BIOGRAPHICAL SKETCH

NAME: Gangwar, Shanti Pal

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

POSITION TITLE: Post-Doctoral Research Scientist

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
Kumaun University, India	MSc	July 2005	June 2007	Biotechnology
Jawaharlal Nehru University, India	PhD	July 2007	Feb 2014	Biophysics/Structural Biology
University of Texas Medical Branch (UTMB), USA	Postdoc	Sep 2014	Jan 2019	Biophysics/Structural Biology/Neuroscience
Columbia University, USA	Postdoc	March 2019	Current	Biophysics/Structural Biology/Neuroscience

A. Personal Statement

My long-term goal is to understand the structural and functional perspective of ion channels involved in neuronal communication and several neurological disorders including Alzheimer's disease, amyotrophic lateral sclerosis, epilepsy, and ischemia. My academic and research training has provided me skills in biophysics, X-ray crystallography, molecular biology, biochemistry, and Cryo-EM. As a graduate student, I learned X-ray crystallography studying transcript factors from human and *Mycobacterium tuberculosis*. As a postdoc under the guidance of **Dr. Gabrielle Rudenko at UTMB,** I was introduced to the scope and importance of neurodevelopmental/neuropsychiatric disorders and I started studying on synaptic proteins. Subsequently, my research findings on the structural and mechanistic details of synapse adhesion molecules (Neuroligin-MDGA1) have suggested strategies to design structure-guided peptides/small molecules modulating protein-protein interactions as therapeutics for neurodevelopmental disorders. Now I am advancing my research further by studying the neuronal ion channels under the supervision of **Dr. Alexander Sobolevsky at Columbia University**. The proposed research on the structural studies of the ionotropic glutamate receptors and its outcomes would expand our understanding of the gating mechanism as well as modulation by small molecules/inhibitor to develop therapeutics. The proposed research outlines a set of career developmental activities such as grant writing, public speaking, management in the lab, mentoring students, and altogether enhancing my abilities in becoming a successful independent investigator. Given the competitive nature of the proposed research area, it will be an excellent opportunity for me to work on the structure-function relationship of ion channels.

- **Gangwar, SP*.,** Green, M.N*., Michard, E*., Simon, A.A., Feijo, J.A., and Sobolevsky, A.I. (2019) Structure of the *Arabidopsis* Glutamate Receptor-like Channel GLR3.2 Ligand-Binding Domain. Structure. https://doi.org/10.1016/j.str.2020.09.006 **(Cover - page)**

B. Honors and Awards

- Awarded **Best Poster** Prize in a poster presentation at *23rd Annual Sealy Center for Structural Biology Symposium*, 28th April 2018, University of Texas Medical Branch, Texas USA.

- Awarded **Best Poster** Prize in a poster presentation at a 4th International Symposium on "*Recent trends in Macromolecular Structure and Function"*, Jan 21-23, 2010, University of Madras, Chennai, India.

- Awarded **Junior Research Fellowship** and **Senior Research Fellowship** from Council of Scientific and Industrial Research (CSIR) and University Grants Commission (UGC) India and Qualified Graduate Aptitude Test in Engineering **(GATE)** 2006 by Department of Higher Education, MHRD, Government of India.

C. Positions and Employment

2014 - 2019 Postdoctoral Researcher, University of Texas Medical Branch, Galveston, TX
2019 - current Postdoctoral Researcher, Columbia University, New York, NY

D. Contributions to Science

Graduate Career

My graduate research contributions focused on the transcription factors from human and *Mycobacterium tuberculosis*. The outcomes of the research were of significate importance that provided insights that full-length Erg is a highly nonglobular protein, which is subjected to DNA binding autoinhibition mechanism. The DNA binding domain (ETS domain) of human Erg is a winged helix-turn-helix and binds to DNA using its particular helix. Modulation of this DNA-Protein interaction by small molecules/peptides may open up new therapeutic avenues in the field of prostate cancer.

The *Mycobacterium tuberculosis* transcriptional regulator EspR contains an N-terminal helix–turn–helix DNA binding domain and a C-terminal dimerization domain. Structural study and comparison of EspR in different crystal forms indicated that the N-terminal helix–turn–helix domain of EspR acquires a rigid structure in different crystal forms. However, significant structural differences were observed in the C-terminal domain of EspR. The interaction, stabilization energy and buried surface area analysis of EspR in the different crystal forms have provided information about the physiological dimer interface of EspR.

Sharma, R., **Gangwar, SP.,** Saxena, A.K. (2018) Comparative structure analysis of the ETSi domain of ERG3 and its complex with the E74 promoter DNA sequence. *Acta Crystallogr. Section F Biol. Crystallogr*.F74. 656-663.

Gangwar, S. P., Meena, S. R. and Saxena, A. K. (2014). Comparison of four different crystal forms of Mycobacterium tuberculosis ESX-1 secreted protein regulator, EspR. *Acta Crystallogr. Section F Biol. Crystallogr*.F70.

