## BIOGRAPHICAL SKETCH

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NAME: Kory, Nora

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

POSITION TITLE: Assistant Professor of Molecular Metabolism

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 |
|---|---|---|---|
| Ludwig-Maximilians University, Munich, Germany | B.S | 10/2008 | Chemistry & Biochemistry |
| Ludwig-Maximilians University, Munich, Germany | M.S | 08/2010 | Biochemistry |
| Yale University, New Haven, CT | Ph.D | 12/2015 | Cell Biology |
| Whitehead Institute for Biomedical Research, Cambridge, MA | Postdoctoral | 09/2020 | Biochemistry, Cell Biology |

### A. Personal Statement

My longstanding research goal is to understand how metabolic processes are organized spatially and the roles that organelles, such as mitochondria, play in compartmentalizing and regulating metabolism. I am pursuing this research in my lab in the Department of Molecular Metabolism at the Harvard T.H. Chan School of Public Health. I am particularly interested in how compartmentalization supports metabolic homeostasis in normal physiology and aging-related diseases. This interest began during my PhD with Dr. Tobias Walther at Yale University, where I identified mechanisms that determine the protein composition of lipid droplets, contributed to defining the lipid droplet proteome of several model organisms, and used these discoveries to understand the molecular mechanisms underlying diseases characterized by aberrant lipid metabolism. In my postdoctoral research as a Damon Runyon Cancer Research Foundation fellow and NCI K99/R00 recipient in Dr. David Sabatini's laboratory at the Whitehead Institute/MIT, I combined CRISPR screens with compartment-specific metabolite profiling to identify SFXN1 as a mitochondrial serine transporter and SLC25A51 as a mitochondrial NAD transporter, both of which are key factors in mitochondrial metabolism and cell proliferation. These findings, particularly the discovery of sideroflexins as an evolutionarily distinct family of mitochondrial transporters, led us to investigate how amino acids and other metabolites critical to cellular homeostasis are distributed between cellular compartments, as well as to understand the missing components of the one-carbon metabolic pathway and its function in supplying metabolic precursors for cell proliferation and epigenetic regulation.

Another major research area in my laboratory is understanding how mitochondria precisely take up and maintain appropriate levels of redox cofactors, such as NAD, and what role mitochondrial cofactor and intracellular metabolite pools play in supporting metabolic regulation, cellular function, and proliferation. This research is part of our larger efforts to determine how cells and organisms establish and maintain chemically and biophysically distinct compartments while efficiently exchanging metabolites between these metabolically connected organelles. Additionally, we aim to understand how these mechanisms can be harnessed to prevent or treat aging-related diseases, including diabetes and cancer. We are employing diverse approaches spanning functional genomics, in vitro biochemistry, metabolomics, cell biological tools, systems analyses of organelles, and mouse physiology to illuminate metabolic compartmentalization and the functions and regulation of

organellar transporters across biological scales. Most recently, we have been developing a direct biochemical screening method to de-orphan transporters.

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

DFS 73-22 Kory (PI) 01/2022–12/2025
Targeting mitochondrial transporters in cancer
The goal of this project is to determine mechanisms of one-carbon unit exchange between the cytosol and mitochondria, and elucidate mitochondrial oxidative stress sensing pathways in cancer.

R35 (MIRA) GM151097 Kory (PI) 07/2023–06/2028
NIH/NIGMS
Dissecting Metabolic Control by Cytosolic-Mitochondrial NAD Compartmentalization
The goal of this project is to determine how cells regulate their mitochondrial $NAD^+$ pool and cellular NAD+ compartmentalization to control metabolism and signaling.

Citations I would like to highlight include:

Tan, S., Dengler, A.S., Darawsheh, R.Z., **Kory, N.** (2024), The iAAA-mitochondrial protease YME1L1 regulates the degradation of the short-lived mitochondrial transporter SLC25A38. *bioRxiv* doi: 10.1101/2024.05.12.593764.

