BIOGRAPHICAL SKETCH

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NAME: Biswas, Mayukh

eRA COMMONS USER NAME (credential, e.g., agency login): M.BISWAS

POSITION TITLE: Assistant Professor

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	Start Date MM/YYYY	Completion Date	FIELD OF STUDY
St. Xavier's College (Autonomous), Kolkata, West Bengal, India Under University of Calcutta	Integrated M.Sc.	07/2008	06/2013	Biotechnology
CSIR – Indian Institute of Chemical Biology, Kolkata, West Bengal, India Jadavpur University	Ph.D.	07/2013	10/2020	Cancer epigenetics, Biochemistry, Molecular and Cellular Biology
Institute for Cancer Genetics, Columbia University in the City of New York, USA	Postdoctoral Research	10/2020	04/2022	Molecular Oncology
Department of Genetics and Development, Columbia University in the City of New York, USA	Postdoctoral Research	05/2022	06/2022	Chromatin Biology & Molecular Epigenetics

A. Personal Statement

My long-standing scientific interest is to understand the epigenetic plasticity associated with tumor initiation and progression, specifically in the context of hematologic malignancies. My academic training and research experience have provided me with a strong background in Epigenetics, Molecular and Cellular Biology and Biochemistry. During my PhD I have worked on epigenetic regulation of hematopoietic stem cells in acute myeloid leukemia under the supervision of Dr. Amitava Sengupta at CSIR - Indian Institute of Chemical Biology, Kolkata, one of the top-notch research institutes in India. My study focused on elucidating and understanding the cellular and molecular mechanisms by which NuRD and SWI/SNF complexes regulate the epigenetic landscape of MDS and AML. In this project, I leveraged the analysis of primary patient samples to demonstrate a previously unrecognized major role of NuRD-mediated chromatin remodeling in AML and demonstrated that human myeloid leukemia frequently show loss of expression of specific NuRD subunits.
In addition, I demonstrated a direct interaction between NuRD and the histone demethylase KDM6A. This interaction in turn amplifies Rac GTPase-GEF *DOCK*s expression affecting leukemia cell trafficking and survival. These studies constituted the core of my thesis work "Nucleosome Remodeler Plasticity in Leukemic Hematopoiesis" at Jadavpur University, which I successfully defended in October 2020. In a separate project I evaluated the role of SWI/SNF in AML and showed that SMARCB1 deficiency associates with nucleation of an altered SWI/SNF complex in human primary AML cells. In this context, loss of SMARCB1 induced recruitment of SWI/SNF and associated HATs to target GEFs for Rac GTPase activation and promoted AML cell migration. Collectively, these findings highlighted tumor suppressor role of SMARCB1 and illustrated SWI/SNF function in maintaining an oncogenic gene expression program in AML.

I joined the laboratory of Dr. Adolfo Ferrando at the Institute for Cancer Genetics at Columbia University as a staff associate in November 2019 for my postdoctoral studies. The research program in the Ferrando lab integrates genomic profiling, transcriptomics, biochemical assays, and animal models to identify and mechanistically dissect driver pathways involved in acute lymphoblastic leukemia (ALL) malignant proliferation and survival. Since then, I have gained advanced experimental skills in biochemistry, epigenetics, cellular and molecular biology and in the design and analysis of genome-wide CRISPR-Cas9 knockout screens. Moreover, I have expanded my research portfolio embracing the isolation of multiprotein complexes, Cut&Run, Cut&Tag, CRISPR gene editing assays and leveraged these to functionally dissect the role of oncogenic and tumor suppressor transcription factors, signaling molecules and epigenetic regulators recurrently mutated in ALL. Previously the Ferrando lab identified Plant Homeodomain Finger 6 (*PHF6*) as a new X-linked tumor suppressor gene and established a primary role for *PHF6* mutations in the initiation of T-ALL. Following on this, we have identified that PHF6 engages with multiple nucleosome remodeling protein complexes, including the NuRD, SWI/SNF and ISWI factors, the replication machinery and DNA repair proteins. In this study we specifically interrogated the role of PHF6 in single DNA breaks, leading to the identification of PHF6 as an important regulator of genomic stability at fragile sites. In another study we have investigated the role of *PHF6* in HSC aging. We showed that *Phf6* ablation in aged adult mice reversed immunophenotypic, transcriptional and functional hallmarks of HSC aging as observed by decrease accumulation of immunophenotypically-defined HSCs, reduced myeloid bias and increased hematopoietic reconstitution capacity with preservation of lymphoid differentiation potential in old *Phf6* knockout HSCs. In a separate study we are currently investigating the molecular mechanisms behind the tumor suppressor activity of PHF6 in T-ALL. Briefly, we have observed that PHF6 recruits NuRD to chromatin and maintains deposition of various histone marks. Concomitantly, loss of PHF6 leads to a global loss of NuRD occupancy and histone modifications followed by loss of PRC2 mediated repression of target genes. The ultimate goal of these studies is to identify specific epigenetic mechanisms and collateral vulnerabilities associated with the loss of PHF6 in T-ALL.

