BIOGRAPHICAL SKETCH

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NAME: Tiwari, Sangeeta

eRA COMMONS USER NAME (credential, e.g., agency login): sangeeta369

POSITION TITLE: Assistant Professor

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)	Completion Date MM/YYYY	FIELD OF STUDY
Guru Nanak Dev University, ASR, India	BS	05/1996	Biology and Chemistry
Guru Nanak Dev University, ASR, India	MS	06/1998	Mol. Biology and Biochemistry
Institute of microbial technology, CHD, India	Ph.D	03/2005	Microbiology and Biochemistry
Yale University, New Haven, CT	Postdoctoral Fellow	10/2011	Cell biology and Immunology
Albert Einstein College of Medicine, Bronx, NY	Reserch Fellow	06/2015	Microbiology and Immunology
Albert Einstein College of Medicine, Bronx, NY	Associate (faculty)	2016-2019	Microbiology and Immunology

A. Personal Statement

I am a new investigator with 13 years of experience in tuberculosis research with specific expertise in Mtb genetics, drug discovery and host immunity against Mycobacterium tuberculosis (Mtb) infection. The focus of my research is to develop tools to cure disease Tuberculosis (TB). It is caused by *Mycobacterium tuberculosis* (Mtb) that infects ~1 billion and kills greater than 1.5 million people each year. My research during my postdoctoral work at Yale University with Dr. J.D. Macmicking was focused on host directed therapy against Mtb. I have successfully identified the Mtb killing mechanism of the interferon inducible host proteins leading to publications in Nature Immunology (1) and Immunity (2). Further during fellowship with Dr. W.R. Jacobs Jr. at Albert Einstein College of Medicine, I extended my research and generated precise null mutants of Mtb and evaluated them as potential drug targets or vaccine candidates. I have successfully identified arginine biosynthesis pathway as a novel drug target to kill persistent Mtb subpopulations that are resistant to killing by present TB drugs and impose greatest impediment in the TB control. These studies lead to publication in PNAS (3). Additionally, during this period I have also identified ESX-5, a type VII secretion of Mtb as a potential TB vaccine candidate in prime boost regimen with BCG using mice and guinea pig models (4). Therefore, my training, expertise and academic environment makes me an ideal candidate to successfully carry out proposed research. During my postdoctoral fellowship I have successfully carried out independent projects leading to several peer-reviewed publications on identification and validation of new drug targets and vaccine candidates against Mtb.

During my research career at Yale University and at Albert Einstein College of medicine, I have mentored several graduate students in laboratory and undergraduate students from programs as Summer Undergraduate Research Fund (SURF) and Phage Phinders. They have presented their work at various forums and awarded prize for their research projects. Now some of them are pursuing PhD at prestigious schools. At City University of New York I have taught immunology course (lecture+lab) and motivated several undergraduate students for research. Depending on the contributions, some of these students have been acknowledged and are coauthors on the papers. Other than training students and staff I have participated in grant writing and serving as reviewer for journals.

a. **Tiwari S**, Choi HP, Matsuzawa T, Pypaert M, MacMicking JD. Targeting of the GTPase Irgm1 to the phagosomal membrane via PtdIns(3,4)P(2) and PtdIns(3,4,5)P(3) promotes immunity to mycobacteria. *Nature Immunology*. 2009 Aug;10(8):907-17.

b. Bougnères L*, Helft J*, **Tiwari S***, Vargas P, Chang BH, Chan L, Campisi L, Lauvau G, Hugues S, Kumar P, Kamphorst AO, Dumenil AM, Nussenzweig M, MacMicking JD, Amigorena S, Guermonprez P. A role for lipid bodies in the cross-presentation of phagocytosed antigens by MHC class I in dendritic cells. *Immunity*. 2009 Aug 21;31(2):232-44. ***** Equal contribution.

