Kabir H Biswas

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Education

Degree	Year	Grades/Awards	Institute/University
Doctor of Philosophy (PhD)	2011	**Mrs. C V Hanumantha Rao Medal** for best PhD thesis	Department of Molecular Reproduction, Development and Genetics, Indian Institute of Science, Bengaluru, Karnataka, India
Master of Science (MS)	2007	CGPA: 6.5 (out of 8)	Division of Biological Sciences, Indian Institute of Science, Bengaluru, Karnataka, India
Bachelor of Science (BSc)	2004	Marks: 76.7%	Department of Biochemistry, Aligarh Muslim University, Aligarh, Uttar Pradesh, India

Employments

Jun 2016 – Present: **Senior Research Fellow**, School of Materials Science and Engineering, Nanyang Technological University, Singapore

Jan 2016 – Jun 207: **Senior Research Fellow**, Mechanobiology Institute, National University of Singapore, Singapore

Dec 2011 - Dec 2015: **Research Fellow**, Mechanobiology Institute, National University of Singapore, Singapore

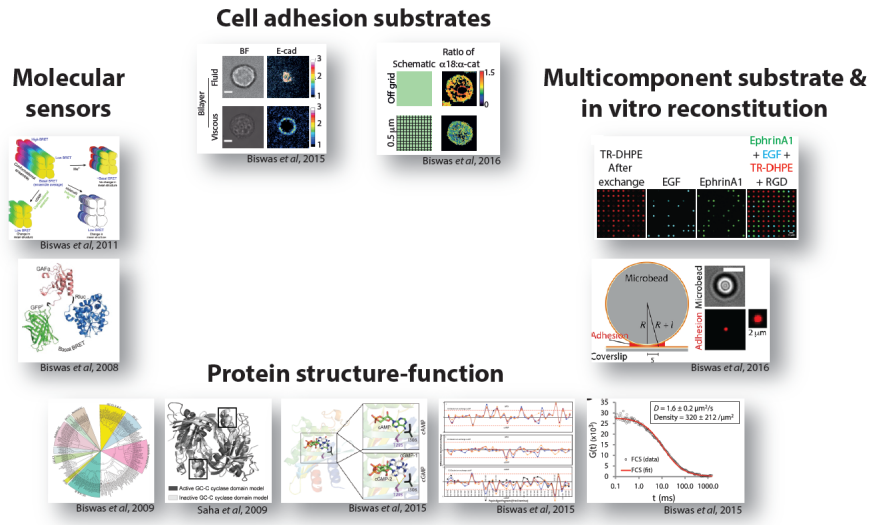
Oct 2011 - Dec 2011: **Senior Research Associate**, Department of Molecular Reproduction, Development and Genetics, Indian Institute of Science, Bangalore, Karnataka, India

Aug 2011 - Oct 2011: **Junior Research Associate**, Department of Molecular Reproduction, Development and Genetics, Indian Institute of Science, Bangalore, Karnataka, India

Research accomplishments

As a Research Fellow at the Mechanobiology Institute (MBI), I have been involved in engineering micro- and nano-patterned supported lipid bilayer substrates for studying biophysical mechanisms of cell-cell adhesion formation, and mechanical signal transduction. Cell-cell adhesions are mediated by E-cadherin in the epithelial tissue, and are required for development in humans. A loss of cell-cell adhesion is associated with cancer development and metastasis. Given the significance of cell-cell adhesion in tissue homeostasis, a number of efforts have been made towards reconstituting it in a hybrid format using a synthetic membrane and a live cell to mimic cell-cell adhesion *in vivo*. However, unlike other reconstitution experiments such as those involving the T-cell receptor or the EphA2 receptor tyrosine kinase, it turned out to be non-trivial. Our ability to successfully reconstitute E-cadherin adhesion is in itself a significant step towards understanding the fundamental features of cell-cell adhesion [Biswas *et al*, *Proc. Natl. Acad. Sci. U. S. A.*, 2015]. These studies showed that E-cadherin clustering is an active, actomyosin tension-dependent process that is mediated by filopodia retraction, and

requires a low mobility bilayer. The later pointed to the presence of a step of nucleation, a property unique to E-cadherin. I envision that this finding will be crucial in developing a functional E-cadherin-based microenvironment.