B. Positions and Honors

Positions and Employment

07/2022-Present	Assistant Professor, Institute of Health Sciences, Presidency University, Kolkata, West Bengal, India
05/2022-06/2022	Postdoctoral Research Scientist, Department of Genetics and Development, Columbia University, New York, NY, United States
10/2020-04/2022	Postdoctoral Research Scientist, Institute for Cancer Genetics, Columbia University, New York, NY, United States
11/2019-09/2020	Staff Associate, Institute for Cancer Genetics, Columbia University, New York, NY, United States
07/2013-10/2019	PhD student, CSIR – Indian Institute of Chemical Biology, Department of Cancer Biology and Inflammatory Disorder Division, Kolkata, West Bengal, India
07/2008-06/2013	Integrated Master student, St. Xavier's College (Autonomous), Kolkata, Department of Biotechnology, West Bengal, India

Honors and awards

2017	ASH Abstract Achievement Award at the 59th ASH Annual Meeting and Exposition (2017) by American Society of Hematology.

2013 Graduate Aptitude Test in Engineering (GATE) in Biotechnology (GATE-2013), organized by Indian Institute of Technology Bombay (IIT Bombay).

2012 UGC Fellowship for pursuing PhD after qualifying National Eligibility Test (NET- 2012 December) conducted jointly by Council of Scientific and Industrial Research (CSIR) and University Grants Commission (UGC), Government of India.

C. Contributions to Science

Elucidation of the role of Chromatin Remodeling complexes in regulation of the epigenetic landscape in myeloid malignancies

Epigenetic reprogramming is implicated in tumor heterogeneity and oncogenic transformation. NuRD and SWI/SNF are major classes of ATP-dependent chromatin remodeling complexes present in the mammalian cells, regulating cell-fate commitment and transcriptional architecture and has important roles to play in development, genome integrity and cell cycle progression. Here we elucidated the role of NuRD and SWI/SNF in the pathogenesis of AML. In this project we have shown that in human primary AML cells, specific subunits of the NuRD complex are not expressed. NuRD complex interacts with the histone demethylase KDM6A resulting in increased Rac GTPase-GEF *DOCK*s expression, leukemia cell trafficking and survival. These results unveiled a novel link between chromatin remodelers NuRD and KDM6A in AML and pointed to DOCK inhibition as potential therapy in this disease (*FASEB J* 2019). In another study we illustrated that human primary AML cells exhibit near complete loss of SMARCB1. This led to an increased recruitment of SWI/SNF and associated HATs to target loci, thereby promoting H3K27Ac and gene expression. Together, SMARCB1 deficiency induced GEFs for Rac GTPase activation and augmented AML cell migration and survival. Collectively, these findings highlight tumor suppressor role of SMARCB1 and illustrate SWI/SNF function in maintaining an oncogenic gene expression program in AML (*Mol Cancer Res* 2018). In a separate study we profiled the gene expression signature of SWI/SNF complex in the HSC compartment of a cohort of patients diagnosed with Aplastic Anemia (AA). Our analysis identified a significant loss of the *SWI/SNF* core component *SMARCC1*, along with *ARID1B*, *ACTL6A*, and *SMARCD1*, in human AA BM $CD34^+$ HSCs and HSPCs compared to normal counterpart. *PBRM1*, *BRD7* and *SMARCA2* expression were significantly upregulated in both untreated and follow-up AA patients. These findings illustrate for the first time SWI/SNF subunit expression heterogeneity in human AA HSPCs (*Exp Hematol* 2018).

- **Biswas M**[1], Chatterjee SS[1], Boila LD, Chakraborty S, Banerjee D, Sengupta A. MBD3/NuRD loss participates with KDM6A program to promote DOCK5/8 expression and Rac GTPase activation in human acute myeloid leukemia. ***FASEB J***. 2019 Apr;33(4):5268-5286 ([1]Co-first authorship).