c. **Tiwari S**✉, van Tonder AJ, Vilcheze C, Mendes V, Thomas SE, Malek A, Chen B, Chen M, Kim J, Blundell TL, Parkhill J, Weinrick B, Berney M and Jacobs WR Jr. ✉ (2018). Arginine-deprivation-induced oxidative damage sterilizes *Mycobacterium tuberculosis. PNAS*, 115 (39): 9779-9784. (✉**Corresponding authors**). ***This article is highlighted*** *as Commentary in PNAS.* Mizrahi V and Warner DF. 2018. Death of Mycobacterium tuberculosis by l-arginine starvation. *PNAS* 115(39): 9658-9660.

d. **Tiwari S***, Dutt T* et al., Prime and Boost with Type-VII secretion system mutants leads to better protection against clinical strains of Mycobacterium tuberculosis, 2020 (manuscript under preparation, * equal first authors)

B. Positions and Honors

Positions and Employment

2000 - 2003	Junior Research fellow, CSIR, Institute of microbial technology, Chandigarh
2003 - 2005	Senior Research Fellow, CSIR, Institute of microbial technology, Chandigarh
2005 - 2010	Post Doctoral Research Fellow, Yale University, New Haven, CT
2010 - 2011	Assistant Research Scientist, Yale University, New Haven, CT
2012 - 2015	Fellow, HHMI, Albert Einstein College of Medicine, Bronx, NY
2016 – 2019	Associate, Albert Einstein College of Medicine, Bronx, NY
2020-	Assistant Professor, University of Texas at El Paso

Honors

1996	University Merit award, BS, Guru Nanak Dev University, India
1998	University Merit Award, MS, Guru Nanak Dev University, India
1998	Merit Fellowship, Indian Army, India
2000 - 2003	Junior Research fellowship, Council of Scientific and Industrial Research, India
2003 – 2005	Senior Research fellowship, Council of Scientific and Industrial Research, India
2015	Invited speaker at Institute of Microbial Technology, a top ranking CSIR Institute, India, Chandigarh
2017	Invited speaker for Microbial Pathogenesis conference, Toronto, Canada.
2017	Travel award for 3rd annual CTVD meeting 21-23 June.
2017	Invited speaker at City University New York, Lehman College, Biological sciences research seminar Member of editorial board for Insights in chest diseases (2017-) and Current trends in Vaccines and Vaccinology (2017-) Associate Editor for International journal for Vaccines and Vaccination (2017-present). Primary peer reviewer for Medical Research Council (MRC) funding (2017)
2018	Invited speaker at University of Texas at El Paso (2018). Invited speaker and travel award for international conference on Vaccine, San Diego, Nov 28-30 (2018) William R. Jacobs Jr. award for active participation in research in the Department of Microbiology and immunology, Albert Einstein college of Medicine (2018) Reviewer for Journal of Archives of Microbiology (2018-present), Journal of Acquired Immune Deficiency Syndromes (2012- Present), Journal of cellular and Molecular medicine (2018-present), PNAS (2018-present).
2019	Invited speaker and travel award for a World Vaccine and Immunotherapy Congress West Coast 2019, San Francisco. Invited speaker at collaborative meeting between University of Texas at El Paso and Texas Tech University at El Paso.

C. Contribution to Science

1. Elucidation of Mtb killing mechanisms of the antimicrobial interferon-inducible host proteins to design host-directed therapeutics. One third of world population is infected with Mtb, but most of the people are able to control the infection hence establishment of the disease. My earlier research accomplishments involve identification of the host directed mechanisms to control Tuberculosis. This work is significant because of the emergence of multi-drug resistant strains of Mtb and other pathogens. As a result identification of host mechanisms required to control pathogens can be exploited to boost host response against Mtb or other pathogens. I have demonstrated the function and mechanism of the interferon inducible immunity related GTPases (IRG), IRGM1 in targeting mycobacterial phagosomes (a cellular compartment where pathogenic microorganisms can be killed) through lipid-mediated interaction (a,b) and this work was published in **Nature Immunology**, 2009. This study was highlighted in "News and Views" in Nature Immunology. I extended my findings further and mechanistically defined how another member of the IRG family - Irgm3 is recruited to lipid bodies/lipid droplets during "cross-presentation" of phagosomally derived antigens (c). This was a genuinely novel finding on an uncharacterized organelle that again attracted attention in the form of a commentary in as Immunity Previews in corresponding issue of **Immunity**, 2009). These findings have broad implications in the design of treatment for diseases beyond tuberculosis as well. I have also written book chapter on role of p47 immunity related GTPases (IRGs) (d).

