BIOGRAPHICAL SKETCH

NOTE: Follow the format and instructions provided by the NIH.

NAME: Bhattacharya, Debadrita

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

POSITION TITLE: Postdoctoral Fellow

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)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Calcutta, Kolkata, India	B.Sc.	06/2013	Microbiology
Tata Institute of Fundamental Research (TIFR), Mumbai, India	M.Sc.	06/2016	Biological Sciences
Cornell University, Ithaca NY, USA	Ph.D.	05/2021	Biochemistry, Molecular & Cell Biology
Stanford University, Palo Alto CA, USA	PostDoc	Present	Cancer Biology

A. **Personal Statement**

I am a scientist passionate about implementing functional genomics techniques to study cell fate plasticity in developmental and cancer biology. My research interests center around understanding the molecular mechanisms that guide cell fate decisions during embryogenesis and how tightly controlled developmental programs are re-activated in an uncontrolled manner during tumorigenesis. My thesis research addressed these questions using the multipotent neural crest stem cells as a model. As a graduate student in the lab of Dr. Marcos Simoes-Costa, I determined the gene regulatory network that temporally and spatially controls neural crest stem cell identity. Additionally, my work uncovered physiological adaptations shared between neural crest and cancer cells and described how progenitor identity is re-established in neural crest-derived cancers such as melanoma.

Having begun to explore the parallels between stem cells and cancer cells towards the end of my Ph.D. I became interested in studying cancer cell plasticity during tumorigenesis. Thus, for my postdoctoral research, I joined Dr. Julien Sage's lab at Stanford, which combines mouse genetics with innovative functional genomics tools to investigate fundamental questions in cancer biology. My research in the Sage lab focuses on uncovering the molecular drivers of cell plasticity in small-cell lung cancer (SCLC). In my work, I have utilized emerging single-cell technologies to characterize cancer cell states and generated relevant *ex vivo* models to identify and functionally validate transcriptional regulators of SCLC heterogeneity.

My long-term research goal is to synthesize my PhD and postdoctoral training to interrogate the parallels between tissue repair/regeneration and the early events of cancer. I am also fascinated by how cancer cells design their unique microenvironment and want to investigate mechanisms that allow them to "mimic" different cell types within their niche. Ultimately, I want to lead an innovative research program aimed at improving the prognosis for devastating diseases such as cancer.

B. Positions, Scientific Appointments and Honors

Positions

2022-Present Robert Black Postdoctoral Fellow (Damon Runyon Cancer Research Foundation), Stanford University
2019 Fall Developmental Biology Teaching Assistant, Cornell University
2019 Summer Graduate Research Intern, Amgen
2018 Fall Biochemistry Teaching Assistant, Cornell University
2018- 2021 Ph.D. candidate, Cornell University
2016-2018 Graduate student, Cornell University
2013-2016 Junior Research Scholar, Tata Institute of Fundamental Research, India

Honors

2025 Leading Edge Postdoctoral Fellow
2022 Best Podium Talk award, NCI Young Investigator Meeting, 2022.
2022 Dean's Postdoctoral Fellow, Stanford School of Medicine (declined).
2022-2026 Damon Runyon Postdoctoral Fellowship.
2019 Paul H. Henion Award, Society of Developmental Biology.
2019 Best Poster Award, Northeastern Society of Developmental Biology Meeting, Woods Hole.
2018-2019 Centre for Vertebrates Genomics Scholars Award, Cornell University.
2018 Best Poster Award, Santa Cruz Developmental Biology Conference, University of Santa Cruz.
2018 Best Short Talk Award, Northeastern Society of Developmental Biology Meeting, Woods Hole.
2016 Award for Distinction for Master's Research, TIFR, India.
2015 EMBO Travel Fellowship.
2014-2015 Junior Research Fellowship, awarded by the University Grants Commission, India, to the top 1% of students who qualify for the National Eligibility Test (UGC-NET).
2013-2016 Graduate Research Fellowship awarded by the Department of Atomic Energy, India.

C. Contributions to Science

Master's thesis research (2013-2016): I conducted my Master's thesis research at Tata Institute of Fundamental Research (TIFR), one of India's foremost academic research institutes. There, in the lab of Professor Dr. Basuthkar J. Rao, I studied the regulation of replication stress-mediated DNA damage signaling. Proliferative cells have a high incidence of replication fork stalling/collapse, which can significantly increase the cell's mutation burden without an appropriate DNA damage signaling response. In mammalian cells, this response is mediated by the DNA damage effector kinase ATR, which phosphorylates downstream repair proteins to restart stalled replication forks**.** My research focused on understanding the dynamics of this signaling, specifically how ATR kinase is activated and attenuated following acute replication stress. My findings revealed a novel role of ATR kinase in mediating its signal attenuation, which is essential for fork restart and cell cycle re-entry after abatement of replication stress. Mechanistically, I uncovered that ATR kinase stabilizes Ser/Thr phosphatases such as PPMID and PPP4 on the chromatin, which in turn dephosphorylate ATR targets to nullify DNA damage signaling. This study thus highlighted the importance of timely inactivation of stress response and informed on a clinically significant role of ATR kinase in rapidly dividing cells such as tumors.