- Chatterjee SS[1], **Biswas M**[1], Boila LD, Banerjee D, Sengupta A. SMARCB1 Deficiency Integrates Epigenetic Signals to Oncogenic Expression Program Maintenance in Human Acute Myeloid Leukemia. ***Mol Cancer Res***. 2018 May;16(5):791-804 ([1]Co-first authorship).

- Sinha S, Chatterjee SS, **Biswas M**, Nag A, Banerjee D, De R, Sengupta A. SWI/SNF Subunit Expression Heterogeneity in Human Aplastic Anemia Stem/Progenitors. ***Exp Hematol***. 2018 Jun;62:39-44.e2.

Determination of the role of PHF6 in coupling chromatin remodeling, replication dynamics and DNA repair

The Plant Homeodomain Finger 6 gene (*PHF6*) encodes a nucleolar and chromatin-associated leukemia tumor suppressor with proposed roles in transcription regulation. Somatic mutations in PHF6 are highly recurrent in T-cell acute lymphoblastic leukemia (T-ALL) and biphentypic T-myeloid leukemias, where they are characteristically early lesions in leukemia transformation. In addition, PHF6 loss can be found in patients with preleukemic clonal hematopoiesis in support of a role for this tumor suppressor in leukemia initiation and hematopoietic stem cell (HSC) function. However, the specific molecular mechanisms mediating PHF6 tumor suppressor activity remain to be established. In this study we have demonstrated that PHF6 engages multiple nucleosome remodeling protein complexes including NuRD, SWI/SNF and ISWI factors, the replication machinery and DNA repair proteins. Moreover, following replicative stress-induced DNA damage, PHF6 localizes

to sites of DNA injury and its loss impairs the resolution of DNA breaks with consequent accumulation of single- and double-stranded DNA lesions. We have illustrated that PHF6 specifically associates with difficult to replicate heterochromatin at satellite DNA regions enriched in H3K9me3 marks. Furthermore, PHF6 prevents unrestricted replication fork progression and single molecule locus-specific analyses identify PHF6 as an important regulator of genomic stability at fragile sites. These results extend our understanding of the molecular mechanisms controlling HSC homeostasis and leukemia transformation by placing PHF6 at the crossroads of chromatin remodeling, replicative fork dynamics and DNA repair.

- Alvarez S[1], Almeida ACS[1], Albero R, **Biswas M**, Barreto-Galvez A, Gunning TS, Shaikh A, Aparicio T, Wendorff A, Piovan E, Vlierberghe PV, Gygi S, Gautier J, Madireddy A, Ferrando AA. Functional mapping of PHF6 complexes in chromatin remodeling, replication dynamics and DNA repair. ***Blood***. 2022 Jun 9;139(23):3418-3429.

Investigation of the role of Phf6 in HSC Aging

In the hematopoietic system, aging is characterized by accumulation of dysfunctional HSCs, which progressively become myeloid biased in their differentiation potential. Epigenetic alterations and genotoxic stress associated with age has been proposed to alter the self-renewal and differentiation capacity of aged HSCs. However, the underlying mechanisms driving these changes and their specific role in the control of the HSC aging program remain rudimentarily understood. Here we corroborated that genetic inactivation of the *Phf6* gene antagonizes and effectively reverses age-associated HSC aging. Analysis of *Phf6* knockout HSCs from old mice by immunophenotypic profiling, single cell transcriptomics and transplantation assays exhibited markedly decreased accumulation of HSCs, reduced myeloid bias and increased hematopoietic reconstitution capacity with preservation of lymphoid differentiation potential. In parallel, ablation of *Phf6* in aged adult mice rewired the chromatin accessibility landscape and reversed immunophenotypic, transcriptional and functional hallmarks of HSC aging. These results identify *Phf*6 as an important epigenetic mediator of HSC aging, whose inactivation counters the functional deterioration of HSC activity associated with age.

- Wendorff AA[1], Quinn SA[1], Alvarez S, Brown JA, **Biswas M**, Gunning T, Palomero T, Ferrando AA. Epigenetic reversal of hematopoietic stem cell aging in *Phf6* knockout mice. ***Nature Aging***. 2022 Nov 10;2:1008-1023.