Gangwar, S. P., Dey, S., and Saxena, A. K. (2012). Structural modeling and DNA binding auto-inhibition analysis of Ergp55, a critical transcription factor in prostate cancer. *PLoS ONE* 7(6), e39850.

Postdoctoral Career

During my postdoc at UTMB, Texas, I have studied the structural perspective of the synapse-related, organizers/adhesion, proteins critical in brain development using X-ray crystallography, and other biophysical methods. The outcomes of this research focus on how a synapse organizer, MDGA1, interacts with Neuroligin and regulates the interaction with Neurexin and Neuroligin. On the basis, of this structural information, we designed small peptides modulating the Neuroligin and MDGA1 interaction and tested their efficacy by related biophysical methods. The next goal of this project is to increase the binding affinity of these peptides by optimizing the peptide sequence making them protease-resistant and then test *in vivo* / in animal models to explore the therapeutic potential to recalibrate excitation-inhibition imbalances at the synapse.

- Fan, S**., Gangwar, SP.,** Machius, M., and Rudenko, G. (2020) Interplay between hevin, SPARC, and MDGAs: modulators of neurexin-neuroligin trans-synaptic bridges. **Structure,** https://doi.org/10.1016/j.str.2021.01.003

- **Gangwar, SP.,** Zhong, X., Seshadrinathan, S., Chen, H., Machius, M., and Rudenko, G. (2017). Molecular Mechanism of MDGA1: Regulation of Neuroligin 2: Neurexin Trans-synaptic Bridges**.** ***Neuron.*** 2017 Jun 21;94(6):1132-1141.e4.

- Kim, M.J., Biag, J., Fass, D.M., Lewis, M.C., Zhang, Q., Fleishman, M., **Gangwar, S.P.**, Machius, M., Fromer, M., Purcell, S.M., Premont, R.T., McCarroll, S.A., Rudenko, G., Scolnick, E.M., Haggarty, S.J. Functional analysis of rare variants found in schizophrenia implicates a critical role for GIT1-PAK3 signaling in neuroplasticity. ***Molecular Psychiatry***.2017, 22(3):417-429.

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

Publications

1. Green, MN*., **Gangwar, SP*.,** Michard, E., Simon, AA., Portes, MT., Barbosa-Caro, J., Wudick, MM., Lizzio, MA., Klykov, O., Yelshanskaya, MV., Feijo, JA., and Sobolevsky, AI. (2021) Structure of the Arabidopsis thaliana Glutamate Receptor-Like Channel GLR3.4. **Mol Cell** https://doi.org/10.1016/j.molcel.2021.05.025 (equal contribution)

2. Fan, S., **Gangwar, SP.,** Machius, M., and Rudenko, G. (2020) Interplay between hevin, SPARC, and MDGAs: modulators of neurexin-neuroligin trans-synaptic bridges. **Structure,** https://doi.org/10.1016/j.str.2021.01.003

3. **Gangwar, SP.,** Bandyopadhyay, A., and Saxena, AK. (2020) Structural studies on *M. tuberculosis* decaprenyl phosphoryl-β-D-ribose epimerase-2 enzyme involved in cell wall biogenesis. **BioRxiv.** doi**:** https://doi.org/10.1101/2020.10.15.341941

4. **Gangwar, SP.,** Green, M.N., Michard, E., Simon, A.A., Feijo, J.A., and Sobolevsky, A.I. (2019) Structure of the *Arabidopsis* Glutamate Receptor-like Channel GLR3.2 Ligand-Binding Domain. **Structure***.* https://doi.org/10.1016/j.str.2020.09.006 **(Cover - page)**

5. Sharma, R., **Gangwar, SP.,** Saxena, A.K. (2018) Comparative structure analysis of the ETSi domain of ERG3 and its complex with the E74 promoter DNA sequence. ***Acta Crystallogr. Section F Biol. Crystallogr*.**F74. 656-663.

6. **Gangwar, SP.,** Zhong, X., Seshadrinathan, S., Chen, H., Machius, M., and Rudenko, G. (2017). Molecular Mechanism of MDGA1: Regulation of Neuroligin 2: Neurexin Trans-synaptic Bridges**.** ***Neuron****.* 2017 Jun 21;94(6):1132-1141.e4.

7. Kim, M.J., Biag, J., Fass, D.M., Lewis, M.C., Zhang, Q., Fleishman, M., **Gangwar, S.P.**, Machius, M., Fromer, M., Purcell, S.M., Premont, R.T., McCarroll, S.A., Rudenko, G., Scolnick, E.M., Haggarty, S.J. Functional analysis of rare variants found in schizophrenia implicates a critical role for GIT1-PAK3 signaling in neuroplasticity. ***Molecular Psychiatry*.** 2017, 22(3):417-429.