**Kory, N**., uit de Bos, J., van der Rijt, S., Jankovic, N., Guera, M., Arp, N., Pena, I.A., Prakash, G., Chan, S.H., Kunchok, T., Lewis, C.A., Sabatini, D.M. (2020), MCART1/SLC25A51 is required for mitochondrial NAD transport. *Science Advances, 6 (43)* eabe5310. PMCID: PMC7577609.

**Kory, N.**, Wyant, G.A., Prakash, G., uit de Bos, J., Bottanelli, F., Pacold, M.E., Chan, S.H., Lewis, C.A., Wang, T., Keys, H.R., Guo, Y.E., Sabatini D.M. (2018). SFXN1 is a mitochondrial serine transporter required for one-carbon metabolism. *Science*, 362 (6416) eaat9528. PMCID: PMC6300058.

Bar-Peled, L.* and **Kory, N.***, Principles and functions of metabolic compartmentalization. *Nat Metab* 2022 Oct 20; 4:1232-1244. PMCID: PMC10155461.

**B. Positions, Scientific Appointments, and Honors**

**Positions**

2024-present Affiliated Member, Broad Institute of MIT and Harvard
2021-present Member Cancer Cell Biology, Dana Farber/Harvard Cancer Center
2020-present Assistant Professor of Molecular Metabolism, Harvard T.H. Chan School of Public Health, Boston, MA

**Scientific Appointments and Committee Service**

2024-present Postdoctoral Association Travel Awards, *Reviewer*
2022-present Biological Sciences in Public Health Summer Internship Program Admissions, *Member*
2020-present Biological Sciences in Public Health Admissions, *Committee Member*
2020-2022 Equity, Diversity, Inclusion & Belonging Committee, *Department Liaison*

**Honors**

2024 Smith Family Awards Program for Excellence in Biomedical Research
2023 NIGMS R35 Maximizing Investigators' Research Award
2021 Damon Runyon Cancer Research Foundation Dale F. Frey Award for Breakthrough Scientists
2019 STAT Wunderkind next generation scientific leader
2019 NCI/NIH K99/R00 Pathway to Independence Award
2019 Organizer's scholarship to attend the GRC on Mitochondria in Health and Disease

| | |
|---|---|
| 2019 | Keystone Symposia Future of Science Fund scholarship for Tumor Metabolism meeting |
| 2018 | Invited speaker at the Young Scholars Symposium, Cold Spring Harbor Laboratories |
| 2018 | Invited speaker at the Rising Star Symposium, University of Utah |
| 2017 | Damon Runyon Cancer Research Foundation HHMI Postdoctoral Fellowship |
| 2017 | American Heart Association Postdoctoral Fellowship, declined |
| 2017 | American Diabetes Association Postdoctoral Fellowship, declined |
| 2013-2014 | American Heart Association Predoctoral Fellowship |
| 2010 | Graduated ranked as No. 1 in class, Ludwig-Maximilians University, Munich, Germany |
| 2010 | Fellow, German Academic Exchange Service (DAAD) |
| 2009-2010 | Bayer Fellowship, Bayer Research and Education Foundation |
| 2008 | Dean's Award, Dept. of Chemistry and Pharmacy, Ludwig-Maximilians University, Munich |
| 2007-2010 | Max Weber Fellow in the German National Academic Foundation (Studienstiftung) |
| 2005 | Fellow, Dr. Bessie F. Lawrence International Summer Science Institute, Weizmann Institute |

