BIOGRAPHICAL SKETCH

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NAME: **Lombard, David B.**

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

POSITION TITLE: Professor and Vice-Chair for Clinical and Translational Research; Physician and Staff Scientist, Miami VA/GRECC

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
Harvard College, Cambridge MA	B.A.	06/1992	Biochemical Sciences
MIT, Cambridge MA	Ph.D.	02/2000	Biology
Harvard Medical School, Boston MA	M.D.	06/2001	
Brigham and Women's Hospital, Boston MA		06/2003	Pathology residency
Children's Hospital, Boston MA		08/2008	Postdoctoral

A. Personal Statement

I am a physician-scientist with broad interests in the biology of sirtuin proteins and their relationships with aging and disease, particularly melanoma; and aging biology, especially how it may be targeted through small molecule-based interventions. I performed my doctoral studies with Lenny Guarente, PhD, at MIT, studying Werner syndrome and related premature aging diseases. After residency in pathology, I pursued postdoctoral work at The Children's Hospital, Boston, where I studied the sirtuins, SIRT3 and SIRT6, supported by an NIA/NIH K08 award. I was the first to describe a central role for SIRT3 in regulating mitochondrial protein acetylation. I established my first independent lab at the University of Michigan in 2008. There, I rose to the rank of tenured Associate Professor and served as Director of the Michigan's Cancer Biology Graduate Program, and principal investigator of the associated NCI T32. In my current position at the University of Miami Miller School of Medicine, I serve as Vice-Chair for Clinical and Translational Research in the Department of Pathology & Laboratory Medicine, Translational Science Leader for the Sarcoma SDG, and co-leader of the Cancer Epigenetics Research Program at the NCI-designated Sylvester Comprehensive Cancer Center (Sylvester). In collaboration with the other research programs, we are leveraging the major strengths of our exceptional investigators and cutting-edge common equipment to generate novel insights into epigenetic dysregulation in cancer, and how it may be targeted for new effective cancer treatments. I am a New Scholar in Aging of the Ellison Medical Foundation, a member of The American Society for Clinical Investigation, a Scholar-Innovator of the Harrington Discovery Institute, and a recipient of an American Association for Cancer Research (AACR) Innovation and Discovery award, and a regular member of the Melanoma Research Alliance Grant Review Panel. My lab frequently employs mitochondrial analysis and metabolomics, coupled with transcriptomics (a-d); many of these studies focus on SIRT5 (e.g. b-d).

<u>Active</u>
NCI R01CA253986
Lombard/Neamati (MPI)
1/28/22-12/31/27
SIRT5 inhibitors and degraders as novel treatments for Ewing sarcoma

DoD CDMRP ME20030 (Mid-career accelerator award)
Lombard (PI)

7/1/21-6/30/24 (NCE→6/25)
Targeting autophagy via the Menin protein to inhibit melanoma metastasis

NIH/NIA R33AG077856 (R21/R33)
Nikolovska-Coleska/Lombard (MPI)
8/1/22-5/31/27
Targeting the longevity regulator PAPP-A with small molecule inhibitors

VA-ORD MERIT 1I01BX006593-01A1
10/1/25-9/30/29
Epigenetic and metabolic mechanisms of cadmium cytotoxicity
Notice of intent to fund received; pending JIT)

Florida Department of Health Bankhead-Coley
Lombard (PI)
4/1/24-3/31/27
Targeting the chromatin scaffold Menin to overcome resistance to targeted therapy in melanoma

V-Foundation DT2023-008
Crane (PI)
5/1/23-5/1/26
Support for cancer research affecting adults or children
Role: Co-I with effort

NCI P30CA240139
Nimer (PI)
7/1/19-6/30/24 (competitive renewal pending)
The Sylvester Cancer Center Support Grant
Role: Co-Lead, Cancer Epigenetics Program

Completed within last 3 years (selected)

NIH/NIGMS R01GM101171
Lombard (PI)
4/1/12-8/31/22
Regulation of one carbon metabolism and epigenetics by SIRT5

