BIOGRAPHICAL SKETCH

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NAME: Lazarus, Michael B.

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

POSITION TITLE: Associate Professor

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
Yale University (New Haven, CT)	B.S.	05/2004	Chemistry
Harvard University (Cambridge, MA)	Ph.D.	05/2010	Chemistry
University of California, San Francisco (San Francisco, CA)	Post Doc	03/2016	Chemical Biology

A. Personal Statement

The major focus of my lab is to study and target the role of nutrient signaling in disease using chemical and structural approaches. We are interested in several cellular pathways related to human disease, including inborn errors of metabolism, and cancer and neurodegenerative diseases. One major area is the lysine metabolism pathway, which plays an important role in diseases like Glutaric Aciduria Type 1 (GA1). My lab solved the first crystal structure of two of the proteins in the pathway, DHTKD1 and AASS (LOR domain). We are now interested in understanding allosteric regulation of AASS, including the full-length protein, by using Cryo-EM to visualize conformational changes upon allosteric activation and inhibition. This will allow us to better design allosteric modulators that can remedy the pathogenic accumulation of metabolic intermediates in GA1 patients. The other major area is proteostasis and specifically degradation of proteins. We are trying to understand the role of ubiquitin ligase complexes for degradation of endogenous proteins and for pharmacological degradation induced by PROTACS molecules. For this area, we are interested in studying the the DDB1-DCAF complexes that can regulate CUL4 mediated degradation. Cryo-EM is the only way we can study these large protein complexes, including with crosslinked substrates bound. For this proposal, we are interested in obtaining structural information of DDB1-DCAF complexes along with molecular glues that take advantage of these complexes to bind their targets. This will enable better understanding of how to design PROTACs drugs that can degrade protein targets.

I have not published or created research products under another name.

Ongoing and recently completed projects that I would like to highlight include:

R35GM124838 (PI: Lazarus)
09/18/17-08/31/27
Chemical and structural tools to study energy homeostasis pathways in cancer and diabetes

R01HD112518 (PI: Houten (contact), DeVita, Lazarus)

9/26/23-8/31/28
Allosteric regulation of lysine degradation as a novel pathophysiological mechanism in glutaric aciduria type 1

Hirschl Career Scientist Award (PI: Lazarus)
01/1/20-12/31/2024
Irma T. Hirschl Weill Trust
Targeting Autophagy in Alzheimer's Disease

Sinsheimer Scholar Award (PI: Lazarus)
7/1/2020-6/30/22
Sinsheimer Foundation
Targeting Autophagy as a Therapeutic Strategy for Alzheimer's Disease

Citations I would like to highlight:

1. Khamrui S, Ung PMU, Secor C, Schlessinger A, Lazarus MB. High-Resolution Structure and Inhibition of the Schizophrenia-Linked Pseudokinase ULK4. J Am Chem Soc. 2020 Jan 8;142(1):33-37. PMCID: PMC7261596.
2. Lazarus MB*, Novotny CJ, Shokat KM*. Structure of the Human Autophagy Initiating Kinase ULK1 in Complex with Potent Inhibitors. *ACS Chem Biol*. 2015;10(1):257-61. PMCID: 4301081.
3. Sung K, Kurowski A, Lansiquot C, Wan KK, Patnaik S, Walsh MJ, Lazarus MB. Selective Inhibitors of Autophagy Reveal New Link between the Cell Cycle and Autophagy and Lead to Discovery of Novel Synergistic Drug Combinations. ACS Chem Biol. 2022 Dec 5. doi: 10.1021/acschembio.2c00710. Epub ahead of print. PMID: 36469692.
4. Leandro J, Khamrui S, Suebsuwong C, Chen PJ, Secor C, Dodatko T, Yu C, Sanchez R, DeVita RJ, Houten SM*, Lazarus MB*. Characterization and structure of the human lysine-2-oxoglutarate reductase domain, a novel therapeutic target for treatment of glutaric aciduria type 1. Open Biol. 2022 Sep;12(9):220179. doi: 10.1098/rsob.220179. Epub 2022 Sep 21. PMID: 36128717; PMCID: PMC9490328.

B. Positions, Scientific Appointments, and Honors

2023-present	Co-Director, PhD Training area in Pharmacology and Therapeutics Discovery (PTD), ISMMS, New York, NY
2023-present	Associate Professor, Department of Pharmacological Sciences, Icahn School of Medicine at Mount Sinai, New York, NY
2016-2022	Assistant Professor, Department of Pharmacological Sciences, Icahn School of Medicine at Mount Sinai, New York, NY
2012-16	Postdoctoral Researcher, University of California, San Francisco. Advisor: Kevan Shokat
2004-12	Graduate Student and Postdoctoral Researcher, Harvard University, Department of Chemistry and Chemical Biology. Advisors: Suzanne Walker and Daniel Kahne.