## C. Contributions to Science

### 1. Discovery of key mechanisms determining the protein composition of lipid droplets.

Energy supply and demand fluctuate in living organisms. To ensure an adequate energy supply and survival at all times, organisms have developed mechanisms to store metabolic energy. Fat, particularly triglyceride, is the most efficient and common form of stored metabolic energy. It is stored in cytoplasmic organelles called lipid droplets. Despite their discovery more than a century ago, the functions of lipid droplets as cellular lipid storage organelles are still poorly understood, and many basic questions remain unanswered. One such question is how protein targeting to lipid droplets is regulated and what mechanisms determine the lipid droplet protein composition. To address these questions in my PhD research, I studied the targeting behavior of lipid droplet proteins during lipolysis, a process in which lipid droplets shrink dramatically. I discovered that peripheral lipid droplet enzymes are removed due to a macromolecular crowding mechanism.[a] Following up on these findings, I showed that large, hydrophobic residues are necessary and sufficient for lipid droplet targeting of CCTα, likely by interacting with packing defects on the lipid droplet surface.[b] Thus, my studies were the first to describe a basic and general mechanism determining lipid droplet protein composition. Lipid droplet protein composition varies between cell types and metabolic states. Defining organelle protein composition is challenging due to the close interactions between organelles and potential purification artifacts. I contributed to the systematic characterization of lipid droplet proteomes with high confidence in different systems by applying mass spectrometry-based protein correlation profiling.[c,d] Our studies have set a standard for future lipid droplet proteomics studies and laid the foundation for my research and that of others investigating lipid droplet protein targeting, defining lipid droplets as organelles. We identified proteins previously unknown to reside on lipid droplets, such as N-glycan biosynthesis enzymes and uncharacterized lipases, implicating lipid droplets in unexpected metabolic pathways.

a. **Kory, N.**, Thiam, A.R., Farese, R.V. Jr. and Walther, T.C. (2015). Protein crowding is a determinant of lipid droplet protein composition. *Dev. Cell*, 34(3):351-63. PMCID: PMC4536137.
b. Prévost, C., Sharp, M.E., **Kory, N.**, Lin, Q., Voth, G.A., Farese, R.V. Jr., Walther, T.C. (2018). Mechanism and determinants of amphipathic helix-containing protein targeting to lipid droplets. *Dev Cell.* 44(1):73-86.e4. PMCID: PMC5764114.
c. Krahmer, N., Hilger, M., **Kory, N.**, Wilfling, F., Stoehr, G., Mann, M., Farese, R.V. Jr., Walther, T.C. (2013). Protein correlation profiles identify lipid droplet proteins with high confidence. *Mol Cell Proteomics*, 12(5):1115-26. PMCID: PMC3650325.
d. Currie, E., Guo, X., Christiano, R., Chitraju, C., **Kory, N.**, Harrison, K., Haas, J., Walther, T.C., Farese, R.V. Jr. (2014). High confidence proteomic analysis of yeast LDs identifies additional droplet proteins and reveals connections to dolichol synthesis and sterol acetylation. *J Lipid Res*, 55(7):1465-1477. PMCID: PMC4076087.

### 2. Determining how aberrations in lipid metabolism lead to disease.

Many proteins targeting the surface of lipid droplets are metabolic enzymes associated with human disorders, such as lipodystrophies and neurodegenerative diseases, making it essential to elucidate their molecular functions to understand underlying disease mechanisms. Following up on my discoveries from proteomic profiling of lipid droplets in my PhD, I characterized a highly conserved cancer-associated lipase using a

knockout mouse model.[a] Building on my mechanistic studies of lipid droplet protein targeting, I found, in collaboration with clinicians, that altered lipid droplet binding likely explains the mechanisms behind lipodystrophy-causing mutations in the lipid droplet protein CCTα.[b] Together with Helen Hobbs' group at UT Southwestern, I uncovered how altered lipid droplet targeting can lead to aberrant lipid accumulation in the liver.[c] I also provided critical expertise in a study identifying *APOE4*-induced altered lipid homeostasis as a mechanism potentially contributing to the development of Alzheimer's disease.[d]

a. **Kory, N.**, Grond, S., Kamat, S.S., Li, Z., Krahmer, N., Chitraju, C., Zhou, P., Fröhlich, F., Semova, I., Ejsing, C., Zechner, R., Cravatt, B.F., Farese, R.V. Jr., Walther, T.C. (2017). Mice lacking lipid droplet-associated hydrolase, a gene linked to human prostate cancer, have normal cholesterol ester metabolism. *J Lipid Res*, 58(1):226-235. PMCID: PMC5234725
b. Payne, F., Lim, K., Girousse, A., Brown, R.J, **Kory, N.,** et al. (2014). Mutations disrupting the Kennedy phosphatidylcholine pathway in humans with congenital lipodystrophy and fatty liver disease. *Proc Natl Acad Sci USA* 111(24): 8901-6. PMCID: PMC4066527.
c. Wang, Y., **Kory, N.**, BasuRay, S., Cohen, J.C., Hobbs, H.H. (2019) PNPLA3, CGI-58, and inhibition of hepatic triglyceride hydrolysis in mice. *Hepatology* 69(6): 2427-2441. PMCID: PMC6563103.
d. Sienski, G., Narayan, P., Bonner, J.M., **Kory, N.**, Boland, S., Arczewska, A.A., Ralvenius, W.T., Akay, L., Lockshin, E., He, L., Milo, B., Graziosi, A., Baru, V., Lewis, C.A., Kellis, M., Sabatini, D.M., Tsai, L.H., Lindquist, S. (2021). *APOE4* disrupts intracellular lipid homeostasis in human iPSC-derived glia. *Sci Transl Med.* 13(583). PMCID: PMC8218593.

