BIOGRAPHICAL SKETCH

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NAME	POSITION TITLE
Maulik R. Patel	Assistant Professor of Biological Sciences
eRA COMMONS USER NAME (credential, e.g., agency login) PATEL.MAULIK	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
Grinnell College, Grinnell, IA	B.A.	05/01	Cognitive Neurophilosophy
Stanford University, Stanford CA	Ph.D.	08/09	Neurosciences
Fred Hutchinson Cancer Research Center, Seattle WA	Postdoctoral Fellow	12/14	Evolution, mitochondria

A. PERSONAL STATEMENT

My laboratory works at the nexus of evolution and functional experimentation. This combination is a product of my genetics training from graduate school and my experience in molecular evolution from postdoc. This combination uniquely positions my laboratory to gain insights into mitochondrial biology and disease that cannot be obtained from evolution or experimentation alone. I started my graduate career in developmental neurobiology, using *C. elegans* as a genetically tractable model to study synapse formation (**Patel et al, 2006** *Nature Neurosci*, **Patel & Shen, 2009** *Science*). My training in genetics gave me a deep appreciation for evolution. Thus, I secured a postdoctoral fellowship from the Helen Hay Whitney Foundation and joined the laboratory of Harmit Malik, one of very few research groups at the forefront of combining evolution with functional experimentation to gain biological insights. There, I build a unique research program to study mitochondria within an evolutionary framework of genetic conflict. My work on the functional consequences of evolution in the mitochondrial antiviral response protein (MAVS) demonstrates the success of combining experimentation with evolutionary analyses (**Patel et al, 2012** *PLoS Biology*, **Patel et al, 2011** *Curr Opin Virol*). The goal of the work I propose to do here is to apply this powerful combination to study the cell biological and evolutionary dynamics of the mitochondrial genome and their disease consequences. This branch of my work represents logical extension of my initial work on mitochondrial coevolution with viruses, to study mitochondrial coevolution with the nuclear genome. I am well positioned to successfully carry out this work using *C. elegans* and *D. melanogaster*. I have extensive experience in working with both proposed model systems. Furthermore, my training in cell and developmental biology from graduate school, combined with my postdoctoral experience in molecular evolution uniquely positions me to carry out the proposed work.

Patel MR, Loo YM, Horner SM, Gale M Jr & Malik HS. Convergent evolution of escape from hepaciviral antagonism in primates. ***PLoS Biology***, 2012. 10: e1001282. PMID: 22427742

- This paper combines functional experimentation with evolutionary analysis to show that mitochondrial antiviral factor MAVS has been subject to viral antagonism throughout evolutionary history of primates. It also demonstrates that MAVS is a genetic determinant of primate susceptibility to modern-day viruses.
- Recommended by Faculty of 1000.
- Previewed by Sedwick C. War Archives: How some primates fought off ancient viruses. PLoS Biology, 2012 10(3): e1001285.

Patel MR, Emerman M & Malik HS. Paleovirology – Ghosts and gifts of viruses past. ***Current Opinion in Virology***, 2011. 1: 304-9. Review. PMID: 22003379

- This conceptual review summarizes emerging concepts in the newly defined field of paleovirology that aims to study ancient viruses. We also propose that adaptive changes in host genes driven by ancient viruses act as 'footprints' that can be used to gain paleoviral insights.

Patel MR & Shen K. RSY-1 is a novel local inhibitor of presynaptic assembly. ***Science***, 2009. 323: 1500-3. PMID: 19286562

- This paper characterized a novel antagonist of synapse development. I identified this antagonist from a genetic screen based on the logic that synapse formation must be balanced by positive and negative forces.

- Previewed by Sigrist SJ. The yin and yang of synaptic active zone assembly. Sci Signal, 2009. 2: pe32.

Patel MR, Lehrman EK, Poon VY, Crump JG, Zhen M, Bargmann CI & Shen K. Hierarchical assembly of presynaptic components in defined C. elegans synapses. ***Nature Neuroscience***, 2006. 9: 1488-98. PMID: 17115039

This paper performed a comprehensive genetic analysis of presynaptic development in vivo.