The hybrid live cell-supported lipid bilayer further proved valuable in understanding and controlling the mechanical signaling from E-cadherin adhesions. Mechanical signaling from cadherin adhesions has been primarily attributed to the force-dependent conformational change in α-catenin, a key adaptor protein associated with cadherin adhesions, from a 'closed' to an 'open' state. Our studies showed that α-catenin is activated during the nucleation and micron-scale clustering of E-cadherin [Biswas *et al*, *Biophys J*, 2016]. Interestingly, once activated, α-catenin is sustained in the active conformation in the absence of cellular actomyosin tension. This finding was contrary to what was believed in the field, and suggests that α-catenin may not function as a versatile mechanosensor at cadherin junctions.

In addition to these, I have developed two simple yet powerful techniques to investigate membrane protein interaction. The first one relates to determining intermembrane receptor-ligand complex dimension (few 10s of nm) using a regular, epi-fluorescence microscope [Biswas & Groves, *Langmuir*, 2016]. Intermembrane receptor-ligand complex dimension is an important dictator of protein segregation, and regulation of signaling at cell-cell junctions. Measurement of the size of minimal adhesions reconstituted between a planar and a microbead supported lipid bilayer followed by simple geometrical transformation proved sufficient to determine the intermembrane receptor-ligand dimension with less than a nanometer precision. The second technique relates to the display of spatially segregated, multiple, bilayer-bound ligands for studying receptor signaling crosstalk at cellular interfaces. This was achieved using micropatterned substrates and stochastic lipid exchange between micropatterned bilayers on a planar substrate and microbead borne bilayers [Biswas & Groves, *USPTO application number 62/463769*].

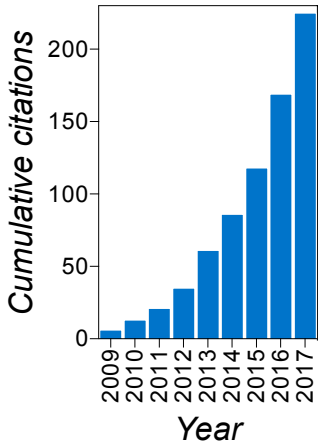
As a graduate student at the Indian Institute of Science, I studied allosteric regulation of proteins in the cyclic guanosine monophosphate (cGMP) signal transduction pathway that is implicated in processes such as visual signal transduction and smooth muscle contraction. These signals are initiated by the activation of guanylyl cyclases (GCs), enzymes that generate cGMP, and are terminated by the activation of phosphodiesterases (PDEs), enzymes that hydrolyze cGMP. In order to precisely and sensitively detect changes in the intracellular levels of cGMP, I developed a genetically encoded, Bioluminescence Resonance Energy Transfer (BRET)-based sensor using a cGMP-binding domain protein [Biswas *et al*, *Biochemistry*, 2008]. A large-scale bioinformatic analysis of all GC found in the database revealed that these enzymes could be regulated by multiple mechanisms via associated domains including the highly conserved linker region between the cyclase and the kinase homology domains [Biswas *et al*, *J Mol Evol*, 2009a]. Understanding gained from this study was then utilized in providing a molecular basis for linker region-mediated regulation of the enzymatic activity [Saha *et al*, *J Biol Chem*, 2009b], and familial diarrhea causing mutation [Fiskerstrand *et al*, *N. Engl. J. Med*, 2012] in the receptor guanylyl cyclase C (GC-C).

Following this, I investigated the mechanism of allosteric regulation in the cGMP-binding, cGMP-specific phosphodiesterase 5 (PDE5), which has been targeted using specific inhibitors such as sildenafil (Viagra™) for the treatment of erectile dysfunction and pulmonary hypertension. PDE5 consists of N-terminal regulatory GAF domains and a C-terminal catalytic domain. Using highly sensitive, genetically encoded, BRET-based conformational sensors, we discovered novel and unexpected modes of allosteric regulation in PDE5 (in addition to recapitulating the known regulations) [Biswas & Visweswariah, *J Biol Chem*, 2011]. For instance, while sildenafil binding to the catalytic domain increased the affinity of the GAFa domain for cGMP, cGMP binding to the GAF domain failed to alter the affinity of the catalytic domain for sildenafil. More importantly, I discovered that the catalytic metal ion differentially regulates cGMP- and sildenafil-induced allosteric effects on PDE5. In addition, I have studied the mechanism of cyclic nucleotide discrimination by the regulatory GAF domains using hydrogen-deuterium exchange mass spectrometry [Biswas *et al*, *PeerJ*, 2015]. In this study, I detailed the differences in the structural change that are induced upon binding of cGMP and cAMP as well as show that the presence of a second GAF domain alters the binding dynamics of the GAF domain. I envisage that these insights will be highly valuable in further fine-tuning of PDE5 inhibition-based therapies.