NCI 5T32CA009676
Castro/Lombard (MPI)
9/30/97-8/31/23
Cancer Biology Training Program **(relinquished 4/22)**

DoD CDMRP NF170044
Lombard (PI)
9/1/18-8/31/21 (NCE→8/22)
SIRT5, a novel therapeutic target for NF1-associated MPNST

Recent relevant citations:

a. **Lombard, D.B.**, Kohler, W.J., Guo, A.H., Gendron, C., Han, M., Ding, W., Lyu, Y., Ching, T.-T., Wang, F.-Y., Chakraborty, T.S., Nikolovsoka-Coleska, N., Duan, Y., Girke, T., Hsu, A.-L., Pletcher, S.D., and Miller, R.A. (2020). High throughput small molecule screening reveals Nrf2-dependent and -independent pathways of cellular stress resistance. *Sci. Advances* 6(40):eaaz7628. doi: 10.1126/sciadv.aaz7628. ¶ corresponding author.
b. Giblin, W., Bringman-Rodenbarger, L., Kumar, S., Skinner, M.E., Guo, A.H., Mostafa, A.M., Azar, M., Mady, A.S.A., Chung, C.H., Kadambi, N., Melong, K.A., Lee, H.-J., Zhang, L., Sajjakulnukit, P., Trefely, S., Varner, E.L., Iyer, S., Wang, M., Wilmott, J.S., Soyer, H.P., Sturm, R.A., Pritchard, A.L., Andea, A., Scoyler, R.A., Stark, M.S., Scott, D.A., Fullen, D.R., Bosenberg, M.W., Chandrasekaran, S., Nikolovska-Coleska, Z., Verhaegen, M., Snyder, N.W., Rivera, M.N., Osterman, A.L., Lyssiotis, C., and **Lombard, D.B.** (2021). The deacylase SIRT5 supports melanoma viability by influencing chromatin dynamics. *J Clin Invest.* June 15;131(12): 138926. PMC8203465.
c. Guo, A.H., Baliira, R.K., Skinner, M.E., Kumar, S., Andren, A., Zhang, L., Goldsmith, R.S., Michan, S., Davis, N.J., Maccani, M.W., Day, S.M., Sinclair, D.A., Brody, M.J., Lyssiotis, C.A., Stein, A.B., and **Lombard, D.B.** (2022). Sirtuin 5 levels are limiting in preserving cardiac function and suppressing fibrosis in response to pressure overload. *Sci Rep*. Jul 18;12(1):12258. PMC9293976.

d. Yuan, T.*, Kumar, S.*, Skinner, M.E., Victor-Joseph, R., Abuaita, M., Keijer, J., Zhang, J., Kunkel, T.J., Liu, Y., Petrunak, E.M., Saunders, T.L., Lieberman, A.P., Stuckey, J.A., Neamati, N., Al-Murshedi, F., Alfadhel, M., Spelbrink, J.N., Rodenberburg, R., de Boer, V.C.J.+, and **Lombard D.B.+**. (2024). Human SIRT5 variants with reduced stability and activity do not cause neuropathology in mice. *iScience* June 21;26(6):109991. PMC11154205.

B. Positions, Scientific Appointments, and Honors

Positions and Employment: Clinical Fellow in Pathology, Harvard Medical School (2001-2004); Research Fellow, Department of Pathology, Brigham and Women's Hospital, Boston (2003-2008); Instructor in Pathology, Harvard Medical School (2004-2008); Assistant (2008-2015) and Associate Professor, with tenure (2015-22), Department of Pathology, University of Michigan; Research Assistant (2008-2015) and Associate (2015-22) Professor, Institute of Gerontology, University of Michigan; Associate Director (2017-2018) and Director (2018-2022), Cancer Biology Training Program, University of Michigan; Professor and Vice Chair for Clinical and Translational Research, Department of Pathology & Laboratory Medicine, University of Miami Miller School of Medicine; Co-Leader, Cancer Epigenetics Program, Sylvester Comprehensive Cancer Center (2022-); Physician and Staff Scientist, Miami VA/GRECC (2023-); Site Disease Group Physician Co-Leader/Translational Science Leader of Sarcoma for the Oncology Service Line (2023-)

