BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors. Follow this format for each person. DO NOT EXCEED FIVE PAGES.

NAME: Shwetha Shivaprasad

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

POSITION TITLE: Postdoctoral researcher

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)	Start Date MM/YYYY	Completion Date MM/YYYY	FIELD OF STUDY
Manipal University, India	B.Sc.	08/2005	06/2008	Biotechnology
Maharaja Sayajirao University, Baroda, India	M.Sc.	07/2008	06/2010	Biotechnology
Indian institute of Science, Bangalore, India	Ph.D.	08/2010	03/2016	Microbiology and Cell Biology
Stanford University	Postdoc	09/2016-Present		Virology

A. Personal Statement

The fatal hemorrhagic fever caused by Ebola portrayed in the movie *Outbreak,* first piqued my curiosity about viruses and RNA molecules as carriers of genetic information. From watching the movie in college to actually working with RNA viruses has been an unexpected and an interesting journey. As a PhD student, I focused on studying the life cycle of Hepatitis C virus in human liver cells and the role of cellular proteins and RNA molecules in the process. In the next few years of my career, I would like to draw on my previous experience to study mosquito borne viruses such as dengue and their interaction with human and mosquito hosts. My long-term interests are to study the regulation of cellular gene expression during infection and disease development, which could help in designing novel intervention strategies.

The PhD program at the Indian Institute of Science gave me an exciting opportunity to work at the interface of RNA biology and pathogenesis using RNA viruses as a model system. Under the guidance of Dr. Saumitra Das, I identified important host proteins and non-coding RNA molecules that interact with the Hepatitis C viral RNA and uncovered a novel mechanism through which these factors influence the viral life cycle. I also realized the importance of studying host-virus interactions in the development of antiviral agents and alleviation of disease symptoms. During this time, my awareness was drawn towards severe outbreaks of Dengue and Chikungunya in India which are RNA viruses transmitted by mosquitoes. My experience in the field of virology and the prevalence of these diseases in my country motivated me to continue research on mosquito borne RNA viruses.

I chose to pursue my postdoctoral research in the laboratory of Dr. Peter Sarnow who has extensive research experience in both the fields of virology and RNA biology for more than a decade. His creative problem solving skills and affable mentorship makes research enjoyable and provides an ideal environment for me to work. As outlined in my research proposal, I plan to study the interactions of the dengue virus with human and mosquito hosts in Peter's lab. In addition, I would like to utilize this period to develop other skills that are imperative for meaningful research including grant writing, big data analysis, collaboration and networking skills. So far, the courses on data analysis that I have attended at Stanford, the collaborations that I have initiated for my project and the interactions with experts in School of Medicine Career Center have been instrumental in expanding my skill set and achieving clarity of thought with respect to project design and career goals.

Altogether, I believe that carrying out my research in the cooperative and creative environment at Stanford would help me grow as an individual and develop expertise in structural and functional aspects of viral propagation which I could carry forward in my career as an independent investigator. As an independent researcher, my end goal is to elucidate the mechanistic basis of perturbation of cellular pathways in disease, centering on the role of regulatory RNA molecules.

B. Positions and Honors

Positions:

- 2005- 2008: Undergraduate student in the Bachelors in Biotechnology program at the Manipal Life Sciences Center, India.
- 2008-2010: Postgraduate student in the Masters in Biotechnology program at the MS University of Baroda, India.
- 2010-2015: PhD candidate at the Department of Microbiology and Cell Biology, Indian Institute of Science, Bangalore, India.
- 2015-2016: Research Assistant at the Department of Microbiology and Cell Biology, Indian Institute of Science, Bangalore, India.
- 2016- Present: Postdoctoral researcher at the Department of Microbiology and Immunology at the Stanford School of Medicine, Stanford University, USA.

Awards:

- 2005-2010: Kishore Vaigyanik Protsahan Yojna scholarship awarded for research in the Basic Sciences by the Department of Science and Technology, Government of India.
- 2010: Gold medal awarded for obtaining the highest GPA in the Masters in Biotechnology Program by the MS University of Baroda, India.
- 2010-2015: Graduate student research fellowship awarded by the Government of India for PhD training at the Indian Institute of Science (All India Rank 3).
- 2015: Best poster award and oral presentation in the 4th Molecular Virology Meeting at the Rajiv Gandhi Centre for Biotechnology, India.