Publications

Total number of citations: **225** (Source: Google Scholar)
h-index: **7** (Source: Google Scholar)

Citation report



[15] **Biswas KH★,** Groves JT★ Mechanical aspects of membrane receptor signaling at cell-cell junctions [invited chapter for the 'Physics of Biological Membranes' book] *[Accepted]*
★Co-corresponding author

[14] Vafaei, S, Tabaei SR, **Biswas KH,** Groves JT, Cho NJ Dynamic Cellular Interactions with Extracellular Matrix Triggered by Biomechanical Tuning of Low-Rigidity, Supported Lipid Membranes *Adv. Healthcare Mater. doi: 10.1002/adhm.201700243*

[13] **Biswas KH★**, Visweswariah SS★ Buffer NaCl concentration regulates *Renilla* luciferase activity and ligand-induced conformational changes in the BRET-based PDE5 sensor *Matters* doi: 10.19185/matters.201702000015
★Co-corresponding author

[12] **Biswas KH★**, Zaidel-bar R★ Early E-cadherin adhesion formation [Invited review] *Experimental Cell Research http://dx.doi.org/10.1016/j.yexcr.2017.02.037*
★Co-corresponding author

[11] **Biswas KH** Allosteric regulation of proteins: a historical perspective on the development of concepts and techniques *Resonance Journal of Science Education* **22**(1): 37-50

[10] **Biswas KH★**, Hartman KL, Zaidel-Bar R★, Groves JT★ (2016) Sustained α-catenin activation at E-cadherin junctions in the absence of mechanical force *Biophysical Journal* **111,** 1044-52
★Co-corresponding author
• Highlighted in/at:
i) Force bistability in adhesion switch, New & Notable by Dustin & Peel, *Biophysical Journal*
ii) Mechanobiology Institute, National University of Singapore, feature article
iii) Recommended at Faculty of 1000 (F1000Prime) by Prof. Vivian Tang

[9] **Biswas KH★** and Groves JT★ (2016) A microbead supported membrane fluorescence imaging assay reveals intermembrane receptor-ligand complex dimension with nanometer precision *Langmuir* **32**(26): 6775–80
★Co-corresponding author

[8] Yu C-h, Rafiq NBM, Cao F, Zhou Y, Krishnasamy A, **Biswas KH**, Ravasio A, Chen Z, Wang Y-H, Kawauchi K, Jones GE, Sheetz MP (2015) Integrin-beta3 clusters recruit clathrin-mediated endocytic machinery in the absence of traction force *Nature Communications* **6**: 8672

[7] **Biswas KH**[#], Hartman KL[#], Yu C-H, Harrison OJ, Song H, Smith AW, Huang WYC, Lin W-C, Guo Z, Padmanabhan A, Troyanovsky SM, Dustin ML, Shapiro L, Honig B, Zaidel-Bar R and Groves JT (2015) E-cadherin junction formation involves an active kinetic nucleation process *Proc Natl Acad Sci U S A* **112**(35): 10932-7

[#]These authors contributed equally to the work

- Highlighted in the Mechanobiology Institute, National University of Singapore, feature article

[6] **Biswas KH**[⋆], Badireddy S, Abinaya Rajendran, Anand GS and Visweswariah SS[⋆] (2015) Distinct binding modes and structural changes induced by cAMP and cGMP in the GAF domain of *Anabaena* adenylyl cyclase, CyaB2 *PeerJ* **3**:e882

[⋆]Co-corresponding author

[5] Fiskerstrand T, Arshad N, Haukanes BI, Tronstad RR, Pham KDC, Johansson S, Håvik B, Tønder SL, Levy SE, Brackman D, Boman H, **Biswas KH**, Apold J, Hovdenak N, Visweswariah SS and Knappskog PM (2012) Familial Diarrhea Syndrome Caused by an Activating GUCY2C Mutation *N Engl J Med* **366**(17): 1586-95