Other Experience: *Ad hoc* reviewer for *Cell, Nature, Molecular Cell, Cell Metabolism, Oncogene*, *Scientific Reports,* and many other journals (2008-); *Ad hoc* member, NIH SEP ZAG1 ZIJ-5 (2009); Reviewer, The Wellcome Trust (2010); Member, editorial board, *Journal of Clinical and Experimental Pathology* (2011-2015); Review editor, *Frontiers in Genetics of Aging* (2011-); Reviewer, Israeli Science Foundation (2010, 2012, 2014, 2015); Associate editor, *CardioRenal Medicine* (2012-); *Ad hoc* member, NIH SEP EMNR K02 (2013); Reviewer, European Research Council (2013); Editorial board, *Aging Cell* (2013-); Peer review board, *Molecular and Cellular Oncology* (2014-); *Ad hoc* member, Cellular Mechanisms of Aging and Development (CMAD) study section (2014-2016); Reviewer, NSERC (2014); Reviewer, Veni, NWO division Earth and Life Sciences (2014); AG000114 T32 steering committee (AG000114) (2014-); *Ad hoc* member, NIH SEP ZAG1 ZIJ-5 (O1) (2015); Reviewer, Israeli Ministry of Science, Technology, and Space (2015); Reviewer, Swiss Cancer League (2015); Editorial board, *JBC* (2016-2024); *Ad hoc* member, NIH SEP ZRG1 CB-L(50) (2016); *Ad hoc* member, NIH SEP ZRG1 F09A Fellowships: Oncology (2016, 2017, 2018); Reviewer, St. Baldrick's Foundation (2017-); Glenn/AFAR Scholarships in the Biology of Aging Reviewer (2017); NIH/NHLBI Division of Intramural Research site visit reviewer (2017); Active Member, AACR (2017-); NIH SEP ZRG1 CB-C (02) (2017; co-Chair); Regular Member, Cellular Mechanisms of Aging and Development (CMAD) study section (2018-2024); Melanoma Research Alliance Grant Selection Committee (2/19, regular member 2/20→); DoD RCRP reviewer (2020, 2021, 2024); DoD PRCRP reviewer (2022-2024 [Chair, 2023]); DoD PRCRP ACCCT-S reviewer (2024)

Selected recent invited seminars: Grand Rounds speaker, Department of Pathology, Yale School of Medicine (12/14); Keystone Symposium "Biology of Sirtuins", Santa Fe, NM (3/15); Department of Oncological Sciences, Icahn School of Medicine at Mt. Sinai (6/15); Department of Cell Biology, Harvard Medical School (7/17); FASEB conference "Reversible Acetylation in Health and Disease", Big Sky, Montana (8/17); Hematology Faculty Conference, Huntsman Cancer Center (11/17); Biomedical Sciences Seminar Series, Cornell University (2/18); Invited seminar speaker, Department of Biology, University of Alabama (3/18); Research Center for Healthy Aging, CMU, Taiwan (12/18); Grand Rounds, Department of Pathology, University of Vermont (5/19); Gerontological Society of America Meeting (11/20); Society for Redox Biology and Medicine Meeting (11/20); University of Miami Sylvester Comprehensive Cancer Center (12/20); Vanderbilt University Department of Pathology (8/21); University of Pittsburgh Aging Institute (9/21); Clinical Translation in Epigenetics in Cancer Therapy workshop, Philadelphia, PA (5/22); FASEB conference "Reversible Acetylation in Health and Disease", Puerto Rico (8/22), Rome Italy (8/24) (conference Chair, 2026)

