BIOGRAPHICAL SKETCH

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NAME: **Srinivas Somarowthu**

eRA COMMONS USERNAME (credential, e.g., agency login): **SOMAROWTHU**

POSITION TITLE: Assistant Professor of Biochemistry and Molecular Biology

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
Andhra Loyola College, Vijayawada, Andhra Pradesh, India	B.S	05/2005	Physics, Chemistry, and Mathematics
Indian Institute of Technology Delhi, New Delhi, Delhi, India	M.S	05/2007	Chemistry
Northeastern University, Boston, MA, USA	Ph.D.	05/2011	Biochemistry and Bioinformatics
Yale University, New Haven, CT, USA	Postdoctoral	08/2016	RNA Biochemistry and Structural Biology

A. Personal Statement

The current focus of my lab is to investigate structure-function relationships in long non-coding RNAs (lncRNAs) with a long-term goal of developing new therapeutics by targeting lncRNAs. LncRNAs are a novel class of regulatory biomolecules whose study present new challenges that demand expertise across disciplines. My research over the past decade not only gave me a unique opportunity to study both proteins and nucleic acids but also exposed me to several key techniques in the fields of biochemistry and computational biology. My career started at the Indian Institute of Technology Delhi, where I developed two computational tools as a part of the pipeline for DNA targeted drug design. My doctoral research at Northeastern University focused on demonstrating the importance of remote residues in enzyme catalysis using both computational and experimental techniques. This information on distant residues is now being used in protein design applications. In addition, using my expertise in computational biology, I developed a web server for functional site prediction in proteins, which has been heavily accessed (>10000 jobs since 2012) by the scientific community. As a postdoctoral researcher at Yale University (Dr. Anna Pyle Lab), I expanded my research skills and scope to study ribozymes and long non-coding RNAs (lncRNAs). Using a combination of computational modeling and RNA structure probing methods, I provided new insights into the splicing mechanism and molecular structures of group II introns (~400-800 nts). I was also involved in developing a workflow for biochemical and structural characterization of lncRNAs and applied them to the lncRNA HOTAIR. I successfully purified HOTAIR *in vitro* using optimized techniques that ensured stability and homogeneity and determined its functional secondary structure through chemical probing and phylogenetic analysis. Most importantly, the experimental approach developed in this work is applicable to studying the many other lncRNAs.

In the past few years, my lab has been involved in characterizing the structure and function of various lncRNAs using both computational tools (Tavares RCA *et al*, J Mol Biol 2019) and a variety of experimental techniques, including next-generation sequencing-based methods (Owens MC *et al*, Int J Mol Sci 2019, Sheonda BB *et a*l, Cell Mol Life Sci, 2021). For this project, we will adapt these techniques to investigate the role of lncRNA H19 in aging.

Ongoing and recently completed projects that I would like to highlight include:

NIH/NIAID R21 AI156728 (Bouchard-PI, Somarowthu-MPI)
12/01/2020 – 11/30/2022
The Role of RNA Structure in the Hepatitis B Virus Lifecycle
The goal of this proposal to define RNA structural elements in HBV pgRNA and their role(s) in the HBV lifecycle, which could identify novel strategies for blocking HBV replication.

NIH/NIA R56 AG071815 (Sell-PI, Somarowthu-Co-I)
06/11/21 – 06/11/22
Novel longevity enhancing pathways regulated by mTOR
The goal of this proposal is to investigate the role of lncRNA H19 in both pluripotency and senescence, as well as stem cell function.

CURE SAP 4100079710 (Somarowthu-PI, Reginato-Co-I)
06/01/2018-06/30/2019
Investigating the molecular mechanism of lncRNA HOTAIR in breast cancer
The goal of this project is to understand the structure-function relationship of lncRNA HOTAIR (HOX transcript antisense RNA) in breast cancer progression.

B. Positions and Honors

Positions

2005 – 2007	**Research Assistant**, Indian Institute of Technology Delhi, Supercomputing Facility for Bioinformatics and Computational Biology.
2007 – 2011	**Graduate Student**, Northeastern University, Department of Chemistry and Chemical Biology.
	Advisor: Mary Jo Ondrechen Co-Advisor: Penny Beuning
2011 – 2016	**Postdoctoral Associate**, Yale University, Department of Molecular, Cellular and Developmental Biology. Advisor: Dr. Anna Marie Pyle.
2016 - current	**Assistant Professor**, Drexel University Biochemistry and Molecular Biology

Honors

2005	Was placed in the top 1% in the national level entrance examination held for admission into Indian Institute of Technology (MS Chemistry program).
2007	Academic Achievement Award, Department of Chemistry and Chemical Biology, Northeastern University.
2011	Dissertation Completion Fellowship, Northeastern University.
2011	Excellence in research award, Department of Chemistry and Chemical Biology, Northeastern University.