Interrogation of the role of KDM6A in DNA damage repair gene regulation in acute myeloid leukemia

KDM6A is a histone-3-lysine-27-demethylase that play context-dependent roles in AML, and we have identified it as a critical regulator of the DNA damage repair (DDR) gene expression programs. Mechanistically, KDM6 family protein expression is regulated by genotoxic stress and loss of both KDM6A (UTX) and KDM6B (JMJD3) impairs the DDR pathway compromising the repair potential. Accordingly, *KDM6A*-mutant human primary AML samples have increased susceptibility to Poly-(ADP-ribose)-polymerase (PARP) inhibition *in vivo.* Moreover, KDM6A loss increased both mitochondrial activity and BCL2 expression and downregulated BCL2A1 sensitizing AML cells to venetoclax. Substantiating the above results, targeting of both PARP and BCL2 was significantly more effective in inducing AML apoptosis compared to the treatments alone and primary AML cells carrying acquired *KDM6A*-domain mutations exhibited maximal sensitivity. Conclusively, our study illustrated a mechanistic rationale in support for a novel combination targeted therapy for human AML based on subtype heterogeneity and establishes KDM6A as an important molecular regulator for determining therapeutic efficacy.

- Boila LD, Ghosh S, Bandyopadhyay S, Lin L, Zeng AMA, Shaikh W, Bhowmik S, Muddineni SSNA, **Biswas M**, Sinha S, Chatterjee SS, Mbong N, Gan O, Bose A, Chakraborty S, Arruda A, Kennedy J, Mitchell A, Lechman E, Banerjee D, Milyavsky M, Minden M, Dick J, and Sengupta A. KDM6 demethylases integrate DNA repair gene regulation and loss of KDM6A sensitizes human acute myeloid leukemia to PARP and BCL2 inhibition. ***Leukemia***. 2023 Jan 31. doi: 10.1038/s41375-023-01833-z.

Identification of the role of PBAF in orchestrating mesenchymal stromal signaling and lineage commitment

In this study we have elucidated the role of PBAF in integrating BMP/Smad signaling and osteogenic gene expression in mammalian MSC lineage commitment. We have shown that expression of *Pbrm1*, *Arid2*, and *Brd7* were significantly upregulated by short-term BMP/Smad signaling as well as long-term osteogenic signals in murine and human primary MSCs. We have illustrated that osteogenic gene expression and osteolineage differentiation was impaired by the loss of *Pbrm1*/PBAFs via a de-regulation of BMP-dependent Smad1/5/8 activation pathway, and *Pbrm1* loss hindered the expression of critical hematopoietic microenvironment/niche factors, resulting in a defective non-cell autonomous support of HSPC activity.

- Sinha S, **Biswas M**[1], Chatterjee SS[1], Kumar S, Sengupta A. Pbrm1 Steers Mesenchymal Stromal Cell Osteolineage Differentiation by Integrating PBAF-Dependent Chromatin Remodeling and BMP/TGF-β Signaling. ***Cell Rep***. 2020 Apr 28;31(4):107570 ([1]Co-authorship).

Defining the role of RNA binding proteins in myelopoiesis and leukemic transformation
Here we have systematically utilized high-throughput transcriptomic data to identify RBPs regulating myelopoiesis. We analyzed the expression data of 1734 RBPs in the various HSC compartments and validated them to identify an oncogenic signature suggesting the dependency of LSCs on altered ribosome dynamics to maintain a cancer-specific translatome and their importance as potential candidates for therapeutic intervention.

- Saha S[1], Murmu KC[1], **Biswas M**, Chakraborty S, Basu J, Madhulika S, Kolkapalli SP, Chauhan S, Sengupta A, Prasad P. Transcriptomic Analysis Identifies RNA Binding Proteins as Putative Regulators of Myelopoiesis and Leukemia. ***Front Oncol***. 2019 Aug 6;9:692.

D. Abstracts

1. **Biswas M[1]**, Chatterjee SS[1], Boila LD, Chakraborty S, Banerjee D, Sengupta A. MBD3/NuRD loss participates with KDM6A program to promote DOCK5/8 expression and Rac GTPase activation in human acute myeloid leukemia. **International Symposium on Frontiers in Development and Molecular Medicine: Models to Insights,** 2019, IICB-Translational Research Unit of Excellence (IICB-TRUE), CSIR-Indian Institute of Chemical Biology, Kolkata, India.

