BIOGRAPHICAL SKETCH

NAME	POSITION TITLE
Krishnan, Navasona	Postdoctoral Fellow
eRA COMMONS USER NAME KRISHNANNA	

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

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Indian Institute of Technology, Madras	MS	2000-2002	Chemistry
University of Nebraska, Lincoln	PhD	2003-2007	Biochemistry
Cold Spring Harbor Laboratory (CSHL), Cold Spring Harbor, NY, U.S.A.	Postdoctoral Fellow	2008-present	Biology/Biochemistry

A. Personal Statement

Dr. Navasona Krishnan is currently working as a postdoctoral fellow with Dr. Nicholas Tonks at Cold Spring Harbor Laboratory. Dr. Krishnan received a PhD in Biochemistry from the University of Nebraska in 2008 and has 10 years of experience in protein biochemistry and enzymology. His research interests include development of methods to identify novel therapeutics, protein structure-function relationship, redox biology and allosteric regulation of signal transduction by endogenous small metabolites.

The protein tyrosine phosphatase PTP1B is a highly validated therapeutic target for the treatment of diabetes, obesity and HER2 positive breast cancer. Dr. Krishnan and Dr. Tonks have identified a novel allosteric site in PTP1B that is targeted by a natural product, MSI-1436. This inhibitor is highly potent in cell and animal models of breast cancer. Furthermore, HER2 transgenic mice treated with MSI-1436 showed marked reduction of tumor growth and importantly metastasis to the lungs was ablated. Currently, patients are being recruited for a phase I study with MSI-1436 for HER2-positive cancer at a reputed cancer hospital. Dr. Krishnan's interest in redox biology has led to the identification of a novel post-translational modification of PTP1B, termed sulfhydration, which occurs specifically in response to endoplasmic reticulum stress.
He has expertise in conducting high-throughput screens using enzymatic and biochemical assays. He has demonstrated success in identifying novel allosteric inhibitors of the protein tyrosine phosphatase PTP1B. He has also successfully developed an assay to screen for small molecule inhibitors that would stabilize the inactive conformation of PTP1B.

Dr. Krishnan is also interested in the identification and characterization of therapeutic targets for the treatment of Autism spectrum disorders (ASD). His current research focus is on the neurodevelopmental disorder, RETT syndrome, primarily caused by mutations in the X-linked gene that encodes for the methyl CpG binding protein MECP2. RETT syndrome is primarily monogenic, however MECP2 regulates a plethora of signaling pathways, which makes targeted therapy very difficult. Dr. Krishnan has identified a novel way to improve BDNF (Brain derived neurotrophin) signaling in RTT. Impaired BDNF signaling has been shown to be associated with RTT, hence this treatment option has the potential to ameliorate symptoms of RTT and improve the quality of life in patients with suffering from RTT syndrome.

B. Positions and Honors

Positions

06/1997-07/2000 Loyola College, Madras, India: Undergraduate Research
07/2001-05/2002 Indian Institute of Technology, Madras, India: Masters Dissertation
07/2003-12/2007 University of Nebraska, Lincoln NE, USA: Ph.D. Thesis
03/2008-present Cold Spring Harbor Laboratory, Cold Spring Harbor NY, USA: Postdoctoral Fellow

Honors

2001 Outstanding Graduate Student from Indian Institute of Technology

2005 Milton Mohr Fellowship for excellence in graduate research

2006 Widamann Trust Travel Fellowship for attending Gordon Research Conference titled "Thiol Based Redox Sensors" held in Biddeford, Maine

2006 Best Poster Award from Redox Biology Center, University of Nebraska, Lincoln

2007 Widamann Trust award for graduate research

2007 Larrick Travel Fellowship for attending the Gordon Conference titled "Stress Proteins in Growth, Development and Disease" held in Oxford, UK

2010 Outstanding Postdoctoral Fellow Poster Prize from Cold Spring Harbor Laboratory, Cold Spring Harbor NY

2011 Lunch and discussion with Mr. Bill Gates on Global Health at the Lindau Nobel Laureate Meeting in Lindau, Germany.

2014 Nominated to present at the Valle Symposium in Boston, MA.

2015 Cold Spring Harbor Laboratory Seminar titled "Drugging the undruggable - Novel PTP1B-directed therapeutics".

C. Clinical Trials involved

1. A Phase I Study of the Safety and Tolerability of Single Agent MSI-1436 in Metastatic Breast Cancer Patients (Protocol IND: 118367) at North Shore-LIJ Health System/Cancer Institute.

2. A Phase I Study of the Safety and Tolerability of CPT157633 in Rett syndrome patients (protocol in preparation).

D. Selected Peer-Reviewed Publications

1. **Navasona Krishnan** and Donald F. Becker. (2005) Characterization of a bifunctional PutA homologue from Bradyrhizobium japonicum and identification of an active site residue that modulates proline reduction of the flavin adenine dinucleotide cofactor. Biochemistry; 44(25): 9130-9.

2. Weimin Zhang, **Navasona Krishnan** and Donald F. Becker. (2006) Kinetic and thermodynamic analysis of Bradyrhizobium japonicum PutA-membrane associations. Arch Biochem Biophys.; 445(1): 174-83.