B. POSITIONS & HONORS

Positions

2001-2003 **Research Technician**, HHMI/Duke University. Lab of Lawrence C. Katz
2003-2009 **Graduate Student**, HHMI/Stanford University. Lab of Kang Shen
2009-2014 **Postdoctoral Associate**, HHMI/Fred Hutchinson Cancer Research Center. Lab of Harmit Malik
2015-Present **Assistant Professor**, Department of Biological Sciences, Vanderbilt University.
2015-Present **Secondary Appointment**, Assistant Professor, Department of Cell and Developmental Biology, Vanderbilt University.
2015-Present **Affiliated Investigator**, Vanderbilt Diabetes Research and Training Center, Vanderbilt University.

Honors

2000 Associated Colleges of the Midwest Minority Scholar, Grinnell College
1999–2001 Herman Muehlstein Foundation Scholarship, Grinnell College
2004 National Science Foundation Graduate Research Fellowship – Honorable mention
2007–2009 Ruth L. Kirschstein National Research Service Award, Stanford University
2010 **Harold M. Weintraub Graduate Student Award**
For outstanding achievement during graduate studies, awarded to 13 students chosen internationally from all areas in the life sciences
2010 Keystone Symposia Scholarship for Viral Immunity Meeting
2012 Keystone Symposia Scholarship for Innate Immunity Meeting
2010-2013 **Helen Hay Whitney Foundation Postdoctoral Fellowship**
2013 Society for Molecular Biology & Evolution Meeting Young Investigator Travel Award

Professional memberships

2015 - Member, Genetics Society of America
2015 - Member, United Mitochondrial Disease Foundation

C. CONTRIBUTIONS TO SCIENCE

1. Elucidating the molecular logic of nervous system wiring: Synapses are fundamental sites of neural communication as well as sites of learning and memory. Despite significant effort that resulted in identification of many synaptic components, it was unclear how these proteins are recruited during development and organized into functioning synapses. A major obstacle to study synapse development in mammalian neurons is the sheer complexity of synaptic patterns, which makes it almost impossible to attain single synapse resolution. I therefore decided to use *C. elegans*, which offers an unprecedented opportunity to study synapse development *in vivo* because it has a simple nervous system with sparsely distributed synapses. Using cell biology in combination with genetics I found that synaptic partner choice and subsequent synapse formation is hierarchically organized into three molecular layers. In the first layer, a transmembrane protein Neph chooses a synaptic partner based on extracellular cues. Next, Neph recruits key scaffold molecules Liprin-alpha and its regulator SYD-1, which constitute the second molecular layer. In the absence of these scaffolds, almost all other synaptic components fail to assemble. Finally, the third layer consists of proteins that make up the functional apparatus for neurotransmitter release. Based on these findings, we can postulate that there must exist a diverse set of transmembrane molecules like Neph, which play important role in choosing a synaptic partner. These specificity molecules then plug into a near universal assembly program operated by few key

molecules such as Liprin-alpha and SYD-1. My studies elucidated this molecular logic of nervous system wiring. This worked spawned many new lines of investigations, especially in the Shen laboratory.

a) Patel MR, Lehrman EK, Poon VY, Crump JG, Zhen M, Bargmann CI & Shen K. Hierarchical assembly of presynaptic components in defined C. elegans synapses. ***Nature Neuroscience***, 2006. 9: 1488-98. PMID: 17115039

b) Chia PH, Patel MR & Shen K. NAB-1 instructs synapse assembly by linking adhesion molecules and F-actin to active zone proteins. ***Nature Neuroscience***, 2012. 15: 234-42. PMID: 22231427

c) Chia PH, Patel MR, Wagner OI, Klopfenstein DR & Shen K. Intramolecular regulation of presynaptic scaffold protein SYD-2/Liprin-α. ***Molecular and Cellular Neuroscience***, 2013, 56C: 76-84. PMID: 23541703

2. Identification of a novel regulator of synapse development: It is equally important to prevent neural synapses from forming at inappropriate locations, as it is to form them at the correct sites. While much was known about synapse formation at the time, factors that inhibit synapse formation were mostly unknown. Hence, I designed a genetic screen in *C. elegans* to identify such regulatory genes. After much effort, I cloned a novel synaptic protein that I named RSY-1 for regulator of synaptogenesis that is critical for inhibiting synapse development. Given its implications for learning and memory as well as development, this work received much attention – it was previewed by Sigrist in *Science Signaling* 2009, and I was invited to present it at the Neural Circuits meeting at Cold Spring Harbor Laboratory. It was also recognized by the Harold M. Weintraub Award for outstanding graduate work, given annually to thirteen students internationally from all areas in the Life Sciences. I carried out all aspects of this work from the conceptual design of the screen to cloning and characterizing rsy-1. This is demonstrated by the fact that I am the sole author along with my advisor on the paper reporting this work.