Honors: Harvard College: *summa cum laude*, PBK (1992); K08, NIA/NIH (2004); Hartford Center of Excellence Career Development award (2007); Scholar, Biological Sciences Scholars Program, University of Michigan (2008); Ellison Medical Foundation New Scholar in Aging (2009); American Federation for Aging Research award (2010); Elsa U. Pardee Foundation award (2010); The American Society for Clinical Investigation (2016); St. Baldrick's Foundation award (2016); Melanoma Research Alliance Team Science award (2016); Harrington Discovery Institute Scholar-Innovator award (2017); AACR-Bayer Innovation and Discovery Award (2017); DoD Melanoma Research Program Mid-Career Accelerator Award (2021)

C. Contributions to Science (*co-first; + co-corresponding)

1. Werner syndrome and other progerias: My interest in the biology of aging began in graduate school. I generated a mouse model of Werner's syndrome (WS), a premature aging-like disease in humans. Although this strain showed a mildly increased cancer predisposition in a sensitized background, overall, it lacked a strong phenotype, an effect we hypothesized might be due to the long telomeres in mice versus humans (a). This idea proved to be correct; in subsequent collaborative studies, we found that experimental telomere shortening in the WS mice we generated provoked a severe multi-system disorder closely resembling human WS (b-c). As a component of this work, together with colleagues in the Guarente lab, I analyzed the localization of the Werner's protein in cells, and found, surprisingly, that localization of this factor differed between mice and humans (d).

a. **Lombard, D.B.**, Beard, C., Johnson, B., Marciniak, R.A., Dausman, J., Bronson, R., Buhlmann, J.E., Lipman, R., Curry, R., Sharpe, A., Jaenisch, R., and Guarente, L. (2000). Mutations in the WRN gene in mice accelerate mortality in a p53-null background. *Mol Cell Biol 20*, 3286-3291. PMC8562
b. Du, X., Shen, J., Kugan, N., Furth, E.E., **Lombard, D.B.,** Cheung, C., Pak, S., Luo, G., Pignolo, R.J., Depinho, R.A., Guarente, L., and Johnson, F.B (2004). Telomere shortening exposes functions for the mouse Werner and Bloom syndrome genes. *Mol Cell Biol 24*, 8437-8446. PMC516757
c. Chang, S., Multani, A.S., Cabrera, N.G., Naylor, M.L., Laud, P., **Lombard, D.**, Pathak, S., Guarente, L., and DePinho, R.A. (2004). Essential role of limiting telomeres in the pathogenesis of Werner syndrome. *Nat Genet 36*, 877-882.
d. Marciniak, R.A.*, **Lombard, D.B.***, Johnson, F.B., and Guarente, L. (1998). Nucleolar localization of the Werner syndrome protein in human cells. *Proc Natl Acad Sci U S A 95*, 6887-6892. PMC22674.

2. SIRT3 and SIRT6 biology: As a postdoctoral fellow in Dr. Fred Alt's laboratory, I was the first to identify SIRT3 as the dominant mitochondrial deacetylase in mammals (a) in a paper >1000 times (Google Scholar). Subsequent studies have revealed that SIRT3 plays major roles in promoting healthspan by suppressing diverse age-associated pathologies. I have contributed to several of these downstream publications. We also showed that SIRT6 suppresses genomic instability (*Cell,* 2006) and tumor development in mice (b) in collaboration with Dr. Raul Mostoslavsky; and that SIRT6 targets histone H3 lysine 56 for deacetylation (c), a site known to be important for maintenance of genomic stability. With Dr. Ao-Lin Hsu, we showed that the *C. elegans* SIRT6 homolog, SIR-2.4, promotes stress resistance via the FOXO homolog DAF-16 (d).