- Highlighted in/at:
  - i) Familial diarrhea syndrome, Research Highlights by Kyle Vogan, *Nature Genetics*
  - ii) Genetic mutation found in familial chronic diarrhea syndrome, News article in Medical Press
  - iii) Chromosome 12 Mutation Linked to Familial Diarrhea, article in DoctorsLounge
  - iv) GUCY2C gene mutation leads to familial diarrhea syndrome, article in News Medical
  - v) Gene May Play Role in Frequent Diarrhea, article in MegPage Today

[4] **Biswas KH** and Visweswariah SS (2011) Distinct Allostery Induced in the Cyclic GMP-binding, Cyclic GMP-specific Phosphodiesterase (PDE5) by Cyclic GMP, Sildenafil, and Metal Ions *J Biol Chem* **286**(10): 8545-54

[3] Saha S, **Biswas KH**, Kondapalli C, Isloor N and Visweswariah SS (2009) The linker region in receptor guanylyl cyclases is a key regulatory module: mutational analysis of guanylyl cyclase C *J Biol Chem* **284**(40): 27135-45

[2] **Biswas KH**, Shenoy AR, Dutta A and Visweswariah SS (2009) The evolution of guanylyl cyclases as multidomain proteins: conserved features of kinase-cyclase domain fusions *J Mol Evol* **68**(6): 587-602

- Cover page article

[1] **Biswas KH**, Sopory S and Visweswariah SS (2008) The GAF domain of the cGMP-Binding, cGMP-specific phosphodiesterase (PDE5) is a sensor and a sink for cGMP *Biochemistry* **47**(11): 3534-43

Manuscripts under various stages of publication/preparation

■ Submitted

[16] **Biswas KH**[⋆], Zhongwen C, Dubey AK, Oh D, Groves JT[⋆] Stochastic lipid delivery-enabled multicomponent membrane substrate for live cell studies *[Submitted]*

[⋆]Co-corresponding author

[17] Zhongwen C, Oh D, **Biswas KH**, Yu C-H, Zaidel-Bar R, Groves JT Probing EphA2 signalling in the context of integrin adhesion using a hybrid of fluid lipid bilayers and immobilized RGD patterns *[Submitted]*

■ Under preparation

[18] Zhongwen C, Oh D, **Biswas KH**, Groves JT Multi-component, micropatterned substrates for investigating cell signaling *[Under preparation]*

[19] **Biswas KH**[⋆], Zhongwen C, Groves JT[⋆] Spatial regulation of EphrinA1-EphA2 clustering by E-cadherin adhesion *[Under preparation]*

[⋆]Co-corresponding author

[20] Oh D, Zhongwen C, **Biswas KH,** Groves JT Competition for Grb2 recruitment between EphA2 and EGFR during ligand activation *[Under preparation]*

[21] **Biswas KH*,** Hara Y, Toyoma Y**,** Zaidel-bar R, Groves JT* Role of actomyosin tension in the regulation of α-catenin dynamics at E-cadherin adhesion *[Under preparation]*
***Co-corresponding author**

[22] **Biswas KH*,** Dubey AK, Zhongwen C, Groves JT* Multicomponent RGD peptide substrate with differential integrin adhesion *[Under preparation]*
***Co-corresponding author**

Patents

[1] **Biswas KH** and Groves JT (2016) Micropatterned substrate displaying multiple, spatially segregated, bilayer-anchored and fixed ligands for live cell studies developed using stochastic lipid delivery process *[USPTO application number 62/463769]*

Teaching experience

Teaching

[2] **MBI Practical Molecular Biology Course** – Conceived, designed and conducted classes for the practical course at the Mechanobiology Institute, National University of Singapore

[1] **Special Topics in Mechanobiology course** at the National University of Singapore - teaching assistant on the topic of Cell-Cell & Cell-Matrix Interaction

Interns/rotation students trained

[7] Alok Kumar Dubey, Mechanobiology Institute, National University of Singapore, Singapore (2015)

[6] Kennedy Nguyen, Mechanobiology Institute, National University of Singapore, Singapore (2014)

[5] Azita Gorzi, Mechanobiology Institute, National University of Singapore, Singapore (2013)

[4] Yang Yang, Mechanobiology Institute, National University of Singapore, Singapore (2013)

[3] Chen Zhongwen, Mechanobiology Institute, National University of Singapore, Singapore (2013)

[2] Anmol Tiwari, Molecular Reproduction, Development and Genetics, Indian Institute of Science, India (2009)

