Curriculum Vitae

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Education:

2001	Ph.D. (Biochemistry)	University of Pune, India
1993	M.Sc. (Biochemistry)	University of Pune, India
1991	B.Sc. (Chemistry)	University of Madras, India

Research Experience:

2010-present	Staff Scientist, Department of Integrative Structural and Computational Biology, The Scripps Research Institute, Jupiter, FL
2007-2010	Research Associate, Department of Cancer Biology, The Scripps Research Institute, Jupiter, FL
2006-2007	Post-doctoral Research Associate, Department of Oncology, St. Jude Children's Research Hospital, Memphis, TN
2001-2006	Post-doctoral Fellow, Department of Biochemistry, McGill University, Montreal, Quebec, Canada

Current Research:

My current research work is focused on structure-function studies of cytoskeletal proteins that regulate focal adhesions and adherens junction. We have gained extensive experience in deciphering the functional significance of scaffolding cytoskeleton proteins, such as vinculin and α-catenin, through three-dimensional structure elucidations and functional studies. Given their dynamic nature, these proteins are highly dynamic and thus difficult to crystallize. Therefore, we needed to adopt or develop specific techniques in each case to obtain their structures. Our current investigation is focused on determining the three-dimensional structures of the cytoskeletal protein complexes to extend the current understanding of their roles within the cellular context.

Future Research:

Our large protein complexes are often unamenable to crystallization or X-ray diffraction can only be obtained at a modest resolution. Thus, we are exploring cryoEM for structure determination of our large cytoskeletal proteins in their native and bound states in particular in their actin cytoskeleton-bound states which are perfect samples for cryoEM. We are further interested the structure determination of several membrane proteins that we initiated through in-house collaborations.

Other Experience and Honors:

2016 Electron Microscopy training (April 11-13) in Dr. Andrew Ward's laboratory at The Scripps Research Institute, La Jolla, CA
2014 Multi Angle Light Scattering Training (December 3-5) at Wyatt Light Scattering University, Santa Barbara, CA
2014 Frontiers of Biological Small Angle X-ray Scattering (October 7-8) at SYBILS beamline, Lawrence Berkeley National Laboratory, Berkeley, CA
1993 CSIR Fellowship for Doctoral Research (Council for Scientific and Industrial Research, Government of India)
1993 GATE Scholarship (Indian Institute of Technology, India)
1993 University Grants Commission, Government of India Fellowship for Doctoral Research
1991 M.Sc. Merit Scholarship (National Chemical Laboratory, Pune, India)

Contributions to Science

1. As a post-doctoral fellow, my work focused on structure-function studies of bacterial proteins from different genomes (K12 and157) that I carried out under the Montreal-Kingston Structural Genomics Initiative. The basic goal of the project was to determine the crystal structures of *E. coli* proteins of known or unknown function with the main focus on small-molecule metabolic pathway enzymes, RNA binding proteins, and proteins that may participate in bacterial pathogenesis. I was involved in crystallization of many enzymes that are part of bacterial biosynthetic pathway and include HisB, PseG, PglD, YdiF, and CaiB, for which structural snapshot were provided using either their substrate, intermediate, or product and aided the elucidation of structure based catalytic mechanisms. Additionally, I determined the structures of hypothetical proteins YdiF and YjhS for which the functions were not known, however, based on the structure the functions was deciphered and validated through biochemical analysis. My efforts led to the publication of 13 articles in peer-reviewed journals and resulted in 27 PDB depositions with the RCSB database.

    a. **Rangarajan ES**, Li Y, Ajamian E, Iannuzzi P, Kernaghan SD, Fraser ME, Cygler M & Matte A (2005)
    Crystallographic trapping of the glutamyl-CoA thioester intermediate of family I CoA transferases
    J Biol Chem 280**:**42919-42928

    b. **Rangarajan ES**, Li Y, Iannuzzi P, Cygler M & Matte A (2005)
    Crystal structure of *Escherichia coli* crotonobetainyl-CoA: carnitine CoA-transferase (CaiB) and its complexes with CoA and carnitinyl-CoA
    Biochemistry 44**:**5728-5738

c. **Rangarajan ES**, Proteau A, Wagner J, Hung MN, Matte A & Cygler M (2006)
Structural snapshots of *Escherichia coli* histidinol phosphate phosphatase along the reaction pathway
J Biol Chem 281**:**37930-3794

d. **Rangarajan ES**, Ruane KM, Sulea T, Watson DC, Proteau A, Leclerc S, Cygler M, Matte A & Young NM (2008)
Structure and active site residues of PglD, an *N*-acetyltransferase from the bacillosamine synthetic pathway required for *N*-glycan synthesis in *Campylobacter jejuni*
Biochemistry 47**:**1827-1836

2. My expertise gained in studying the structure-function relationship of bacterial proteins provided an exciting opportunity to work on human proteins, namely metavinculin, an isoform of vinculin, which plays an important role in the cytoskeleton organization in the heart and its mutants has been implicated in various cardiomyopathy conditions. I obtained stability as well as the X-ray diffraction quality of metavinculin crystals by developing a streak seeding protocol. This allowed me to solve the metavinculin structures (wild type as well as its cardiomyopathy associated Leu-954 deletion mutant) to about 3.4 Å resolution. Importantly, the vinculin project as a whole provided an excellent opportunity to carry out various *in vivo* studies, which boosted my overall expertise on the functional side as well. In addition, we also performed structural and functional studies involving vinculin in complex with raver1, a ribonucleoprotein that shuttles between the nucleus and cytoplasm.