Memberships

American Chemical Society
RNA Society
International Society of Computational Biology

C. Contributions to Science

1. ***Structural and biochemical characterization of long non-coding RNAs*:** Long noncoding RNAs (lncRNAs) have recently emerged as crucial players in fundamental cellular processes and diseases, but their functions are poorly understood. As a postdoctoral associate in Dr. Anna Pyle lab at Yale University,

I determined the secondary structure of lncRNA HOTAIR, a 2148-nt-long lncRNA molecule that is involved in epidermal development and cancer progression. I showed that HOTAIR is composed of four independent and modular structural domains. The overall process included developing a pipeline of protocols that are applicable for biochemical and structural characterization of any large RNA. For example, using these protocols, I have also contributed to characterize the secondary structure of lncRNA RepA. The structures determined in these studies now serve as a guide to investigate the molecular function of lncRNA HOTAIR and RepA.

a) Somarowthu, S., Legiewicz, M., Chillon, I., Marcia, M., Liu, F. & Pyle, A. M. (2015). HOTAIR forms an intricate and modular secondary structure. **Mol Cell** 58, 353-61. PMC4406478

b) Liu, F., Somarowthu, S. & Pyle, A. M. (2017). Visualizing the secondary and tertiary architectural domains of lncRNA RepA. **Nature Chem Biol**. Mar;13(3):282-289.

c) Owens MC, Clark SC, Yankey A, & Somarowthu, S. (2019). Identifying Structural Domains and Conserved Regions in the Long Non-Coding RNA lncTCF7. **Int J Mol Sci**. pii: E4770.

2. ***Modeling large RNAs*:** Like proteins, RNA molecules carry out functions by forming specific three-dimensional structures. Understanding the function of a particular RNA, therefore, requires detailed knowledge of its structure. However, determining the experimental structures of RNA is exceptionally challenging. In the absence of crystal structures, computational models can provide valuable insights and guide the experiments. As a postdoctoral associate in Dr. Anna Pyle lab at Yale University, I modeled the all-atom three-dimensional structure of the ai5γ group IIB intron (~800 nts), using a combination of homology and de-novo modeling methods. I have validated the model experimentally using model-guided mutagenesis and various RNA structure probing methods. The resulting model, which was the first RNA tertiary structure modeled from a remote homolog, provided major insights into the mechanism of splicing in group II introns.

a) Somarowthu, S., Legiewicz, M., Keating, K. S. & Pyle, A. M. (2014). Visualizing the ai5gamma group IIB intron. **Nucleic Acids Res** 42, 1947-58. PMC3919574

b) Somarowthu S. (2016). Progress and current challenges in modeling large RNAs. **J Mol Biol**. 428(5 Pt A):736-47. PMC4789162

c) Marcia, M., Somarowthu, S. & Pyle, A. M. (2013). Now on display: a gallery of group II intron structures at different stages of catalysis. **Mob DNA** 4, 14.

3. ***Developing computational tools for protein function prediction*:** As a Ph.D. Student in Dr. Mary Ondrechen Lab at Northeastern, I was involved in developing and validating POOL (Partial Order Optimum Likelihood), a machine-learning-based computational tool for functional site prediction in proteins. This computational web server is available free to the scientific community. The predicted information about active site residues is being used to discover the function of proteins with unknown function and to give guidance to protein engineering and drug discovery applications.

a) Somarowthu, S. & Ondrechen, M. J. (2012). POOL server: machine learning application for functional site prediction in proteins. **Bioinformatics** 28, 2078-9.

b) Somarowthu, S., Yang, H., Hildebrand, D. G. & Ondrechen, M. J. (2011). High-performance prediction of functional residues in proteins with machine learning and computed input features. **Biopolymers** 95, 390-400.

c) Wang, Z., Yin, P., Lee, J. S., Parasuram, R., Somarowthu, S. & Ondrechen, M. J. (2013). Protein function annotation with Structurally Aligned Local Sites of Activity (SALSAs). **BMC Bioinformatics** 14, S13. PMC3584854

4. ***Investigating the importance of remote residues in enzyme catalysis*:** Understanding the efficiency and specificity of enzymes is a fundamental question in the biochemistry of great practical importance. Although progress in biochemical and structural studies has enriched our knowledge of enzymes, the role of remote residues in enzyme catalysis is largely unexplored. As a Ph.D. Student in Dr. Mary Ondrechen and Dr. Penny Beuning Labs at Northeastern, I investigated the importance of remote

residues in enzyme catalysis using both computational and experimental techniques. Two enzymes, ketosteroid isomerase (KSI) and phosphoglucose isomerase (PGI), are investigated, and the role of remote residues in their catalysis is explored. These two isomerases belong to the same enzyme class E.C. 5.3 and catalyze similar reactions, but computational tools predicted significantly different degrees of participation by remote residues in the enzymatic catalysis. For KSI, a compact active site of mostly first-shell residues is predicted, but for PGI, an extended active site in which residues in the first, second, and third layers around the reacting substrate are predicted to be essential for catalysis. I tested the predictions experimentally by site-directed mutagenesis and enzyme kinetics. The results of these experiments demonstrated that, as predicted, remote residues are critical in PGI catalysis but make only small contributions to catalysis in KSI.

a) Somarowthu, S., Brodkin, H. R., D'Aquino, J. A., Ringe, D., Ondrechen, M. J. & Beuning, P. J. (2011). A tale of two isomerases: compact versus extended active sites in ketosteroid isomerase and phosphoglucose isomerase. **Biochemistry** 50, 9283-95.

b) Brodkin, H. R., DeLateur, N. A., Somarowthu, S., Mills, C. L., Novak, W. R., Beuning, P. J., Ringe, D. & Ondrechen, M. J. (2015). Prediction of distal residue participation in enzyme catalysis. **Protein Sci** 24, 762-78. PMC4420525

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