C. Contributions to Science

I have been fortunate in obtaining several opportunities to contribute to advancements in Science during the course of my career, both as an undergraduate and as a PhD candidate.

1. **Early career:**

Being a recipient of the KVPY research scholarship awarded by the Government of India, I could participate in short term summer projects in top research institutes in India even as an undergraduate. This exposure to creative research environments was inspiring and strongly motivated me to pursue a career in the Life Sciences. As a Bachelors student, I worked on the regulation of innate and adaptive immune responses in cells under the guidance of Dr. Dipankar Nandi at the Department of Biochemistry in the Indian Institute of Science. The extensive knowledge I gained in the field is summarized in a review article titled “The major players in adaptive immunity” published in the “Resonance” journal. My project involved studying the role of metal ions in interferon mediated cell death. Findings from the study showed that iron promotes cell survival and reduces the generation of harmful reactive oxygen species in IFN treated cells. It demonstrated the importance of ferrous ions in regulating the cellular redox environment during immune response.

In my Master’s program, I was part of a study on the role of non-coding RNAs in the pathogenicity of the bacterium Pseudomonas aeruginosa, carried out under the supervision of Dr. Mrinalini Nair in the Biotechnology department of M.S.University in India. The project explored the effect of small RNAs on the secretory pathway of Pseudomonas which is responsible for its virulence. This was my first introduction to the captivating field of RNA biology and its implications in disease and pathogenesis. It has fascinated me ever since and I continue to study the role of regulatory RNAs in different model systems in my career.

Published work:

Ahmed, A., Saha, B., Patwardhan, A. et al. Reson (2009) 14: 455. doi:10.1007/s12045-009-0046-0
Ahmed, A., Saha, B., Patwardhan, A. et al. Reson (2009) 14: 610. doi:10.1007/s12045-009-0067-8

2. Graduate career:

As a graduate student, my most important contributions to Science were in the field of virology. I studied the biology of Hepatitis C virus under the guidance of Dr. Saumitra Das at the Department of Microbiology and Cell Biology in the Indian Institute of Science. HCV is a RNA virus that infects around 170 million people in the world. Since the virus causes extensive damage to the human liver leading to hepatocellular carcinoma, my focus was to understand the factors that influence the viral life cycle in human liver cells. I identified three host proteins (Human antigen R, Polypyrimidine tract binding protein and the La protein) which affect viral replication through association with the HCV RNA. For the first time, we demonstrated a possible mechanism by which remodeling of protein complexes at the viral RNA could regulate viral replication. Our studies indicated that the displacement of PTB by HuR and recruitment of La enhanced circularization of the viral RNA and thus promoted HCV replication.

In addition to viral proteins, we also studied the role of microRNAs and long non-coding RNAs in HCV replication and pathogenesis. We profiled the expression of 940 human miRNAs in the serum of HCV infected patients and identified several differentially regulated miRNAs, including miR-320c, miR-483-5p and miR-125b. Further studies in HCV infected cells validated the effect of some of these miRNAs on HCV replication and also indicated a possible regulation of HuR by miR-125b, thus providing a connecting link between proteins and miRNAs that regulate the viral life cycle. One of the most important pathogenic effects triggered by HCV in infected liver cells is a transition into a more dedifferentiated state (epithelial mesenchymal transition). We identified the long non-coding RNA, MALAT1 to be involved in this process. Altogether, these findings provide mechanistic insights into the roles of host proteins and non-coding RNAs in the regulation of HCV replication and pathogenesis, which provides a deeper understanding of how the virus interacts with its host to cause disease. A major part of this research has been published in peer reviewed journals listed below.

Published work:
Shwetha S, Kumar A, Mullick R, Vasudevan D, Mukherjee N, Das S. HuR displaces PTB to facilitate La binding to the 3'UTR and enhances HCV replication. Journal of Virology (2015).

