**APPLICANT BIOGRAPHICAL SKETCH**

| NAME | POSITION TITLE |
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| SINGH APPU K. | Post-doctoral scientist |

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)* | MM/YY | FIELD OF STUDY |
|---|---|---|---|
| University of Delhi, India | B.Sc. | 06/05 | Zoology (Hons.) |
| Indian Institute of Technology, Roorkee, India | M.Sc. | 07/08 | Biotechnology |
| Institute of Microbial Technology, CSIR, India | Ph.D. | 02/14 | Structural Biology and Thermodynamics Structural |
| Columbia University, New York, NY | Postdoctoral | 02/14 | Biology, Biochemistry, Biophysics |

**A. Personal Statement**

The dream goal of my research interest is to develop and combine the knowledge of inextricably linked crystallography and Cryo-EM to facilitate the structure determination of biological molecular membrane protein and assign them with native compositional variation in working architecture. I firmly believe that Cryo-EM and Crystallography can be studied together to get insight into understanding of mechanistic insight on how diverse molecular interactions guide the intricate dynamic process of selectivity and permeation through the mammalian ion channels.

The post-doctoral work involves structure elucidation of the Transient receptor potential (TRP) channels that constitute a large and functionally diverse family of cation conducting channel proteins, which are considered as polymodal cell sensors, implicated in many physiological functions ranging from pure sensory functions such as nociception, taste transduction, thermal sensation, touch, vision, over motor functions such as muscle contraction, vaso-motor control, to homeostatic functions such as Ca2+ and Mg2+ reabsorption and osmoregulation. The malfunctioning of the members of this intriguing ion channel family are highlighted in wide range of pathophysiological and therapeutic conditions. We have solved the first crystal structure of TRPV6 and establish the foundation for the calcium permeation. This work has been published in Nature article, where I am being the co-first author on the paper. In addition, I am lucky enough to have opportunity to work on the AMPA receptor in Sobolevksy's lab. This part of my work elucidates the structural bases of AMPA receptor noncompetitive inhibition by antiepileptic drugs. AMPA-subtype ionotropic glutamate receptors (iGluRs), which mediate the majority of excitatory neurotransmission, and consequently their malfunction is involved in devastating disease such as epileptogenesis and stroke and ischemia. Therefore, dissecting out the molecular mechanisms of their regulation would help in the design of safer and more effective drugs. In this context we have discovered the novel binding site for the noncompetitive inhibitor binding on AMPA receptor that provides important template for finding new therapies to fight epilepsy and other excitatory neurotransmission-related diseases.

During my doctoral studies, I have gained practical working experience of structural (MR, S-SAD, SAD) , Biophysical (ITC, BioCore, Analytical ultra-centrifuge, Fluorescence spectroscopy) expertise to dissect out the mechanism of Protein-DNA, Protein-Ligand, Protein-Peptide interaction and role of ligand binding on the assembly state of protein Fad35R. I have solved the first structure of Fad35R, a TetR type transcription regulator by SAD phasing to 3.4Å (PDB ID: 4G12), which reveal for the first, time formation of alternative dimer through N-terminal DNA binding domain and its role in oligomerization. Beside this, i am lucky enough to get the rare crystallographic snapshot of structural view of strerio-chemical feature of Dug1p di-peptidase (PDB ID: 4G1P) active site in complex with the cleaved product bound di-peptide. My work on cysteine synthase complex(CSC), with a series of structural snapshot of enzyme-inhibitor (PDB ID: 4LI3), enzyme-substrate (PDB ID: 4MII) in pre-reactive form, enzyme-reaction intermediate form (PDB ID: 4LHG), ternary enzyme-inhibitor-substrate(PDB ID: 4MIL) and tetra-nary enzyme-substrate-inhibitor-reaction-intermediate (PDB ID:4MII) reveals a novel mechanism of competitive inhibition between inhibitor and substrate for a same active site in CysK.

**B. Positions and Honors**

**Positions and Employment**

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| 2002-2005 | Bachelor of Science (Zoology Hons.), University of Delhi, India |
| 2006-2008 | Master of Science, Biotechnology, Indian Institute of Technology, Roorkee, India |
| 2009-2014 | Doctoral Research Fellow, Protein Science and Engineering Dept. Institute of Microbial Technology, CSIR, India |
| 2014-present | Post-doctoral Research Fellow, Dept of Biochemistry and Molecular Biophysics, Columbia University, New York, NY. |

**Honors**

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| 2009 | Awarded Junior Research fellowship and Senior Research Fellowship from February. 2009-2014 by Council for Scientific and Industrial Research (CSIR), Govt. of India. |
| 2009 | Qualified CSIR NET JRF (National Eligibility Test for Lectureship/Junior research fellowship), conducted jointly by the Council of Scientific and Industrial Research (CSIR) and University Grants Commission (UGC), India. |
| 2008 | Qualified GATE in February 2008 conducted by IITs ( Indian institute of technology) and IISc (Indian institute of science) Bangalore .Fellowship awarded during the Master's program In Biotechnology from IITR from 2006-2008. |
| 2008 | Qualified JNU-Ph.D-SBT (School of Biotechnology) Fellowship for Junior Research Fellowship |
| 2008 | Qualified JNU-Ph.D-SLS (School of Life Sciences) Fellowship for Junior Research Fellowship |
| 2006 | Qualified National Scholarship of Joint Admission Test to M.Sc (JAM) for admission to M.Sc |