**3. Identification of central mitochondrial transporters and their roles in cellular metabolism.**

Cells rely on metabolic pathways and mitochondrial function to fuel their growth, proliferation, and complex biology. These pathways are often dysregulated in significant human diseases and represent pharmacologically targetable nodes. During my postdoctoral studies, I focused on identifying unknown mitochondrial transporters in the metabolic pathways central to cell proliferation and growth, which could serve as potential chemotherapeutic targets. Using CRISPR/Cas9-based genetic screens, I identified and characterized SFXN1 as a mitochondrial serine transporter required for one-carbon metabolism.[a] My finding resolved a long-standing question in metabolism research and provides a potential molecular target to specifically inhibit the mitochondrial branch of one-carbon metabolism, whose enzymes are among the most differentially expressed metabolic genes between normal and tumor tissues. In studies building on functional genomics gene essentiality data, I identified SLC25A51/MCART1 as the previously unknown mammalian mitochondrial transporter for nicotinamide adenine dinucleotide (NAD), an enzymatic cofactor in many cellular and mitochondrial redox reactions and a regulator of metabolic flux.[b] More recently, my lab has identified a proteolytic regulatory mechanism controlling the abundance of a mitochondrial transporter involved in heme synthesis and erythropoiesis.[c] Besides my studies on mitochondrial transport, I have contributed to characterizing the metabolic vulnerabilities of tumors.[d]

a. **Kory, N.**, Wyant, G.A., Prakash, G., uit de Bos, J., Bottanelli, F., Pacold, M.E., Chan, S.H., Lewis, C.A., Wang, T., Keys, H.R., Guo, Y.E., Sabatini D.M. (2018). SFXN1 is a mitochondrial serine transporter required for one-carbon metabolism. *Science*, 362 (6416) eaat9528. PMCID: PMC6300058.
b. **Kory, N**., uit de Bos, J., van der Rijt, S., Jankovic, N., Guera, M., Arp, N., Pena, I.A., Prakash, G., Chan, S.H., Kunchok, T., Lewis, C.A., Sabatini, D.M. (2020), MCART1/SLC25A51 is required for mitochondrial NAD transport. *Science Advances, 6 (43)* eabe5310. PMCID: PMC7577609.
c. Tan, S., Dengler, A.S., Darawsheh, R.Z., **Kory, N.** (2024), The iAAA-mitochondrial protease YME1L1 regulates the degradation of the short-lived mitochondrial transporter SLC25A38. *bioRxiv* doi: 10.1101/2024.05.12.593764.
d. Ilic, N., Birsoy, K., Aguirre, A.J., **Kory, N.**, Pacold, M.E., Singh, S., Moody, S.E., DeAngelo, J.D., Spardy, N.A., Freinkman, E., Weir, B.A., Tsherniak, A., Cowley, G.S., Root, D.E., Asara, J.M., Vazquez, F., Widlund, H.R., Sabatini, D.M., Hahn, W.C. (2017). PIK3CA mutant tumors depend on oxoglutarate dehydrogenase. *Proc Natl Acad Sci U S A*, 114(17):E3434-E3443. PMCID: PMC5410781.

**Complete List of Published Work:**
https://www.ncbi.nlm.nih.gov/myncbi/nora.kory.2/bibliography/public/?sortby=pubDate&sdirection=descending