Honors

2021 - 2022	Sinsheimer Scholar Award
2021	REC ADRC fellow at Mount Sinai
2020 - 2024	Irma T. Hirschl Career Scientist Award
2018 - present	Member, Tisch Cancer Institute, NCI designated Cancer Center (P30CA196521)
2017 - present	NIH R35 MIRA award for Early Stage Investigators
2016 - 2019	Mallinckrodt Foundation Grant Award
2016 - 2017	NCI K22 Transition Career Award
2013 - 2016	Helen Hay Whitney Foundation Postdoctoral Fellowship
2012	A.P. Giannini Fellowship Finalist (declined)
2012	Bowes Research Fellowship Finalist (declined)
2005	Certificate of Distinction in Teaching awarded

2004 B.S. in Chemistry awarded cum laude with distinction in major, Yale University

Service

2022-2023 Institutional representative for diversity from Pharmacological Sciences department.
2022 Reviewer for NIH Special Emphasis Panel: 2023/01 ZCA1 RPRB-H (J2) S
2016-present Reviewer for scientific journals including: Nature Chemical Biology, Journal of the American Chemical Society, ACS Chemical Biology, Proceedings of the National Academy of Sciences, Chemical Science, eLife
2016-2022 Department of Pharmacological Sciences Seminar co-organizer and Equipment Committee leader.

C. Contributions to Science

1. We have worked on the enzyme O-GlcNAc transferase, the sole mammalian intracellular glycosyltransferase that is responsible for modifying over 1,000 proteins and couples nutrient status to signaling and transcriptional outputs, beginning with my graduate studies and continuing up to this R35 award. Not much was known about the mechanism of the enzyme, how it recognizes substrates, and how it recognizes the sugar. Because of the importance of the enzyme in so many cellular processes, there was great interest in understanding its structure and function. I was able to solve the first crystal structure of the enzyme, by using a truncated version that had full activity and by obtaining experimental phasing. I also solved the structure of OGT bound to a peptide substrate, which revealed conformational changes required to recognize substrates. Using the structures as a guide, I helped hypothesize and prove the kinetic mechanism of the protein. Finally, I was able to obtain structures along the entire kinetic pathway, with ternary substrate and product complexes, the first for any glycosyltransferase.

    a. Lazarus MB, Nam Y, Jiang J, Sliz P, Walker S. Structure of human O-GlcNAc transferase and its complex with a peptide substrate. *Nature*. 2011;469(7331):564-7. PMCID: 3064491
    b. Lazarus MB, Jiang J, Gloster TM, Zandberg WF, Whitworth GE, Vocadlo DJ, Walker, S. Structural snapshots of the reaction coordinate for O-GlcNAc transferase. *Nat Chem Biol*. 2012;8(12):966-8. PMCID: 3508357.
    c. Lazarus MB, Jiang J, Kapuria V, Bhuiyan T, Janetzko J, Zandberg WF, Vocadlo DJ, Herr W, Walker S. HCF-1 is cleaved in the active site of O-GlcNAc transferase. *Science*. 2013;342(6163):1235-9. PMCID: 3930058.
    d. Martin SES, Tan ZW, Itkonen HM, Duveau DY, Paulo JA, Janetzko J, Boutz PL, Törk L, Moss FA, Thomas CJ, Gygi SP, Lazarus MB*, Walker S*. Structure-Based Evolution of Low Nanomolar O-GlcNAc Transferase Inhibitors. *J Am Chem Soc*. 2018 Oct 4. doi: 10.1021/jacs.8b07328. PMCID: PMC6261342

