minna, J.D., **and Martinez, E.D.** Taxane-Platin Resistant Lung Cancers Co-develop Hypersensitivity to JumonjiC Demethylase Inhibitors. Cell Reports (2017) doi.org/10.1016/j.celrep.2017.04.077.
- Bayo J, Tran TA, Wang L, Peña-Llopis S, Das AK, **and Martinez, ED**. Jumonji inhibitors overcome radioresistance in cancer through changes in H3K4 methylation at double-strand breaks. Cell Reports (2018); 25(4):1040-1050.e5. PMID:30355483 PMCID:PMC6245670.
- Zhang, Q.J., Tran, T.A., Wang, M, Ranek, M.J., Kokkonen, K., Gao, J., Luo, X., Wei, T., Krychenko, V., Liao, L., Xu, J., Hill, J.A., Olson, E.N., Kass, D.A., **Martinez, E.D.**** and Liu, Z.P.** *Histone lysine dimethyl-demethylase KDM3A controls pathological cardiac hypertrophy and fibrosis*. Nature Communications, 2018, Vol 9, Article number: 5230 (2018). **co-corresponding authors

Complete List of Published Work in MyBibliography:
https://www.ncbi.nlm.nih.gov/myncbi/elisabeth.martinez.1/bibliography/public/