2. Chatterjee SS[1], **Biswas M[1]**, Boila LD, Banerjee D, Sengupta A. SMARCB1 Deficiency Integrates Epigenetic Signals to Oncogenic Expression Program Maintenance in Human Acute Myeloid Leukemia. **International Symposium on Frontiers in Development and Molecular Medicine: Models to Insights,** 2019, IICB-Translational Research Unit of Excellence (IICB-TRUE), CSIR-Indian Institute of Chemical Biology, Kolkata, India.

3. Chatterjee SS[1], **Biswas M[1]**, Boila LD, Chakraborty S, Sinha S, Banerjee D, Sengupta A. UTX and MBD3 epistasis regulates Rac GTPase activation and sensitizes human acute myeloid leukemia cells to DOCK inhibition. **ASH Annual Meeting,** 2018, San Diego, California, USA.

4. Chatterjee SS[1], **Biswas M[1]**, Sengupta A. Transcriptional Cooperativity between SWI/SNF and NuRD Chromatin Remodelers in Acute Myeloid Leukemia. **47th Annual Scientific Meeting of International Society for Experimental Hematology,** 2018, UCLA, Los Angeles, California, USA.

5. Chatterjee SS[1], **Biswas M[1]**, Sengupta A. SWI/SNF and NuRD Chromatin Remodelers Display Transcriptional Cooperation in Myeloid Malignancies. **SINP International Cancer Meeting 2018, Cancer Biology: Still A Challenge In 21st Century & SINP School On Epigenetics,** Saha Institute of Nuclear Physics, Kolkata, India.

6. **Biswas M[1]**, Chatterjee SS[1], Boila LD, Banerjee D, Sengupta A. Epigenetic Plasticity in ATP-Dependent Chromatin Remodeling Complexes in Human Acute Myeloid Leukemia. **Indo-Japan Conference on Epigenetics and Human Disease,** 2018, Bose Institute, Kolkata, India.

7. **Biswas M[1]**, Chatterjee SS[1], Boila LD, Banerjee D, Sengupta A. Epigenetic Plasticity in ATP-Dependent Chromatin Remodeling Complexes in Human Acute Myeloid Leukemia. **59th American Society of Hematology**

(ASH) Annual Meeting & Exposition: Disordered Gene Expression in Hematologic Malignancy, including Disordered Epigenetic Regulation (602), 2017, Georgia World Congress Center, Atlanta, Georgia, USA.

8. **Biswas M[1]**, Chatterjee SS[1], Boila LD, Sinha S, Chakraborty S, Banerjee D, Sengupta A. NuRD plasticity in human myelodysplasia/acute myeloid leukemia stem/progenitor cells. **Keystone Symposia Conference: Hematopoiesis (B1)**, 2017, Fairmont Banff Springs, Banff, Alberta, Canada.

9. **Biswas M[1]**, Chatterjee SS[1], Boila LD, Sinha S, Chakraborty S, Banerjee D, Sengupta A. Nucleosome remodelers in pre/leukemic hematopoiesis. **19th Transcription Assembly Meeting**, 2016, Bose Institute, Kolkata, India.

10. Chatterjee SS[1], **Biswas M[1]**, Boila LD, Sinha S, Chakraborty S, Banerjee D, Sengupta A. SWI/SNF chromatin remodelers in human hematopoietic stem/progenitor cell activity. **Keystone Symposia Conference: Chromatin & Epigenetics (C2)**, 2016, Whistler Conference Center, Whistler, British Columbia, Canada.

11. Chatterjee SS[1], **Biswas M[1]**, Boila LD, Sinha S, Chakraborty S, Banerjee D, Sengupta A. Deciphering chromatin remodeling in Myelodysplastic Syndrome. **A Conference of New Ideas in Cancer: Challenging Dogmas,** 2016, Tata Memorial Center, Mumbai, India.

12. **Biswas M[1]**, Chatterjee SS[1], Boila LD, Sinha S, Chakraborty S, Banerjee D, Sengupta A. Hematopoietic stem and progenitor cell-autonomous epigenetic dysregulation in myeloid leukemia. **2nd Indian Society of Hematology & Blood Transfusion (ISHBT) & European Hematology Association (EHA)**, 2016, Mumbai, India.

13. Boila LD, **Biswas M,** Chatterjee SS, Saha S, Banerjee D, Sengupta A. Understanding Polycomb-mediated Hox gene regulation in hematopoietic stem cell and progenitor transformation in leukemia. **EMBO Workshop**, 2014, Upstream and Downstream of Hox genes. CCMB, Hyderabad, India.