BIOGRAPHICAL SKETCH

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NAME: Lazarus, Michael B.

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

POSITION TITLE: Assistant 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 metabolism and proteostasis in disease using chemical and structural approaches. One major area of research is the autophagy pathway, a conserved process by which cellular components from proteins to organelles are recycled in large membrane vesicles. Autophagy is thought to play a major role in neuronal health, including minimizing protein aggregation and normal brian development. My training in chemical and structural biology and pharmacology enables me to be uniquely positioned to target this pathway. I have developed the first inhibitors of ULK1 and solved the first crystal structure of the ULK1 kinase. I then developed improved inhibitors that show selectivity and efficacy in cells in blocking autophagy. Recently, ULK4 was found to be genetically linked to schizophrenia, bipolar disorder, and depression, but its function is completely unknown, including the role of the ATP-binding pocket in the pseudokinase domain. I solved the first crystal structure of ULK4 as well and published the first inhibitors of that pseudokinase. All of our work on kinases has been aided by high resolution x-ray structures of the kinases in complex with different inhibitors.

In this project, we are interested in learning about larger protein complexes, for which cryo-EM is more amenable than x-ray crystallography. For one of them, an enzyme involved in lysine metabolism, AASS is a major target of our drug discovery team for treating glutaric aciduria type I (GA1). We are interested in understanding the enzyme at a structural level, which is thought to exist as a tetramer. This is important because it is a bifunctional enzyme and it is unknown how the domains communicate. For the other project, we are interested in proteostasis and how ubiquitinating enzymes recognize their substrates and can be targeted by PROTACS small molecules. We have obtained complexes of E3 ligase complexes with different associated factors and molecular glues and are trying to gain insight into how they assemble. For some of them, there are not even crystal structures of the associated factors, so the Cryo-EM structures will be enormously valuable for understanding how they assemble. My role is the PI on these experiments and to lead the cryo-EM work on these projects and supervise the biochemical and structural studies in my lab. We are excited to be able to collect additional data on these complexes using the resources at NCCAT at the NYSBC.

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)
09/18/17-08/31/22
Chemical and structural tools to study energy homeostasis pathways in cancer and diabetes

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

R01CA251425 (PI: Pan) Role: Co-I
7/1/2020-6/30/2025
Modulate Cullin-RING E3 ubiquitin ligases by small molecule agents

R03 AG072020 (PI: Lazarus)
4/1/2021-3/31/2023
Exploring autophagy as a target for Alzheimer's Disease.

Edward Mallinckrodt Jr. Foundation (PI: Lazarus)
10/1/16 - 9/30/19
Targeting autophagy in pancreatic cancer

Citations:

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. 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.
3. 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.
4. 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. Positions, Scientific Appointments, and Honors

Positions and Employment

2016-present	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

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. Lazarus MB, Levin RS, Shokat KM. Discovery of new substrates of the elongation factor-2 kinase suggests a broader role in the cellular nutrient response. *Cellular Signaling*. 2016 Oct 17;29:78-83. PMCID: PMC5138099.
d. 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.

3. My lab at Mount Sinai has made major contributions in collaborative structural projects, focusing on enzyme mechanisms and structure-based drug design. 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, 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.
b. Zhang X, Nemeria NS, Leandro J, Houten S, Lazarus MB, Gerfen GJ, Ozohanics O, Ambrus A, Nagy B, Brukh R, Jordan F. Structure-function analyses of the G729R 2-oxoadipate dehydrogenase genetic variant associated with L-lysine metabolism disorder. *Journal of Biological Chemistry*. Online April, 2020. PMCID: PMC7278340.
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/