2. Our lab is focused on the family of autophagy initiating kinases, the ULK proteins. I initially focused on the kinase ULK1, which is the first enzyme in the pathway and the prime druggable target. There is tremendous interest in autophagy as a fundamentally important pathway and as a novel therapeutic target in cancer. It has been found that many cancers, including particularly pernicious ones, such as KRAS driven pancreatic cancer, rely on autophagy for growth and survival. Moreover, it has also been shown that tumors often use autophagy to resist treatment, from radiation to cytotoxic chemotherapy to targeted therapy. I am interested in evaluating ULK1 as a therapeutic target in cancer. I developed the first bacterial expression system for ULK1, which is now requested by autophagy groups around the world. I then developed the first inhibitors for ULK1 and solved the first crystal structure of the enzyme. Using the structure, I was able to develop selective inhibitors that block autophagy in pancreatic cancer cells and impede growth. We have received recognition for our work on this family of enzymes, including the Helen Hay Whitney Postdoctoral Fellowship, K22 NCI Career Transition Award, and the Mallinckrodt Foundation Grant Award. In my lab now we are focusing on the role of ULK1 in Alzheimer's Disease, and on other ULK family of proteins as novel drug targets. We recently solved the first structure of ULK4, which is linked to schizophrenia, and have published that work. Our lab is a leader in ULK family structural biology and pharmacology.

a. Lazarus MB*, Novotny CJ, Shokat KM*. Structure of the Human Autophagy Initiating Kinase ULK1 in Complex with Potent Inhibitors. *ACS Chem Biol*. 2015;10(1):257-61. PMCID: 4301081.
b. Lazarus MB, Shokat KM. Discovery and structure of a selective inhibitor scaffold of the autophagy initiating kinase ULK1. *Bioorg Med Chem*. 2015;23(17):5483-8. PMCID: PMC4864979.
c. Khamrui S, Ung PMU, Secor C, Schlessinger A, Lazarus MB. High-Resolution Structure and Inhibition of the Schizophrenia-Linked Pseudokinase ULK4. J Am Chem Soc. 2020 Jan 8;142(1):33-37. PMCID: PMC7261596.
d. Sung K, Kurowski A, Lansiquot C, Wan KK, Patnaik S, Walsh MJ, Lazarus MB. Selective Inhibitors of Autophagy Reveal New Link between the Cell Cycle and Autophagy and Lead to Discovery of Novel Synergistic Drug Combinations. ACS Chem Biol. 2022 Dec 5. doi: 10.1021/acschembio.2c00710. Epub ahead of print. PMID: 36469692.

3. My lab at Mount Sinai has made major contributions in collaborative structural projects, focusing on enzyme mechanisms and structure-based drug design related to nutrient sensing and metabolism. In collaboration with the Houten and DeVita labs here, we have solved a number of structures of exciting drug targets, including the first structure of DHTKD1 and novel structures of DYRK1A in complex with inhibitors.

   a. Leandro J, Khamrui S, Suebsuwong C, Chen P-J, Secor C, Dodatko T, Yu C, Sanchez R, DeVita RJ, Houten SM*, Lazarus MB* (2022) Characterization and structure of the human lysine-2-oxoglutarate reductase domain, a novel therapeutic target for treatment of glutaric aciduria type 1. Open Biol 12(9):220179. PMCID: PMC9490328
   b. Leandro J, Khamrui S, Wang H, Suebsuwong C, Nemeria NS, Huynh K, Moustakim M, Secor C, Wang M, Dodatko T, Stauffer B, Wilson CG, Yu C, Arkin MR, Jordan F, Sanchez R, DeVita RJ, Lazarus MB*, Houten SM* (2020) Inhibition and Crystal Structure of the Human DHTKD1-Thiamin Diphosphate Complex. ACS Chem Biol. 2020 Aug 21;15(8):2041-2047. doi:10.1021/acschembio.0c00114. Epub 2020 Jul 9. PMCID: PMC7890914.
   c. Kumar K, Wang P, Swartz EA, Khamrui S, Secor C, Lazarus MB, Sanchez R, Stewart AF, DeVita RJ. Structure–Activity Relationships and Biological Evaluation of 7-Substituted Harmine Analogs for Human β-Cell Proliferation. *Molecules*. 2020;25 (8). PMCID: PMC7221803.
   d. Kumar K, Wang P, Wilson J, Zlatanic V, Berrouet C, Khamrui S, Secor C, Swartz E, Lazarus MB, Sanchez R, Stewart AF, Garcia-Ocana A, DeVita RJ. Synthesis and Biological Validation of a Harmine-based, Central Nervous System (CNS)-Avoidant, Selective, Human β-Cell Regenerative Dual-Specificity Tyrosine Phosphorylation-Regulated Kinase A (DYRK1A) Inhibitor. *J Med Chem*. 2020, 63(6), 2986-3003. PMCID: PMC7388697.

*Co-corresponding author

Complete List of Published Work in MyBibliography:
https://www.ncbi.nlm.nih.gov/myncbi/1Fa-ffNfdc0AO/bibliography/public/