a. **Lombard, D.B.***, Alt, F.W., Cheng, H.L., Bunkenborg, J., Streeper, R.S., Mostoslavsky, R., Kim, J., Yancopoulos, G., Valenzuela, D., Murphy, A., Yang, Y., Chen, Y., Hirschey, M.D., Bronson, R.T., Haigis, M., Guarente, L.P., Farese, R.V., Jr., Weissman, S., Verdin, E., and Schwer, B.* (2007). Mammalian Sir2 homolog SIRT3 regulates global mitochondrial lysine acetylation. *Mol Cell Biol 27*, 8807-8814. PMC2169418
b. Sebastian, C., Zwaans, B.M., Silberman, D.M., Gymrek, M., Goren, A., Zhong, L., Ram, O., Truelove, J., Guimaraes, A.R., Toiber, D., Cosentino, C., Greenson, J.K., MacDonald, A.I., McGlynn, L., Maxwell, F., Edwards, J., Giacosa, S., Guccione, E., Weissleder, R., Bernstein, B.E., Regev, A., Shiels, P.G., **Lombard, D.B.+**, and Mostoslavsky, R.+ (2012). The histone deacetylase SIRT6 is a tumor suppressor that controls cancer metabolism. *Cell 151*, 1185-1199. PMC3526953
c. Yang, B., Zwaans, B.M., Eckersdorff, M., and **Lombard, D.B.** (2009). The sirtuin SIRT6 deacetylates H3 K56Ac in vivo to promote genomic stability. *Cell Cycle 8*, 2662-2663. PMC2728171
d. Chiang, W.C.*, Tishkoff, D.X.*, Yang, B.*, Wilson-Grady, J., Yu, X., Mazer, T., Eckersdorff, M., Gygi, S.P., **Lombard, D.B.+**, and Hsu, A.L.+ (2012). C. elegans SIRT6/7 Homolog SIR-2.4 Promotes DAF-16 Relocalization and Function during Stress. *PLoS Genet 8*, e1002948. PMC3441721.

3. The deacylase SIRT5: Until recently, SIRT5 was a fairly poorly characterized sirtuin. A series of studies – several of which we contributed to – revealed that SIRT5 removes non-canonical modifications from its targets: succinyl, malonyl, and glutaryl moieties. To expand our understanding of SIRT5 biology, in collaboration with Dr. Yingming Zhao, we carried out a large-scale proteomic identification of SIRT5 targets in fibroblasts and liver tissue (a). We found that SIRT5 plays a key role in modulating mitochondrial energetics through Pyruvate Dehydrogenase and Succinate Dehydrogenase. We are actively generating small molecule SIRT5 inhibitors, in collaboration with the Kennedy and Neamati groups at Michigan (b and others). We have contributed to many other publications in the SIRT5 field (*e.g.* (c) and many others; 21 SIRT5 publications total). Although the phenotypes of SIRT5 deficiency in normal cells and tissues are relatively modest, we have recently identified a crucial requirement by melanoma cells and other specific cancer types for this sirtuin, via modulation of chromatin acetylation and methylation (d). We are pursuing roles for SIRT5 in other cancer types, specifically Ewing sarcoma and malignant peripheral nerve sheath tumor, in work supported by the DoD and NCI.

a. Park, J.*, Chen, Y.*, Tishkoff, D.X., Peng, C., Tan, M., Dai, L., Xie, Z., Zhang, Y., Zwaans, B.M., Skinner, M.E., **Lombard, D.B.+**, and Zhao, Y.+ (2013). SIRT5-mediated lysine desuccinylation impacts diverse metabolic pathways. *Mol Cell 50*, 919-930. PMC3769971
b. Giblin, W. … **Lombard, D.B.** (2021). The deacylase SIRT5 supports melanoma viability by influencing chromatin dynamics. *J Clin Invest.* June 15;131(12): 138926. PMC8203465.
c. Liu, Y., Debnath, B., Kumar, S., **Lombard, D.B.+**, and Neamati, N.+ (2022). Identification of 2-Hydroxybenzoic Acid Derivatives as Selective SIRT5 Inhibitors. *Eur J Med Chem*. Nov 5;241:114263.
d. Yuan, T.*, Kumar, S.* …de Boer, V.C.J.+, and **Lombard D.B.+**. (2024). Human SIRT5 variants with reduced stability and activity do not cause neuropathology in mice. *iScience* June 21;26(6):109991. PMC11154205.