a. **Tiwari S**, Choi HP, Matsuzawa T, Pypaert M, MacMicking JD. Targeting of the GTPase Irgm1 to the phagosomal membrane via PtdIns(3,4)P(2) and PtdIns(3,4,5)P(3) promotes immunity to mycobacteria. *Nature Immunology*. 2009 Aug;10(8):907-17.

b. **Tiwari S**, Macmicking JD. Bacterial phagosome acidification within IFN-gamma-activated macrophages: role of host p47 immunity-related GTPases IRGs). *Methods Mol Biol*. 2008;445:407-15.

c. Bougnères L[*], Helft J[*], **Tiwari S**[*], Vargas P, Chang BH, Chan L, Campisi L, Lauvau G, Hugues S, Kumar P, Kamphorst AO, Dumenil AM, Nussenzweig M, MacMicking JD, Amigorena S, Guermonprez P. A role for lipid bodies in the cross-presentation of phagocytosed antigens by MHC class I in dendritic cells. *Immunity*. 2009 Aug 21;31(2):232-44. ***** Equal contribution**.**

d. **Tiwari S** and Macmicking, JD (2008). Bacterial phagosome acidification within IFN-gamma-activated macrophages: role of host p47 immunity-related GTPases (IRGs). Methods in Molecular Biology, Autophagosome and Phagosome, Humana Press, NY.

2. ***Identification and elucidation of novel mechanisms of interferon-inducible antimicrobial host proteins.*** I have contributed in the identification and understanding of the mechanistic role of new interferon inducible p65 family of GTPases in host immunity against tuberculosis and other pathogens. This research in published in a Science article (a) that showed how other proteins from the GTPase family could play a crucial role in combating gastrointestinal illnesses caused by food-borne bacteria, as well as pulmonary diseases caused by a pathogen very similar to the one responsible for TB. We showed that these proteins could help to deliver antimicrobial enzymes to attack foreign pathogens once they enter the host cell, thereby killing the bacteria (b). This work has not only contributed to understandings leading to host-directed anti-tuberculosis therapies but also opened new avenues for treatment against other pathogens involving Listeria, Salmonella and Toxoplasma. In work is published in Science and highlighted by **Nature Reviews Immunology**, and featured in **Scientist Magazine and Medical Xpress**.

a. Kim BH, Shenoy AR, Kumar P, Das R, **Tiwari S**, MacMicking JD. A family of IFN-γ-inducible 65-kD GTPases protects against bacterial infection. *Science*. 2011 May 6;332(6030):717-21.

b. Shenoy AR, Kim BH, Choi HP, Matsuzawa T, **Tiwari S**, MacMicking JD. Emerging themes in IFN-gamma-induced macrophage immunity by the p47 and p65 GTPase families. *Immunobiology*. 2007; 212 (9-10): 771-84.

3. ***Identification of potential vaccine candidates and novel virulence factors of Mtb:*** Using specialized transduction I have generated precise null deletion mutants of secretion systems of Mtb and validated their potential as potential vaccine candidates (a). I have established that type VII secretion mutant; Δ*esx-3* of *M. smegmatis* is highly attenuated and can be used as backbone to express immunogenic antigens (b). I have generated complete null deletion mutant of Δ*esx-5* and showed its safety and vaccine efficacy using mice and

guinea pigs as models (c). Further I have contributed to the studies and showed that phosphorylation of KasB is required for virulence of Mtb. In Addition I have contributed to the studies showing impact of the aging on lymph transport and pathogen clearance (d).

a. **Tiwari S✉,** Casey R, Hingley-Wilson S, Jacobs WR Jr. ✉ (2019). Inject and infect; how *mycobacterium tuberculosis* utilizes its major virulence-associated type VII secretion system ESX-1, *Microbiology spectrum*, 7(3):1-14. (✉**Corresponding authors**).