[1] Gurudutta Panda, Molecular Reproduction, Development and Genetics, Indian Institute of Science, India (2008)

Awards & Honors

[9] **Yamaguchi Medal**, Asian-Pacific Association for Biomechanics, Nogoya University, Japan (2017)

[8] Senior Research Fellowship, Mechanobiology Institute, National University of Singapore, Singapore (2016)

[7] **Mrs. C V Hanumantha Rao Medal**, Indian Institute of Science, Bangalore, India (2012)

[6] Research Fellowship, Mechanobiology Institute, National University of Singapore, Singapore (2011)

[5] International Travel Support Grant, Department of Science and Technology (DST), Ministry of Science and Technology, Government of India (2010)

[4] International Travel Grant, Council of Scientific and Industrial Research (CSIR), Government of India (2010)

[3] **Senior Research Fellowship**, Council of Scientific and Industrial Research (CSIR), Government of India (2009)

[2] **Junior Research Fellowship**, Council of Scientific and Industrial Research (CSIR), Government of India (2007)

[1] **Integrated PhD Fellowship**, Indian Institute of Science, Bangalore, India (2004)

Invited Talks

[14] "Multicomponent supported membrane microarray fabrication by stochastic lipid delivery", **Discussion Meeting on Understanding Structure, Function and Dynamics of Biomembranes)**, Indian Institute of Science, Bangalore, India (2017)

[13] "Receptor nucleation and clustering in cellular adhesion & mechanical signaling", **XXVI Congress of the International Society of Biomechanics-9th Asian-Pacific Conference on Biomechanics (AP Biomech 2017)**, Brisbane, Australia (2017)

[12] "Receptor nucleation and clustering in cellular adhesion & mechanical signaling", **Biophysical Society 61st Annual Meeting**, New Orleans, Louisiana (2017)

[11] "Mechanism of E-cadherin adhesion and mechanical signal transduction", 2016 Berkeley Symposium on Membrane Signaling, Mammoth Lakes, California (2016)

[10] "E-cadherin junction formation involves an active nucleation process", Biophysics of Proteins at surfaces: assembly, activation, signaling (**Biophysical Society thematic meeting**), Complutense University of Madrid, Madrid, Spain (2015)

[9] "E-cadherin junction formation involves an active nucleation process", 3D Lab Exchange Symposium - Interaction of Nano-Biotechnology, Chemical Biology and Medical Sciences, Mechanobiology Institute, National University of Singapore, Singapore (2015)

[8] "A nucleation-dependent large-scale assembly of E-cadherin clusters regulate α-catenin conformation", Department of Biological Sciences, Indian Institute of Science Education and Research (IISER) – Kolkata, Kolkata, West Bengal, India (2015)

[7] "Learning from our postdocs", an informal talk and discussion session organized by the MBI graduate students association (MBI Graduate Seminars), Mechanobiology Institute, National University of Singapore, Singapore (2014)

[6] "E-cadherin junction formation involves an active nucleation process", **Gordon Research Conference** on Signaling by Adhesion Receptors, Bates College, Lewinston, Maine, USA (2014)

[5] "Reduced mobility of E-cadherin is necessary for efficient cell-cell junction formation", Bioengineering Seminars, Indian Institute of Science, Bangalore, Karnataka, India (2013)

[4] "Distinct allostery induced by different ligands in multidomain PDE5", Science & Communication Workshop, The Wellcome Trust/DBT India Alliance, Hyderabad, Andhra Pradesh, India (2010)

[3] "Molecular mechanics - Distinct structural states of PDE5", Advanced School on Living Mechanics – Cells, Tissues and Organisms, National Centre for Biological Science, Bangalore, Karnataka, India (2010)

[2] "Allosteric regulation of cGMP binding, cGMP specific PDE (PDE5) as monitored by Bioluminescence Resonance Energy Transfer ($BRET^2$)", **Gordon Research Seminar** on "Biomolecular Interactions and Methods", Hotel Galvez, Galveston, Texas, USA (2010)

[1] "A novel $BRET^2$-based cGMP sensor", 30th All India Cell Biology Conference & Symposium - Molecules to Compartments: Cross-Talks and Networks, Indian Society of Cell Biology, Department of Zoology, University of Delhi, New Delhi, India (2007)