4. Screening for small molecules targeting the aging process: Relatively recently, my group has become interested in modulating stress resistance and aging via small molecules. In this regard, I served as Deputy Site of the Interventions Testing Program at Michigan, an NIA-supported, multi-site effort to identify compounds that extend lifespan in mice (a). I led a large multi-laboratory collaborative Glenn Foundation-supported effort to identify small molecules that promote stress resistance in mammalian cells, and increased longevity in *C. elegans* and *Drosophila,* to prioritize compounds for lifespan testing in mammals. In this effort, by transcriptomic analysis we nominated Nrf2/SKN-1 signaling as a pathway meriting further study in this regard (b). I have authored many chapters and reviews in the area of aging (*e.g.* (c-d)).

a. Miller, R.A., Harrison, D.E., Allison, D.B., Bogue, M., Diaz, V. Fernandez, E., Galecki, A., Garvey, W.T., Kumar, N., Javors, M.A., Ladiges, W.C., Macchiarini, F., Nelson, J., Reifsnyder, P., Rosenthal, N.A., Salmon, A.B., Smith, D.L., Snyder, J.M, **Lombard, D.B.**, and Strong, R. (2020). Canagliflozin extends lifespan in genetically heterogeneous male but not female mice. *JCI Insight* Sep 29:140019. PMC7710304.
b. **Lombard, D.B.¶**, Kohler, W.J., Guo, A.H., Gendron, C., Han, M., Ding, W., Lyu, Y., Ching, T.-T., Wang, F.-Y., Chakraborty, T.S., Nikolovsoka-Coleska, N., Duan, Y., Girke, T., Hsu, A.-L., Pletcher, S.D., and Miller, R.A. (2020). High throughput small molecule screening reveals Nrf2-dependent and -independent pathways of cellular stress resistance. *Sci. Advances* 6(40):eaaz7628. doi: 10.1126/sciadv.aaz7628. PMC7852388 ¶ corresponding author.
c. Kumar S., **Lombard D.B**. (2016). Finding Ponce de Leon's Pill: Challenges in Screening for Anti-Aging Molecules. *F1000Res*. 2016;5. PMC4813637.
d. Kumar, S., Giblin, W. and **Lombard D.B.** (2021). Sirtuins, healthspan, and longevity in mammals. In *Handbook of the Biology of Aging*, 9th ed., Musi and Hornsby, eds. London, UK: Elsevier; pp. 77-149.

5. Melanoma: Our work in sirtuin biology has led us to studies of melanoma, where we observe that many melanoma genotypes require SIRT5 for viability via regulation of histone acetylation and methylation (a). We were fortunate enough to secure a Team Science Award from the Melanoma Research Alliance to support this work, and I now participate as a member of their Grants Review Committee. We have begun to purse other melanoma-related efforts, and I contributed to recent publications examining the consequences of germline mutations in *POT1*, a shelterin component, for melanoma in affected families (b,d). I contributed to a recent wide-ranging review of current melanoma models, published in *Cancer Cell* (c).

a. Giblin, W. ... **Lombard, D.B.** (2021). The deacylase SIRT5 supports melanoma viability by influencing chromatin dynamics. *J Clin Invest.* June 15;131(12): 138926. doi: 10.1172/JCI138926.
b. Wong, K. … **Lombard, D.B.**, and Adams, D.J. (2019). *POT1* germline missense variant p.I78T and its association with familial melanoma. *JAMA Dermatology 155*, 604-609. PMCID: PMC6506889.
c. De Boy E.A. … **Lombard D.B.** … Armanios M. (2023). Familial Clonal Hematopoiesis in a Long Telomere Syndrome. *NEJM*, doi: 10.1056/NEJMoa2300503. Epub 2023 May 4.
d. Patton E.E. … **Lombard, D.B.** … Merlino, G. (2021). Melanoma models for the next generation of therapies. *Cancer Cell 10*;39(5):610-631.

Complete List of Published Work in MyBibliography (105 total):
https://www.ncbi.nlm.nih.gov/myncbi/1zAIVMLSBH9Qt/bibliography/public/