b. Junqueira-Kipnis AP, de Oliveira FM, Trentini MM, **Tiwari S**, Chen B, Resende DP, Silva BD, Chen M, Tesfa L, Jacobs WR Jr, Kipnis A. Prime-boost with Mycobacterium smegmatis recombinant vaccine improves protection in mice infected with Mycobacterium tuberculosis. *PLoS One*. 2013 Nov 8;8(11):e78639.

c. **Tiwari S***, Dutt T* et al., Prime and Boost with Type-VII secretion system mutants leads to better protection against clinical strains of *Mycobacterium tuberculosis*, 2020 (manuscript under preparation, * equal first authors)

d. Zolla V, Nizamutdinova IT, Scharf B, Clement CC, Maejima D, Akl T, Nagai T, Luciani P, Leroux JC, Halin C, Stukes S, **Tiwari S**, Casadevall A, Jacobs WR Jr, Entenberg D, Zawieja DC, Condeelis J, Fooksman DR, Gashev AA, Santambrogio L. Aging-related anatomical and biochemical changes in lymphatic collectors impair lymph transport, fluid homeostasis, and pathogen clearance. *Aging Cell*. 2015 Aug;14(4):582-94.

4. ***Identification of novel drug targets of Mtb:*** During my study of Mtb regulatory proteins involved in the process of signal transduction, I studied Nucleoside diphosphate kinase (NDK). It plays a role in signal transduction and is predominantly involved in nucleoside triphosphate (NTP) synthesis in bacteria. Despite being a well-known enzyme, its enzymatic properties are not fully understood. I established that certain amino acids involved in autophosphorylation and phosphotransfer activities are distinct in Mycobacterium tuberculosis NDK. This research work has implications for the design of inhibitors for mycobacteria NDK that can be used in new antimicrobial drugs.

a. **Tiwari S**, Kishan KV, Chakrabarti T, Chakraborti PK Amino acid residues involved in autophosphorylation and phosphotransfer activities are distinct in nucleoside diphosphate kinase from Mycobacterium tuberculosis. *J Biol Chem*. 2004 Oct 15;279(42):43595-603.

b. **Tiwari S✉,** van Tonder AJ, Vilcheze C, Mendes V, Thomas SE, Malek A, Chen B, Chen M, Kim J, Blundell TL, Parkhill J, Weinrick B, Berney M and Jacobs WR Jr. ✉ (2018). Arginine-deprivation-induced oxidative damage sterilizes *Mycobacterium tuberculosis. PNAS*, 115 (39): 9779-9784. (✉**Corresponding authors**). ***This article is highlighted*** *as Commentary in PNAS.* Mizrahi V and Warner DF 2018. Death of Mycobacterium tuberculosis by l-arginine starvation. *PNAS* 115(39): 9658-9660.

c. **Patent:** "Double auxotrophic Mycobacterium and uses thereof" (Provisional patent application No. 62/764, 696 Filed, USA, Albert Einstein College of Medicine, 2018)). Inventors William R. Jacobs Jr. and Sangeeta Tiwari.

Complete list of my bibliography:
https://www.ncbi.nlm.nih.gov/myncbi/collections/mybibliography

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

Ongoing Research support

1. Rising star award, University of Texas Sangeeta Tiwari (PI) 01/16/2020-01/16/2022
Major Goal: This funding aims to provide equipment resources to pursue tuberculosis research at UTEP.
Role: PI

Completed Research support

1. Bill and Melinda Gates Foundation W.R Jacobs Jr (PI) 10/30/2018-10/31/2019.
Generation of Precise Null Mutants of *Mtb.*
Major Goal: The goal of this project was to develop delta-argB-based human TB vaccine candidates that can eventually advance to clinical development.
Role: Key personnel

2. Council of scientific and industrial research fellowship 06/01/2000-06/01/2005.
Molecular and biochemical characterization of Mycobacterial nucleoside diphosphate kinase (mNdK).
Major Goal: The goal of this funding was to characterize mNdK to develop it as drug target against Mtb.