BIOGRAPHICAL SKETCH

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NAME: **Prashant Mishra, M.D., Ph.D.**

POSITION TITLE: **Assistant Professor, Children's Medical Center Research Institute (CRI), University of Texas Southwestern Medical Center**

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 University, Cambridge, MA	A.B.	06/1999	Biochemical Sciences
University of Texas Southwestern Medical Center, Dallas, TX	Ph.D.	08/2007	Biophysics
University of Texas Southwestern Medical Center, Dallas, TX	M.D.	06/2009	Medicine
California Institute of Technology, Pasadena, CA	Postdoctoral Training	10/2015	Biology

A. Personal Statement

I am a research scientist with a lab focused on the basic biology of mitochondria. Our goal is to understand the relationship between mitochondrial behavior and metabolic homeostasis, with a particular emphasis on the implications for mitochondrial dysfunction and disease. Coupled with this, we are assessing how mitochondrial functions are altered in mouse models of mitochondrial disease, which we hope will generate ideas for developing novel tools and treatment options. My post-doctoral training focused on the interface between mitochondrial behavior and metabolism, with an emphasis on the compartmentalization of dysfunctional organelles in mitochondrial myopathies. During this time, I developed tools to image and follow mitochondrial function in myofibers, and my lab is now expanding to mouse models of mitochondrial disease, and mitochondrial function in cancers. Our long term goal is to uncover novel aspects of mitochondrial biology in the disease setting and use these discoveries to engineer new therapeutic options. My lab collaborates extensively with Dr. Ralph DeBerardinis (UT Southwestern, a leader in cancer metabolism), Dr. Ronald Haller (UT Southwestern, a leader in the skeletal muscle physiology), Dr. Sean Morrison (UT Southwestern, leader in stem cell biology and cancer), and Dr. Hao Zhu (UT Southwestern, leader in hepatocellular carcinoma and liver disease).

B. Positions and Honors

Positions and Employment

1996 – 1996 Research Assistant, Department of Molecular Modeling, Biogen, Inc.
1997 – 1998 Undergraduate Research Assistant, Department of Genetics, Harvard University, in the laboratory of Alan Michelson, M.D., Ph.D.
1999 – 2000 Research Assistant I, Department of Protein Chemistry, Transkaryotic Therapies, Inc.
2002 – 2009 Graduate student, Biophysics Graduate Program, University of Texas Southwestern Medical Center, in the laboratory of Rama Ranganathan, M.D., Ph.D.
2009 – 2015 Postdoctoral Scholar, Division of Biology, California Institute of Technology, in the laboratory of David C. Chan, M.D., Ph.D.

2010 – 2013 Postdoctoral Fellowship, Jane Coffin Childs Memorial Fund for Medical Research
2015 – present Assistant Professor, Children's Medical Center Research Institute (CRI), University of Texas Southwestern Medical Center

Honors

1999 Harvard University Graduation with honors, A.B., Magna Cum Laude
2004 "Best Talk" award at the 2004 UT Southwestern Molecular Biophysics Retreat
2004 "Best Abstract" award at the 2004 UT Southwestern Sigma Xi Research Forum
2007 "Best Talk" award at the 2007 UT Southwestern Molecular Biophysics Retreat
2007 Annual Alfred Gilman Award from the Department of Pharmacology, UT Southwestern
2017 Chairman's Award, United Mitochondrial Disease Foundation

C. Contribution to Science

1. Metabolic flexibility in the setting of mitochondrial dysfunction: The mitochondrion integrates key biochemical pathways regulating nutrient utilization. In the presence of organellar dysfunction (for instance, mutations in the mitochondrial genome), metabolic reprogramming allows cells to adapt and maintain viability. Recently, my lab has elucidated a module of solute carrier family members which regulates metabolic reprogramming in the setting of pathogenic mitochondrial DNA mutations in patient-derived cell lines. This module targets amino acid metabolism, but co-regulates glucose utilization via the production of the metabolic intermediate alpha-ketobutyrate. Using heavy isotope tracing, we have now turned to investigating metabolic flexibility in animal models of mitochondrial dysfunction, including myopathies and hepatopathies.
   a. Shin CS, Mishra P, Watrous JD, Carelli V, D'Aurelio M, Jain M, Chan DC. "The glutamate/cystine xCT antiporter antagonizes glutamine metabolism and reduces nutrient flexibility." *Nature Communications*, 8:14074, 2017. PMID: 28429737 PMCID: PMC5413954
   b. Onder Y, Laothamatas I, Berto S, Sewart K, Kilaru G, Bordieanu B, Stubblefield JJ, Konopka G, Mishra P*, Green CB*. "The Circadian Protein Nocturnin Regulates Metabolic Adaptation in Brown Adipose Tissue." *iScience*, 19:83, 2019. PMID: 31357170.
      *, co-corresponding author.
   c. Lesner NP, Gokhale A., Kota K, Carelli V, DeBerardinis RJ, Mishra P. "Altered amino acid metabolism regulates residual respiratory activity in mtDNA mutant cells." *in revision, Metabolic Engineering.*

