BIOGRAPHICAL SKETCH

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NAME: BHATTACHARYA, DEBADRITA

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

POSITION TITLE: POST DOCTORAL 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 & Immunology
Tata Institute of Fundamental Research (TIFR), Mumbai, India	M.Sc.	06/2016	Biological Sciences
Cornell University, New York, USA	Ph.D.	05/2021	Biochemistry, Molecular & Cell Biology

A. **Personal Statement**

My research interests center around understanding the molecular mechanisms that guide cell fate decisions during embryogenesis and oncogenesis. I am also interested in studying how tightly controlled developmental programs are re-activated in an uncontrolled manner during tumorigenesis. My thesis research aimed at addressing these questions using the neural crest stem cells as a model system. As a graduate student in the lab of Dr. Marcos Simoes-Costa, I determined the core transcriptional machinery that temporally and spatially controls neural crest stem cell identity. Additionally, my work uncovered physiological adaptions that are shared between neural crest and cancer cells and described a mechanism of how progenitor identity is re-established in neural crest-derived cancers such as melanoma.

Through my Ph.D. work, I have gained considerable experience in utilizing cutting-edge genomic techniques to delineate gene regulatory networks guiding cell state transitions. Additionally, my thesis projects allowed me to carve out a scientific niche and identify the research questions that inspired my curiosity. Particularly, having studied the parallels between embryonic stem cells and tumor cells towards the end of my Ph.D., I wanted to apply my training to address questions related to early events of oncogenesis. Thus, for my postdoctoral research, I decided to train as a cancer biologist with Dr. Julien Sage, whose lab combines mouse genetics with innovative single-cell techniques to study SCLC tumorigenesis. My research in the Sage lab will focus on uncovering the molecular basis of intra-tumoral heterogeneity using Small Cell Lung Cancer (SCLC) as a model system. I believe my training as a developmental biologist uniquely positions me to tackle this fundamental question in cancer biology, and I am excited to pursue this proposed project for my postdoctoral research.

B. Positions and Honors

Positions

2013-2016 Junior Research Scholar, Tata Institute of Fundamental research, India

2016-2018 Graduate student, Cornell University
2018- 2021 Ph.D. candidate, Cornell University
2018 Fall Biochemistry Teaching Assistant, Cornell University
2019 Summer Graduate Research Intern, Amgen
2019 Fall Developmental Biology Teaching Assistant, Cornell University

Honors
2013-2016 Graduate Research fellowship awarded by Department of Atomic Energy, India.
2014-2015 Junior Research Fellowship, awarded by University Grants Commission, India to top 1% students who qualify National Eligibility Test (UGC-NET).
2015 EMBO Travel Fellowship.
2016 Award for Distinction for Master's Research, TIFR, India.
2017 Best Poster Award, 4th Stem Cell Symposium, Cornell University, Ithaca.
2018 Best Short Talk Award, Northeastern Society of Developmental Biology Meeting, Woods Hole.
2018 Best Poster Award, Santa Cruz Developmental Biology Conference, University of Santa Cruz.
2018-2019 Centre for Vertebrates Genomics Scholars Award, Cornell University.
2019 Best Poster Award, Northeastern Society of Developmental Biology Meeting, Woods Hole.
2019 Paul H. Henion Award, Society of Developmental Biology.

C. Contributions to Science

Masters 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 in the absence of 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 important role of ATR kinase in rapidly dividing cells such as tumors.

Publication:

- **Bhattacharya D**, Hiregange D and Rao BJ (2018). ATR kinase regulate its attenuation via PPM1D phosphatase recruitment to chromatin during recovery from DNA replication stress signaling. *Journal of Biosciences*, 0250-5991, doi:10.1007/s12038-018-9736-70508-5

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 which 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 strategy to delineate the molecular basis of neural crest multipotency. First, taking a candidate-based approach, I characterized the function of the pluripotency factor Lin28 in early NC stem cells where this gene is highly enriched. This led me to uncover a regulatory circuit composed of *Lin28a* and the *let-7* miRNAs, which is 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 expression of Lin28 in pre-migratory NC, which in turn inhibits *let-7* miRNAs. As neural crest cells migrate away from the Wnt niche, their levels of Lin28 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, in the lab, we performed time-course ATAC-seq and RNA-seq of primary avian NC cells. This analysis revealed a surprising role of the Yamanaka factors OCT4 and SOX2 in the formation of NC stem cells. I found 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 Lin28, 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 Paula 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
- **Hovland AS**[*], **Bhattacharya D**[*], Rothstein M, Simoes-Costa M (2021). Pluripotency factors are repurposed to shape the epigenomic landscape in neural crest stem cells. *In Revision, Developmental Cell*

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.

Short Talk:

- **Debadrita Bhattacharya**, Megan Rothstein, Ana Paula Azambuja and Marcos Simoes-Costa "Control of neural crest multipotency by Wnt signaling and the Lin28/let-7 axis", Northeastern Society of Developmental Biology meeting, Woods Hole, 2018.

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 especially invasive, making it one of the most aggressive forms of cancer. In an attempt 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 the tumorigenesis is essentially embryogenesis happening in reverse, in the wrong time and wrong place.

Publications:

- **Debadrita Bhattacharya**, Ana Paula 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

- **D Bhattacharya**, AP Azambuja, J Copeland, AC White, M Simoes-Costa (2021) Co-option of developmental gene circuits in neural crest-derived cancers. *Manuscript submitted.*

Review:

- **D Bhattacharya**, BM Khan, and M 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

Short Talk:

- **Debadrita Bhattacharya**, Ana Paula Azambuja and Marcos Simoes-Costa "Neural crest cells undergo metabolic reprogramming during the onset of migration," Gordon Research Seminar on Neural Crest and Placodes, Italy, 2019.
- **Debadrita Bhattacharya**, Marcos Simoes-Costa "Co-option of developmental transcriptional circuit by neural crest-derived cancers", Mechanisms and Models of Cancer, Cold spring Harbor Laboratories, 2020.