Shwetha S, Gouthamchandra K, Chandra M, Ravishankar B, Khaja MN, Das S. Circulating miRNA profile in HCV infected serum: novel insight into pathogenesis. Scientific Reports (2013).

Bhat P, *Shwetha S*, Sharma DK, Joseph AP, Srinivasan N, Das S. The beta hairpin structure within ribosomal protein S5 mediates interplay between domains II and IV and regulates HCV IRES function. Nucleic Acids Research (2015).

Gouthamchandra K, Kumar A, *Shwetha S*, Mukherjee A, Chandra M, Ravishankar B, Khaja MN, Sadhukhan PC, Das S. Serum proteomics of hepatitis C virus infection reveals retinol-binding protein 4 as a novel regulator. J Gen Virol (2014).

Mukherjee K, Ghoshal B, Ghosh S, Chakrabarty Y, *Shwetha S,* Das S, Bhattacharyya SN. Reversible HuR-microRNA binding controls extracellular export of miR-122 and augments stress response. EMBO Rep (2016).

Invited oral presentations:
"HuR orchestrates interplay between viral and host proteins at the 3'UTR to regulate HCV replication" 4th Molecular Virology Meeting, Rajiv Gandhi Centre for Biotechnology, Thiruvananthapuram, 2015.

Poster presentations:
"miR-125b regulates hepatitis C virus (HCV) replication through the RNA binding protein, Human antigen R (HuR)" "EMBL symposium: The Non-coding Genome", EMBL, Heidelberg, Germany, October 2015.

"Role of circulating miRNAs, miR-320c and miR-483-5p in HCV pathogenesis and disease progression" 20th International Symposium on Hepatitis C Virus and Related Viruses, Melbourne, Australia 2015.

"HuR binding to 3'UTR influences translation and replication of Hepatitis C Virus" in the Sixth RNA Group Meeting at the Indian Institute of Science, Bangalore, India, 2012.

3. Postdoctoral career:

As a post doctoral research in Dr. Peter Sarnow's lab, I am using my experience in virology and RNA biology to explore the life cycle of dengue virus. Since dengue is transmitted to humans through mosquitoes, my current research addresses the structural and functional differences in the viral life cycle in both these host organisms. Currently, we have cloned certain host-specific variants of the dengue RNA in a suitable vector to identify the interacting protein partners. We have also standardized a RNA duplex mapping strategy in the lab to study long range RNA-RNA interactions in dengue infected cells in the mammalian and mosquito hosts.

A complete list of my published work can be accessed using the following **URL**: https://www.ncbi.nlm.nih.gov/sites/myncbi/1B9hnmlDq7p54/bibliography/51911050/public/?sort=date&direction=ascending

D. Additional Information: Research Support and/or Scholastic Performance

YEAR	SCIENCE COURSE TITLE	GRADE	YEAR	OTHER COURSE TITLE	GRADE
2006	Cell Biology	79	2006	Mathematics	95
2006	Biophysics	96	2006	Chemistry	93
2006	Biochemistry	96	2007	Biomedical Engineering	90
2007	Microbiology	87	2007	Anatomy	82
2007	Molecular Biology	84	2007	Human Physiology	92
2007	Genetics	86	2007	Computers and Bioinformatics	84
2009	Introductory Microbiology	80	2007	Plant Biotechnology	86
2009	Immunity and Infection	84	2007	Pharmacology	88
2009	Biochemistry	90	2008	Project work	192/200
2009	Genetics	78	2010	Laboratory Animal Care and Use	-
2009	Developmental Biology	90	2017	Introductory course in R	-
2010	Molecular Biology	75			
2010	Industrial Biotechnology	80			
2010	Cell Biology and Enzyme kinetics	80			
2010	Genetic engineering	83			
2010	Genomics and molecular medicine	83			
2011	Proteins: Structure and Function	A			
2011	Essentials in Microbiology	A			
2011	Virology	A			
2011	RNA Biology	A			
2011	Principles of Genetic Engineering	A			