2. Metabolic regulation of mitochondrial fusion and function in skeletal muscle: As a post-doctoral fellow in David Chan's laboratory, I examined regulatory mechanisms of mitochondrial behavior, specifically mitochondrial fusion. We developed an in vitro fusion assay using purified organelles, and discovered that the fusion event could be directly regulated via the metabolic activity of the mitochondrion. Through a series of mechanistic studies, we found that proteolytic cleavage of Opa1 was activating for inner membrane fusion, and the proteases themselves were under metabolic control. This regulatory mechanism was disturbed in cells from patients with mitochondrial DNA mutations, and regulated compartmentalization of mitochondrial defects in skeletal muscle. To study the basis for the compartmentalization, I developed a stochastic lineage-tracing method to follow mitochondrial proteins originating from a singly myonucleus *in vivo*. With this tool, we found that mitochondrial compartmentalization was developmentally regulated and partially controlled by local organelle fusion and fission rates. This lead us to propose a model by which the organism can prevent spreading of mitochondrial defects through local reductions in organelle dynamics.
   a. Mishra, P., Pham, A.H., Carelli, V., Manfredi, G., and Chan, D.C. "Proteolytic cleavage of Opa1 stimulates mitochondrial inner membrane fusion and couples fusion to oxidative phosphorylation." *Cell Metabolism*, 19:630-641, 2014. PMID: 24703695 PMCID: PMC4018240
   b. Del Dotto, V., Mishra, P., Vidoni, S. Fogazza, M., Maresca, A., Caporali, L., McCaffery, J.M., Cappelletti, M., Baruffani, E., Lenaers, G., Chan, D.C., Rugolo, M., Carelli, V., Zanna, C. "OPA1 isoforms in the hierarchical organization of mitochondrial functions." *Cell Reports*, 19:2257-2271, 2017. PMID: 28636943

c. Mishra, P.*****, Varuzhanyan, G.*, Pham, A., Chan, D.C. “Mitochondrial dynamics is a distinguishing feature of skeletal muscle fiber types and regulates organellar compartmentalization.” *Cell Metabolism,* 22:1033-1044, 2015. (*, co-first author). PMID: 26603188 PMCID: PMC4670593

d. Wang, X., Shelton S.D., Bordieanu, B., Anderson, F., Yi, Y., Venigalla, S.S.K., Gu, Z., Glogauer, M., Chandel, N.S., Zhao, H., McFadden, D.G., Mishra, P. “Oxidative stress stimulates removal of damaged muscle stem cells by inducing stem cell-myofiber fusion.” *In revision, Science..*

3. Dynamic scaffolding in signaling systems. As a PhD student, I became interested in a basic question: how is information faithfully transmitted during a signaling event. Visual transduction in *Drosophila* was an ideal model system to address this issue, as G protein based-signaling occurred with efficiency approaching 100%, and with a speed (<50 msec) unmatched by other systems. Critical to these properties is the scaffolding protein InaD, which serves to colocalize common components of the cascade, thereby enhancing efficiency and speed. Through a combination of X-ray crystallography, genetics, electrophysiology and behavioral studies, we discovered that InaD acted dynamically during visual transduction in order to adjust signaling efficiency. Intriguingly, these dynamics were important to mediate an escape behavior of diurnal flies, and were not present in nocturnal flies. Together, our results suggested that scaffolding proteins can not only act dynamically during signaling, but they can also serve as evolutionary control centers to engineer novel properties into signaling cascades.

   a. Mishra, P., Socolich, M., Wall, M.A., Graves, J., Wang, Z., and Ranganathan, R. “Dynamic scaffolding in a G protein-coupled signaling system.” *Cell* 131:80-92, 2007.

Complete List of Published Work in MyBibliography

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