Conferences & Workshops

[17] Poster presentation titled “A microbead supported membrane-based fluorescence imaging assay reveals intermembrane receptor-ligand complex dimension with nanometer precision”, Joint symposium on bioimaging between Singapore and bioimaging society of Japan, National University of Singapore, Singapore (2017)

[16] Poster presentation titled “Sustained α-catenin activation at E-cadherin junctions in the absence of mechanical force”, Biophysical Society thematic meeting – Mechanobiology of Disease, National University of Singapore, Singapore (2016)

[15] Poster presentation titled “Large-scale assembly of E-cadherin clusters regulates α-catenin conformation at adherens junctions”, Annual meeting of the American Society for Cell Biology, San Diego, California, USA (2015)

[14] Poster presentation titled “Dissecting cell signaling using supported lipid membranes”, TethMem 2015 Tethered Membrane 2015 Conference in Singapore, Nanyang Technical University, Singapore (2015)

[13] Poster presentation titled “E-cadherin junction formation involves an active nucleation process”, Biophysics of Proteins at surfaces: assembly, activation, signaling**,** Complutense University of Madrid, Madrid, Spain (2015)

[12] Poster presentation titled “E-cadherin junction formation involves an active nucleation process”, 3D Lab Exchange Symposium - Interaction of Nano-Biotechnology, Chemical Biology and Medical Sciences, Mechanobiology Institute, National University of Singapore, Singapore (2015)

[11] Poster presentation titled “E-cadherin junction formation involves an active nucleation process”, Biomembrane Days 2014, Max Planck Institute of Colloids and Interfaces, Berlin, Germany (2014)

[10] Poster presentation titled “E-cadherin junction formation involves an active nucleation process”, Gordon Research Seminar and Gordon Research Conference on Signaling by Adhesion Receptors, Bates College, Lewinston, Maine, USA (2014)

[9] Poster presentation titled “Lateral immobilization of E-cadherin is necessary for efficient cell-cell junction formation”, 7th Asia-Pacific Organization for Cell Biology Congress and ASCB Workshops, Matrix, Biopolis, Singapore (2014)

[8] Poster presentation titled “Reduced mobility of E-cadherin is necessary for efficient clustering and junction formation on supported lipid bilayers”, Joint Weizmann/MBI Mechanobiology Conference: Dynamic Architecture of Cells and Tissues, The Fullerton Hotel, Singapore (2013)

[7] Poster presentation titled “Studying E-cadherin-mediated cell-cell junction formation using supported lipid bilayers”, Biophysical Society - Mechanobiology of Proteins and Cells, Mount Desert Island Biological Laboratory, Salisbury Cove, Maine, USA (2013)

[6] Poster presentation titled “Studying E-cadherin-mediated cell-cell junction formation using supported lipid bilayers”, Annual meeting of the American Society for Cell Biology, San Francisco, California, USA (2012)

[5] Science & Communication Workshop, The Wellcome Trust/DBT India Alliance, Hyderabad, Andhra Pradesh, India (2010)

[4] Advanced School on Living Mechanics – Cells, Tissues and Organisms, National Centre for Biological Science, Bangalore, Karnataka, India (2010)

[3] Poster presentation titled “Allosteric regulation of cGMP binding, cGMP specific PDE (PDE5) as monitored by Bioluminescence Resonance Energy Transfer (BRET^2)”, Gordon Research Conference on “Biomolecular Interactions and Methods**”**, Hotel Galvez, Galveston, Texas, USA (2010)

[2] Poster presentation titled “GAFa domain of PDE5 is a sensor and sink for cGMP”, Integrating Physics, Chemistry, Mathematics and Biology to Understand Living Systems (IPCMB), Bose Institute, Kolkata, West Bengal, India (2008)

[1] Drug Design Workshop, Satish Dhawan Auditorium, CSIC Building, Indian Institute of Science, Bangalore, Karnataka, India (2007)

Selected services

- Reviewed research articles for a number of international journals
- Served as the **safety lead** for the Groves lab at MBI and actively participated in safety meetings
- Helped organize the Berkeley-Singapore symposium
- Actively participated in meetings for career advancement of students and research fellows
- Hosted school kids from India and introduced them to various facets of MBI
- Hosted Swedish delegation touring MBI
- Successful IORC application for grant release
- Generated an online database of materials available in the laboratory
- Organized scientific events as a member of the Science Awareness Society, Malda, West Bengal, India