**C. Peer-reviewed Publications**

1. **Singh, A. K***., McGoldrick, L. L*., Twomey, E. C., and Sobolevsky, A. I. (2018) Structure and gating mechanism of the transient receptor potential channel TRPV3." ***Nature Structural & Molecular Biology***. (Featured as NSMB cover Page, and F1000 article)
2. **Singh, A. K***., McGoldrick, L. L*., and Sobolevsky, A. I. (2018) Mechanism of calmodulin inactivation of the calcium selective TRP channel TRPV6." ***Science Advances*** **4**(8).
3. **Singh, A. K***., Saotome, K*., McGoldrick, L. L., and Sobolevsky, A. I. (2018) Structural bases of TRP channel TRPV6 allosteric modulation by 2-APB. ***Nat Commun*** **9**, 2465
4. **Singh, A. K**., McGoldrick, L. L., Saotome, K., and Sobolevsky, A. I. (2018) X-ray crystallography of TRP channels. ***Channels (Austin)*** **12**, 137-152
5. McGoldrick, L. L*., **Singh, A. K***., Saotome, K., Yelshanskaya, M. V., Twomey, E. C., Grassucci, R. A., and Sobolevsky, A. I. (2018) Opening of the human epithelial calcium channel TRPV6. ***Nature*** **553**, 233-237
6. **Singh, A. K***., Saotome, K*., and Sobolevsky, A. I. (2017) Swapping of transmembrane domains in the epithelial calcium channel TRPV6. ***Sci Rep*** **7**, 10669
7. **Singh, A. K***., Ekka, M. K*., Kaushik, A*., Pandya, V., Singh, R. P., Banerjee, S., Mittal, M., Singh, V., and Kumaran, S. (2017) Substrate-Induced Facilitated Dissociation of the Competitive Inhibitor from the Active Site of O-Acetyl Serine Sulfhydrylase Reveals a Competitive-Allostery Mechanism. ***Biochemistry*** **56**, 5011-5025
8. Saotome, K., **Singh, A. K**., and Sobolevsky, A. I. (2017) Determining the Crystal Structure of TRPV6. in ***Calcium Entry Channels in Non-Excitable Cells*****,** CRC Press. pp 275-292
9. Mittal, M., **Singh, A. K**., and Kumaran, S. (2017) Structural and biochemical characterization of ligand recognition by CysB, the master regulator of sulfate metabolism. ***Biochimie*** **142**, 112-124
10. Yelshanskaya, M. V., **Singh, A. K**., Sampson, J. M., Narangoda, C., Kurnikova, M., and Sobolevsky, A. I. (2016) Structural Bases of Noncompetitive Inhibition of AMPA-Subtype Ionotropic Glutamate Receptors by Antiepileptic Drugs. ***Neuron*** **91**, 1305-1315
11. Yelshanskaya, M. V., Saotome, K., **Singh, A. K.**, and Sobolevsky, A. I. (2016) Probing Intersubunit Interfaces in AMPA-subtype Ionotropic Glutamate Receptors. *Sci Rep* **6**, 19082
12. Saotome, K*., **Singh, A. K***., Yelshanskaya, M. V., and Sobolevsky, A. I. (2016) Crystal structure of the epithelial calcium channel TRPV6. ***Nature*** **534**, 506-511
13. **Singh, A. K***., Manjasetty, B*., Balasubramani, G. L., Koul, S., Kaushik, A., Ekka, M. K., Singh, V., and Kumaran, S. (2015) Crystal Structure of Fad35R from Mycobacterium tuberculosis H37Rv in the Apo-State. ***PLoS One*** **10**, e0124333
14. **Singh, A. K***., Singh, M*., Pandya, V. K., G, L. B., Singh, V., Ekka, M. K., Mittal, M., and Kumaran, S. (2014) Molecular basis of peptide recognition in metallopeptidase Dug1p from Saccharomyces cerevisiae. ***Biochemistry*** **53**, 7870-7883
15. Biswas, D., Pandya, V., **Singh, A. K**., Mondal, A. K., and Kumaran, S. (2012) Co-factor binding confers substrate specificity to xylose reductase from Debaryomyces hansenii. ***PLoS One*** **7**, e45525
16. Anand, S*., Singh, V*., **Singh, A. K***., Mittal, M*., Datt, M., Subramani, B., and Kumaran, S. (2012) Equilibrium binding and kinetic characterization of putative tetracycline repressor family transcription regulator Fad35R from Mycobacterium tuberculosis. ***FEBS J*** **279**, 3214-3228
17. Kaur, H., Datt, M., Ekka, M. K., Mittal, M., **Singh, A. K**., and Kumaran, S. (2011) Cys-Gly specific dipeptidase Dug1p from S. cerevisiae binds promiscuously to di-, tri-, and tetra-peptides: Peptide-protein interaction, homology modeling, and activity studies reveal a latent promiscuity in substrate recognition. ***Biochimie*** **93**, 175-186
18. **Singh A.K***., McGoldrick, L.L*., and Sobolevsky, A.I.(2018) Expression, purification and crystallization of the transient receptor potential channel TRPV6. ***Methods in Molecular Biology*** (Book chapter accepted).

*Authors contributed equally