Publication:

- **Debadrita Bhattacharya**, Disha Hiregange and Basuthkar J. Rao (2018). ATR kinase regulates its attenuation via PPM1D phosphatase recruitment to chromatin during recovery from DNA replication stress signaling. *Journal of Biosciences*, Mar;43(1):25-47, doi:10.1007/s12038-018-9736-70508-5. PMID: 29485113

Graduate Research (2016-2021): My doctoral research in the lab of Dr. Marcos Simoes-Costa at Cornell University aimed at identifying recurring themes between embryonic development and oncogenesis. To this end, I focused on the embryonic stem cell population Neural Crest (NC) and compared the processes that guide its

development to those that underlie melanoma progression. Being a neural crest-derived cancer, melanoma formation involves reactivation of the progenitor's transcriptional program, which is essential for tumorigenesis. For my thesis research, I worked on two distinct projects that uncovered regulatory programs that re-activate progenitor identity in melanoma cells.

Delineating the Regulation of Neural Crest Multipotency: In the first part of my thesis work, I adopted a two-pronged approach to elucidate the molecular basis of neural crest multipotency. First, taking a candidate-based approach, I characterized the function of the pluripotency factor Lin28A in early NC stem cells where this gene is highly enriched. This led me to delineate a regulatory circuit composed of *Lin28a* and the *let-7* miRNAs, activated downstream of Wnt signaling, to control the deployment and subsequent silencing of the neural crest multipotency program. My findings revealed that high levels of Wnt signaling in the dorsal neural tube induce the expression of Lin28A in pre-migratory NC, which in turn inhibits *let-7* miRNAs. As neural crest cells migrate away from the Wnt niche, their levels of Lin28A drop and *let-7* miRNAs increase, which directly targets and inhibits NC multipotency genes. This work thus highlighted a mechanism by which the NC multipotency program is post-transcriptionally silenced upon differentiation. Next, to more comprehensively define the epigenomic and transcriptional profile of the NC stem cells and evaluate how it changes upon differentiation, we performed time-course ATAC-seq and RNA-seq pf primary avian NC cells. This analysis revealed a surprising role of the Yamanaka factors OCT4 and SOX2 in NC stem cell formation. I uncovered that the OCT4-SOX2 heterodimer interacts with NC-specific pioneer factors to regulate thousands of genomic regions active in early NC cells. However, similar to Lin28A, the regulatory targets of the OCT4-SOX2 dimer in multipotent NC cells were completely distinct from their targets in pluripotent ES cells. Together, these studies show that though components of the pluripotency network are repurposed during NC formation, the multipotent state established downstream of these ES cell factors is characterized by a distinct gene regulatory network that manifests the unique properties of cell type.

Publications:

- **Debadrita Bhattacharya**, Megan Rothstein, Ana P. Azambuja, and Marcos Simoes-Costa (2018). **Control of neural crest multipotency by Wnt signaling and the Lin28/let-7 axis**. *Elife*, doi.org/10.7554/eLife.40556.023. PMID: 30520734

- Austin S. Hovland*, **Debadrita Bhattacharya***, Ana P. Azambuja, Dimitrius Pramio, Jacqueline Copeland, Megan Rothstein, Marcos Simoes-Costa (2022). **Pluripotency factors are repurposed to shape the epigenomic landscape in neural crest stem cells**. *Developmental Cell,* doi.org/10.1016/j.devcel.2022.09.006. *, co-first authors. PMID: 36182685

Review:

- Megan Rothstein, **Debadrita Bhattacharya**, Marcos Simoes-Costa (2018). **The Molecular basis of neural crest axial identity**. *Developmental Biology*, doi: 10.1016/j.ydbio.2018.07.026. PMID: 30071217