a. Lee JH, **Rangarajan ES**, Yogesha SD & Izard T (2009)
Raver1 interactions with vinculin and RNA suggest a feed-forward pathway in directing mRNA to focal adhesions
Structure 17**:**833-842

b. **Rangarajan ES**, Lee JH, Yogesha SD & Izard T (2010)
A helix replacement mechanism directs metavinculin functions
PLoS One 5**:**e10679

c. **Rangarajan ES**, Lee JH & Izard T (2011)
Apo raver1 structure reveals distinct RRM domain orientations
Protein Sci 20**:**1464-1470

d. Lee JH, **Rangarajan ES**, Vonrhein C, Bricogne G & Izard T (2012)
The metavinculin tail domain directs constitutive interactions with raver1 and vinculin RNA
J Mol Biol 422**:**697-704

3. In another cell adhesion project, I studied the structural aspects of α-catenin, which is a scaffold protein similar to vinculin that participates in adherens junctions to interlink the E-cadherin, a single pass transmembrane protein, to the actin cytoskeleton. Human α-catenin, has been shown to exist both as a monomer and as a dimer. I was able to improve the initial X-ray diffraction from 6 Å to 3.7 Å through systematic optimization of a novel phosphate and malonate mediated dehydration protocol. Furthermore, I identified the distinct orientation of the two F-actin binding domains and identified the mechanism of interaction with F-actin. This was a huge accomplishment as α-catenin was long thought to be a protein 'not suitable for crystallization studies'. In addition, I was able to solve the structure of vinculin *N*-terminal domain (Vh1) with the vinculin-binding domain of α-catenin that showed that the latter could dimerize upon binding to vinculin. Collectively, the vinculin and α-catenin projects have yielded 10 PDB depositions and exciting peer-reviewed articles.

    a. **Rangarajan ES** & Izard T (2012)
    The cytoskeletal protein α-catenin unfurls upon binding to vinculin
    J Biol Chem 287**:**18492-18499, PMCID=3365723

    b. **Rangarajan ES** & Izard T (2013)
    Dimer asymmetry defines α-catenin interactions
    Nat Struct Mol Biol 20**:**188-193, PMCID=3805043

    c. Chinthalapudi K, **Rangarajan ES**, Brown D & Izard T (2016)
    Differential lipid binding of vinculin isoforms promotes quasi-equivalent dimerization
    Proceeding of the National Academy of Sciences USA
    113:9539-9544

4. More recently, as a collaborative effort with the laboratory of Dr. Kendall Nettles, I have been involved intensively and determined several crystal structures of the estrogen receptor-α (ERα) with different ligands from several distinct scaffolds where I optimized the ERα crystallization conditions to go from a 3 - 6 week turn around to overnight crystal growth with an additional elimination of extended incubation periods for complex formation prior to crystallization. The goal of this project is to develop the next generation anti-estrogen therapies for treatment of breast cancer using structure based design and a method to stratify patient responders. Our data showed that treatment of human MCF-7 breast cancer cells with IL1β or TNFα results in ERα-dependent activation of gene expression and proliferation, in the absence of ligand as well as the presence of 4OH-

tamoxifen and we defined ERα as an independent transcriptional effector of cytokine-induced IKKβ signaling.

a. Stender JD, Nwachukwu JC, Kastrati I, Kim Y, Strid T, Yakir M, Srinivasan S, Nowak J, Izard T, **Rangarajan ES**, Carlson KE, Katzenellenbogen JA, Yao XQ, Grant BJ, Leong HS, Frasor J, Nettles KW, & Glass CK (2017)
Structural and molecular mechanisms of cytokine-mediated endocrine resistance in human breast cancer cells
Mol Cell 16:1122-1135

b. Nwachukwu JC, Srinivasan S, Bruno NE, Nowak J, Wright NJ, Minutolo F, **Rangarajan ES**, Izard T, Yao XQ, grant BJ, KOjetin DJ, Elemento O, Katzenellenbogen JA & Nettles KW (2017)
Systems structural biology analysis of ligand effects on ERα predicts cellular response to environmental estrogens and anti-hormone therapies
Cell Chem Biol 24:35-45

5. My latest efforts involve another project, in collaboration with Dr. Kendall Nettles laboratory, aimed to develop next generation glucocorticoids targeting inflammation, improved muscle function, and treatment of cancer. For the current grant proposal, I have standardized the expression, production, and purification conditions for the glucocorticoid receptor (GR) protein domains. Our current purification protocol allows us to produce pure protein in large quantities (several milligrams) suitable for crystallization. Furthermore, our modified protocol for GR/ligand protein complex production has led to the identification of conditions suitable to produce crystals within 24 hours and is amenable to screening several ligands concurrently.

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/myncbi/browse/collection/47586236/?sort=date&direction=descending