BIOGRAPHICAL SKETCH

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

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

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		10/2015	Biology (Postdoctoral Training)
Harvard University, Cambridge, MA	A.B.	06/1999	Biochemical Sciences

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. We are developing high-throughput methods to measure multiple aspects of mitochondrial function in response to metabolic perturbations, which we will follow up with mechanistic analyses to further our understanding of the organelle. 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.

B. Positions and Honors

Positions and Employment

6/1996 – 8/1996 Research Assistant, Department of Molecular Modeling, Biogen, Inc.
6/1997 – 7/1998 Undergraduate Research Assistant, Department of Genetics, Harvard University, in the laboratory of Alan Michelson, M.D., Ph.D.
7/1999 – 5/2000 Research Assistant I, Department of Protein Chemistry, Transkaryotic Therapies, Inc.
8/2002 – 6/2009 Graduate student, Biophysics Graduate Program, University of Texas Southwestern Medical Center, in the laboratory of Rama Ranganathan, M.D., Ph.D.
7/2009 – 10/2015 Postdoctoral Scholar, Division of Biology, California Institute of Technology, in the laboratory of David C. Chan, M.D., Ph.D.
6/2010 – 6/2013 Postdoctoral Fellowship, Jane Coffin Childs Memorial Fund for Medical Research
11/2015 - Assistant Professor, Children's Medical Center Research Institute (CRI), University of Texas Southwestern Medical Center

Other Experience and Professional Memberships

Honors

6/1999	Harvard University Graduation with honors, A.B., Magna Cum Laude
6/2004	"Best Talk" award at the 2004 UT Southwestern Molecular Biophysics Retreat
11/2004	"Best Abstract" award at the 2004 UT Southwestern Sigma Xi Research Forum
6/2007	"Best Talk" award at the 2007 UT Southwestern Molecular Biophysics Retreat
12/2007	Annual Alfred Gilman Award from the Department of Pharmacology, UT Southwestern

C. Contribution to Science

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.

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. While the fusion process is known to be important to the overall health of the organelle population, as well as the whole organism, very little is known about how this event might be regulated. 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. This regulation occurred not only in organelles, but extended to cultured cells, and even murine skeletal muscle. Intriguingly, regulatory control of fusion impinged on the step of inner membrane fusion, implicating the dynamin-related protein Opa1. 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. Thus, the proteases (Yme1L and Oma1) serve as a metabolic sensors and regulators of mitochondrial physiology. This regulatory mechanism was disturbed in cells from patients with mitochondrial DNA mutations, emphasizing the role of mitochondrial fusion in these diseases.

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.

Compartmentalizaiton of mitochondrial defects in skeletal muscle. Mutations in mitochondrial DNA often result in skeletal muscle weakness and dysfunction. Patient biopsies indicate that these mutations are compartmentalized in small regions of the muscle fiber, suggesting that mechanisms exist to prevent further spreading of the defect. To study the basis for the comparmentalization, I developed a stochastic lineage-tracing method to follow mitochondrial proteins orginating from a singly myonucleus *in vivo*. With this tool, we found that mitochondria were indeed compartmentalized, and this compartmentalization was developmentally regulated. Intriguingly, the extent of compartmentalization was 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.***, 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).

Complete List of Published Work in MyBibliography

http://www.ncbi.nlm.nih.gov/sites/myncbi/1xsjwdNmBzg59/bibliograpahy/49274550/public/?sort=date&direction=ascending

D. Research Support

Ongoing Research Support

None

Completed Research Support

Division of Cellular and Molecular Biology Training Grant 8/2004 – 8/2007
Title: Dynamic scaffolding in a G protein-coupled signaling system.
The major goals of this project were to investigate the role of the scaffolding protein InaD in *Drosophila* visual transduction, and to assess the importance of dynamic disulfide-mediated changes within the scaffold itself.

Postdoctoral Fellowship 6/2010 – 6/2013
Jane Coffin Childs Memorial Fund for Medical Research
Title: Regulation of mitochondrial fusion.
The major goals of this project was to use an *in vitro* organellar fusion assay to identify modes of regulation, dissect the underlying mechanisms, and assess the importance of this regulation *in vivo*.

Baxter Senior Postdoctoral Fellowship 5/2014 – 11/2015
California Institute of Technology
Title: *Investigating the role of mitochondrial fusion in satellite cell function.*
The major goals of this project were to develop assays to monitor satellite cell function *in vivo*, and assess the importance of mitochondrial fusion in satellite cells.