3. **Navasona Krishnan** and Donald F. Becker. (2006) Oxygen reactivity of PutA from Helicobacter species and proline-linked oxidative stress. J Bacteriol.; 188(4): 1227-35.

4. Navarathna DH, Hornby JM, **Krishnan N**, Parkhurst A, Duhamel GE, Nickerson KW. (2007) Effect of farnesol on mouse model of systemic candidiasis, determined by use of a DPP3 knockout mutant of Candida albicans. Infect Immun.; 75(4): 1609-18.

5. White TA, **Krishnan N**, Becker DF, Tanner JJ. (2007) Structure and kinetics of monofunctional proline dehydrogenase from Thermus thermophilus. J Biol Chem.; 282(19): 14316-27.

6. **Navasona Krishnan**, Martin B Dickmann and Donald F. Becker. (2008) Proline modulates the intracellular redox environment and protects mammalian cells against oxidative stress. Free Radic Biol Med.; 44(4): 671-81. PMCID: PMC2268104

7. **Navasona Krishnan**, Alan F Doster, Gerald E. Duhamel and Donald F. Becker. (2008) Characterization of a Helicobacter hepaticus putA mutant strain in host colonization and oxidative stress. Infect Immun.; 76(7): 3037-44. PMCID: PMC2446744

8. **Navasona Krishnan**, Dae Gwin Jeong, Suk-kyeong Jung, Seong Eon Ryu, Andrew Xiao, C. David Allis, Seung Jun Kim and Nicholas K. Tonks. (2009) Dephosphorylation of the C-terminal tyrosyl residue of the DNA damage-related histone H2A.X is mediated by the protein phosphatase Eyes Absent (EYA). J Biol Chem.; 284(24): 16066-70. PMCID: PMC2713548

9. Srivatsava D, Schuermann JP, White TA, **Navasona Krishnan**, Sanyal N, Becker DF and Tanner JJ. (2010) Crystal structure of the bifunctional proline utilization A flavoenzyme from Bradyrhizobium japonicum. PNAS; 107(7): 2878-83. PMCID: PMC2840367

10. **Navasona Krishnan**, Cexiong Fu, Darryl Pappin and Nicholas K. Tonks. (2011) H2S-induced sulfhydration of PTP1B and its role in the endoplasmic reticulum stress response. Science Signaling; 4(3): ra86. PMCID: PMC3328411

11. **Navasona Krishnan**, Gyula Bencze, Philip Cohen and Nicholas K. Tonks (2013) The anti-inflammatory compound BAY 11-7082 is a potent inhibitor of Protein Tyrosine Phosphatases. FEBS J. 280: 2830-2841.

12. Moxley MA, Sanyal N, **Navasona Krishnan,** Tanner JJ, Becker DF. Evidence for hysteretic substrate channeling in the proline dehydrogenase and Δ1-pyrroline-5-carboxylate dehydrogenase coupled reaction of proline utilization A (PutA). J Biol Chem. 2014 Feb 7;289(6):3639-51.

13. **Navasona Krishnan**, Dorothy Koveal, Daniel H. Miller, Bin Xue, Sai Dipikaa Akshinthala, Jaka Kragelj, Malene Ringkjøbing Jensen, Carla-Maria Gauss, Rebecca Page, Martin Blackledge, Senthil K. Muthuswamy, Wolfgang Peti and Nicholas K. Tonks. Targeting the disordered C-terminus of PTP1B with an allosteric inhibitor. Nature Chemical Biology. 2014 Jul;10(7):558-66.

14. Ulla Schwertassek, Aftabul Haque, **Navasona Krishnan**, Tobias P. Dick and Nicholas K. Tonks. Reactivation of oxidized PTP1B and PTEN by Thioredoxin1 FEBS J. 2014 Jun 30.

15. **Navasona Krishnan**, Keerthi Krishnan and Nicholas K. Tonks. Enhanced BDNF signaling through PTP1B inhibition provides a novel therapeutic strategy for RETT syndrome (Journal of Clinical Investigation, under revision).

16. Mathangi Ramesh, **Navasona Krishnan**, Senthil Muthuswamy and Nicholas K. Tonks. A Novel Phosphatidic Acid- Protein Tyrosine Phosphatase D2 Signaling Axis is Essential for the ERBB2

Pathway in Mammary Epithelial Cells. Journal of Biological Chemistry, 2015 Feb 13. pii: jbc.M114.627968. (Epub ahead of print).

E. Patents

Treatment of Rett syndrome - This invention relates to agents and methods for treating or ameliorating symptoms of autism spectrum disorders, such as Rett Syndrome (patent filed).

F. Research Support

The Gladowsky Breast Cancer Foundation, The Don Monti Memorial Research Foundation, Hansen Memorial Foundation, West Islip Breast Cancer Coalition for Long Island, Glen Cove CARES, Find a Cure Today (FACT), Constance Silveri, Robertson Research Fund and the Masthead Cove Yacht Club Carol Marcincuk Fund.