Identifying Warburg Effect as an upstream regulator of neural crest migration: The most striking similarity between neural crest and melanoma cells is their ability to undergo epithelial-to-mesenchymal transition and migrate extensively within the developing embryo and the adult body, respectively. It is hypothesized that the neural-crest origin of melanoma renders it highly invasive, making it one of the most aggressive forms of cancer. To identify upstream regulators of neural crest migration that are shared with melanoma invasion, I performed a time-course transcriptomic analysis of the progenitor population at various stages of development. This unexpectedly revealed that the metabolic adaptation called the Warburg effect is a crucial regulator of neural crest migration. Warburg effect potentiates the Yap/Tead signaling, which functions to activate the migratory module of the neural crest gene regulatory network. Excitingly, my subsequent work directly characterizing the NC-like stem cells in melanoma tumors revealed that the Yap/Tead pathway is essential for re-emergence of the NC regulatory network in cancer cells and is causal to melanoma de-differentiation. Together, these studies

provided two distinct examples supporting the now long-standing postulate that tumorigenesis is essentially embryogenesis happening in reverse, at the wrong time and place.

Publications:

- **Debadrita Bhattacharya**, Ana P. Azambuja and Marcos Simoes-Costa (2020). **Metabolic Reprogramming promotes neural crest migration via Yap/Tead signaling**. *Developmental Cell*, doi: 10.1016/j.devcel.2020.03.005. PMID: 32243782

Review:

- **Debadrita Bhattacharya**, Behram M Khan, and Marcos Simoes-Costa (2021) **Neural crest metabolism: at the crossroads of development and disease**. *Developmental Biology*, https://doi.org/10.1016/j.ydbio.2021.01.018. PMID: 33548210

Postdoctoral Research (07/2021-Current): My postdoctoral research in the lab of Dr. Julien Sage at Stanford University focuses on uncovering regulators of cancer cell plasticity using small cell lung cancer (SCLC) as a model. Cancer cell plasticity drives intratumoral heterogeneity (ITH), often associated with poor prognosis. This is exemplified in SCLC, where plasticity and ITH are hallmarks of multi-therapy resistance. However, currently, we lack insights into the cell states that underlie tumor heterogeneity and the molecular drivers that promote SCLC cell fate diversification. To address this, I used single-cell multi-omics to profile chromatin accessibility and gene expression in SCLC cancer cells from a pre-clinical murine model. These datasets revealed several cancer cell states with unique epigenetic and transcriptional programs and identified novel candidate regulators of SCLC heterogeneity. Building on these findings, my future work aims to spatially characterize these cell states within the tumor and evaluate the role of specific transcription factors in promoting SCLC heterogeneity.

Publications:

- Xavier Rovira-Clavé, Alexandros P. Drainas, Sizun Jiang, Yunhao Bai, Maya Baron, Bokai Zhu, Alec E. Dallas, Myung Chang Lee, Theresa P. Chu, Alessandra Holzem, Ramya Ayyagari, **Debadrita Bhattacharya**, Erin F. McCaffrey, Noah F. Greenwald, Maxim Markovic, Garry L. Coles, Michael Angelo, Michael C. Bassik, Julien Sage, Garry P. Nolan (2022). **Spatial epitope barcoding reveals clonal tumor patch behaviors**. *Cancer Cell,* doi: 10.1016/j.ccell.2022.09.014. PMID: 36240778

- Yoko Nishiga, Alexandros P. Drainas, Maya Baron, **Debadrita Bhattacharya,** Amira A. Barkal, Yasaman Ahrari, Rebecca Mancusi, Jason B. Ross, Nobuyuki Takahashi, Anish Thomas, Maximilian Diehn, Irving L. Weissman, Edward E. Graves, Julien Sage (2022) **Radiotherapy in combination with CD47 blockade elicits a macrophage-mediated abscopal effect**. *Nature cancer*, doi 10.1038/s43018-022-00456-0. PMID: 36411318

- Julie H Ko, Kyle E Lambert, **Debadrita Bhattacharya**, Myung Chang Lee, Caterina I Colon, Haley Hauser, Julien Sage (2023). **Small cell lung cancer plasticity enables NFIB-independent metastasis**. *Cancer Research*, doi: 10.1158/0008-5472.CAN-23-1079. PMID: 37963187

- Fangfei Qu, Siqi C. Brough, Wojciech Michno, Chioma J. Madubata, Griffin G. Hartmann, Alyssa Puno, Alexandros P. Drainas, **Debadrita Bhattacharya**, Erwin Tomasich, Myung Chang Lee, Dian Yang, Jun Kim, Maria Peiris-Pagès, Kathryn L. Simpson, Caroline Dive, Matthias Preusser, Angus Toland, Christina Kong, Millie Das, Monte M. Winslow, Anca M. Pasca, Julien Sage (2023). **Crosstalk between small-cell lung cancer cells and astrocytes mimics brain development to promote brain metastasis**. *Nature Cell Biology*, doi: 10.1038/s41556-023-01241-6. PMID: 37783795

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