8. **Gangwar, S. P.,** Meena, S. R. and Saxena, A. K. (2014). Comparison of four different crystal forms of Mycobacterium tuberculosis ESX-1 secreted protein regulator, EspR. ***Acta Crystallogr. Section F Biol. Crystallogr***.F70.

9. **Gangwar, S. P.,** Meena, S. R. and Saxena, A. K. (2014). Structure of the carboxy-terminal domain of *M. tuberculosis* CarD protein: an essential rRNA transcriptional regulator. ***Acta Crystallogr. Section F Biol. Crystallogr****. F70.*

10. **Gangwar, S. P.,** Dey, S., and Saxena, A. K. (2012). Structural modeling and DNA binding auto-inhibition analysis of Ergp55, a critical transcription factor in prostate cancer. ***PLoS ONE*** 7(6), e39850.

11. **Gangwar, S. P.,** Meena, S. R., and Saxena, A. K. (2012). Purification, crystallization and preliminary X-ray crystallographic analysis ETS domain of Ergp55 in complex with *c-fos* promoter DNA sequence. ***Acta Crystallogr. Section F Biol. Crystallogr****. F68,* 1333-1336.

12. Meena, S. R., **Gangwar, S. P.** and Saxena A. K. (2012). Purification, crystallization and preliminary X-ray crystallographic analysis of ATPase domain of TAP in nucleotide-free, ADP, vanadate and azide inhibited form. ***Acta Crystallogr. Section F Biol. Crystallogr. F****68,* 655-658

13. **Gangwar, S. P.,** Meena, S. R. and Saxena, A. K. (2011). Cloning, purification, crystallization and preliminary X-ray analysis of EspR: a secreted transcription factor from *M. tuberculosis*. ***Acta Crystallogr. Section F Biol. Crystallogr****. F67*, 83-86.

Symposia/Conference paper presentations

- **Gangwar SP,** Zhong X, Seshadrinathan S, Chen H, Machius M and Rudenko G. (2017) Structural Insights Into The Regulation Of Neuroligin2: Neurexin Trans-Synaptic Bridge By MDGA1. 27th Annual Keck Center Research Conference: *Innovations in Interdisciplinary Neuroscience,* October 27, 2017, Houston, Texas.

- **Gangwar, S. P. (**2013) Structural and functional dissection of the human Ergp55 oncoprotein.*42nd National seminar on crystallography and International workshop on the application of X-ray diffraction for drug discovery*, November 21-23, New Delhi- India.
- **Gangwar, S. P.,** Meena, S. R. and Saxena, A. K. (2012). Structure and functional analysis of key proteins involved in Mtb ESX-1 protein export pathway: potential drug targets. *National symposium of microbes in Health and Agriculture,* March 12-13, JNU, New Delhi, India. **(Best poster presentation award).**

- Meena, S. R., **Gangwa**r, **S. P.,** and Saxena, A. K. (2010) Elucidation of the mechanism of ATP hydrolysis cycle of the Transporter Associated with Antigen Processing (TAP). *4th International Symposium on Recent Trends in Macromolecular Structure and Function,* January21-23, Chennai, India. **(Best poster presentation award)**.

- Meena, S. R., **Gangwar, S. P.** and Saxena, A. K. (2008) Structure analysis of Transporter Associated with Antigen Processing (TAP). *International Symposium on Novel Strategies for Targeted Prevention and Treatment of Cancer*, JNU, India.

- **Gangwar, S. P.,** Meena, S. R., and Saxena, A. K. (2008) Structure analysis of ERG oncoprotein: A potential target to develop a prostate cancer drug. *International Symposium on Novel Strategies for Targeted Prevention and Treatment of Cancer,* JNU, India.

Skills and Techniques

- **Protein expression and Purification:** Membrane protein as well as soluble protein from *E. coli*, Insect cell line, and Mammalian cells.

- **Macromolecular Crystallography:** Crystallization of proteins and protein-DNA complexes. Crystal handling and mounting, Crystal soaking, Data collection at home source and synchrotron (BM14 beamline at ESRF, LS-CAT, 19ID SBC-CAT at APS). Data processing using iMOSFLM and HKL2000. Structure determination by experimental Phasing (using Selenomethionine and Iodide, SAD) and Molecular replacement using CCP4 suite and Phenix suite, structure visualization, and refinement using coot.

- **Cryo-EM:** Sample preparation, Vitrobot handling, data processing using Relion and CryoSparc

- **Techniques:** Genomic and plasmid DNA isolation, PCR, Gene cloning. Affinity, size exclusion, ion exchange Chromatography, Western blotting, Dot-blot, CD spectroscopy, Fluorescence polarization assay, ITC, Protein thermal shift assay, SPR, BLAST, ClustalW, Modweb and Swiss-Model, Molecular dynamics simulation using Gromacs and structure visualization using Pymol.