a) Patel MR & Shen K. RSY-1 is a novel local inhibitor of presynaptic assembly. ***Science***, 2009. 323: 1500-3. PMID: 19286562

3. Functional consequences of evolution: The advent of whole genome sequencing and the development of phylogenetic tools to decipher positive selection (adaptive evolution) has revolutionized evolutionary biology. Numerous studies have applied these tools to study positive selection. However, there are exceedingly few studies that back up phylogenetic analysis with functional experiments to gain tangible insights. I recognized that combining my experimental skills in genetics and cell biology with my interests in evolution provided a unique opportunity to functionally study adaptive evolution. Hence, I used this strategy to study host-virus coevolution. I discovered that a mitochondrial immune factor MAVS has independently acquired resistance to antagonism by hepatitis C virus (HCV) in multiple primates. I also showed that remarkably, MAVS from all these primates have evolved the same mechanism of escape from HCV antagonism. Finally, by functionally characterizing viruses from non-human primates, I found compelling evidence that HCV-like hepaciviruses were responsible for driving this evolution in MAVS.

There are two direct significances of this work. This is the first study to implicate host genetics in determining the outcome of hepaciviral infections. Second, this study helps shed light on the origins of HCV. We had previously made a theoretical argument that virus driven adaptive evolution of host immune factors essentially represents viral 'footprints,' the study of which has the power to reveal the biology of ancient viruses (paleoviruses). While this idea clearly captured the imagination of both virologists and evolutionary biologists, it had remained theoretical. My study provides the first experimental demonstration of this approach and has become the standard reference citation for all subsequent paleovirology papers. It also sparked collaboration with the virology group of Carolyn Coyne, in which my evolutionary analysis provided insights into the evolution of resistance in host protein RIP3 against coxsackievirus antagonism.

a) Harris KG, Morosky SA, Drummond C, Patel MR, Kim C, Stolz DB, Bergelson JM, Cherry S & Coyne CB. RIP3 regulates autophagy and is required for Coxsackievirus B3 infection of polarized intestinal epithelial cells. ***Cell Host & Microbe***, 2015. 18:221-32. PMID: 26269957.

b) Patel MR, Loo YM, Horner SM, Gale M Jr & Malik HS. Convergent evolution of escape from hepaciviral antagonism in primates. ***PLoS Biology***, 2012. 10: e1001282. PMID: 22427742

c) Patel MR, Emerman M & Malik HS. Paleovirology – Ghosts and gifts of viruses past. ***Current Opinion in Virology***, 2011. 1: 304-9. Review. PMID: 22003379

4. Isolation of male-harming mitochondrial mutations: Mitochondrial dysfunction is associated with many diseases. Intriguingly, men appear to be more susceptible to mitochondrial dysfunction than women. For instance, Parkinson's disease, a neurodegenerative disorder is more prevalent in men. One hypothesis has the potential to provide a unifying explanation for this sex bias. According to this hypothesis, maternal inheritance of the mitochondrial genome (mtDNA) renders selection ineffective against mutations that are specifically harmful to males. As a consequence, preponderance of 'male-harming' mtDNA mutations are predicted to exist. However, there is a relative paucity of characterized mtDNA mutations with sex-specific effects to support this hypothesis. In order to overcome this challenge, I devised and carried out a directed evolution scheme to isolate mtDNA mutations with male-specific effects in *D. melanogaster*. From this effort, I discovered and functionally characterized a mitochondrial missense mutation ($COII^{G177S}$) that is specifically deleterious in males. I used a combination of phenotypic, cell biological and biochemical analyses to functionally characterize this mutation. I found that the $COII^{G177S}$ specifically disrupts sperm development and function, which leads to an age- and temperature-dependent decrease in male fertility. Remarkably, this mutation has little consequence on other aspects of male and female fitness (aging, female fertility, neuronal function). These results provide one of the first and most detailed characterizations of a 'male-harming' mtDNA mutation in animals. Manuscript of this work is currently under review.

a) Patel MR, Miriyala GK, Littleton AJ, Yang H, Trinh K, Young JM, Yamashita YM, Pallanck L & Malik HS. Experimental evolution uncovers a male-harming mitochondrial mutation in *Drosophila* melanogaster. ***In review***.

D. RESEARCH SUPPORT

None