BIOGRAPHICAL SKETCH

NAME OF APPLICANT: **NILAY SETHI**

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

POSITION TITLE: **MEMBER OF FACULTY, DANA-FARBER CANCER INSTITUTE and INSTRUCTOR IN MEDICINE, HARVARD MEDICAL SCHOOL**

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	START DATE	END DATE	FIELD OF STUDY
The College of New Jersey (Ewing, New Jersey)	B.S.	08/2001	05/2004	Biology
Rutgers Robert Wood Johnson Medical School (Piscataway and New Brunswick, New Jersey)	M.D.	08/2005	05/2012	Medicine
Princeton University (Princeton, New Jersey)	Ph.D.	08/2007	06/2010	Molecular Biology
University of California, San Francisco (San Francisco, California)	*(Intern and Resident)*	07/2012	06/2014	Internal Medicine
Dana-Farber Cancer Institute (Boston, Massachusetts)	*(Fellow)*	07/2014	06/2018	Medical Oncology
Dana-Farber Cancer Institute (Boston, Massachusetts)	*(Postdoctoral)*	09/2015	06/2020	Cancer Genomics

A. PERSONAL STATEMENT

Many invaluable experiences impacted my development, guided important decisions, and ultimately inspired a career in medical oncology and investigative cancer research. I initially engaged academia through teaching opportunities. My interest derived primarily from the feeling of gratitude towards my teachers and mentors as they were instrumental in fueling my enthusiasm for learning and channeling my excitement in constructive directions. I enjoyed illustrating the way new hypotheses are generated and the methodical approach used to investigate these emergent hypotheses. These experiences helped me discover an academic community bonded by scholarship and nourished by mentorship.

My first exposure to investigative research was as an undergraduate. I was fortunate to work under the supervision of Dr. Diego Cadavid studying the pathogenesis of Lyme disease and Dr. Paul Schedul investigating the role of Hedgehog signaling in germ cell migration using the Drosophila fly model. These early research experiences inspired the pursuit of a combined MD-PhD program. My subsequent experiences in medical school and internal medicine residency motivated me towards a career in oncology. Learning about the limitations of current treatment strategies for advanced gastrointestinal cancers, I was determined to guide my research efforts towards understanding these challenging diseases.

Today, I am a dedicated physician-scientist who treats patients with gastrointestinal cancer in the clinic and conducts basic and translational research in the laboratory. I am particularly committed to better understanding the specific genomic alterations and fundamental molecular mechanisms that promote gastrointestinal cancers with the hope that such insight will translate into clinical advances. My passion for investigative research is fundamentally dependent on its power to impact our understanding of human disease and ultimately improve patient care. I am inspired by the unyielding resolve demonstrated by patients with cancer. Witnessing only a fraction of their battle against cancer has provided me with a lifetime of motivation. I am determined to improve the outcomes in these patients. By fulfilling my career promise as a gastrointestinal medical oncologist and cancer investigator, I hope that I will come one step closer to this goal.

B. POSITIONS AND HONORS

Research and Professional Experience:

2012-2013	Intern in Internal Medicine, University of California, San Francisco (UCSF), San Francisco, CA
2013-2014	Intern in Internal Medicine, University of California, San Francisco (UCSF), San Francisco, CA
2014-2018	Medical Oncology Fellow, Dana-Farber Cancer Institute/MGH/BWH, Boston, MA
2017-current	Medical Oncologist, Center for Gastrointestinal Oncology, Dana-Farber Cancer Institute, Boston, MA
2017-current	Instructor in Medicine, Harvard Medical School, Boston, MA
2020-current	Principal Investigator, Division of Molecular and Cellular Oncology, Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA

Professional Memberships

2008 – current	Associate Member, American Association for Cancer Research
2019 – current	Member, American Gastroenterological Association

Awards and Honors:

2003	Joseph Vina Junior Award (The College of New Jersey)
2004	Bristol Myers Squibb Senior Award (The College of New Jersey)
2008	New Jersey Commission on Cancer Research Predoctoral Fellowship
2010	MD/PhD Scholarship (Conference Award: MGH-KI-Cell Press Days of Molecular Medicine: Systems Biology Approaches to Cancer and Metabolic Disease)
2010	Scholar-in-Training Award (AACR-MRS Joint Conference on Metastasis and the Tumor Microenvironment)
2011	New Jersey Cancer Research Award for Scientific Excellence (New Jersey Commission on Cancer Research)
2011	Gallo Award for Scientific Excellence (New Jersey Commission on Cancer Research)
2012	Outstanding Achievement in the MD-PhD Program (Robert Wood Johnson Medical School/ Rutgers University/ Princeton University Tri-institutional MD-PhD Program)
2012	Dean's Research Award: Best Publication by a Medical Student
2013	Favorite Doctor: Staff Holiday Awards (UCSF Medical Center)
2017-19*	KL2/Catalyst Medical Investigator Training (CMeRIT) Award
2018-20	Claudia Barr Program in Cancer Research Award
2018-19	Perry Fellow (Center for Gastrointestinal Cancer and Pan-Mass Challenge/Perry Team)
2019-24	NIDDK K08 Mentored Clinical Scientist Research Career Development Award
2019	AACR Scholar-in-Training Award (Environmental Carcinogenesis Conference)
2020	ASCI Young Physician-Scientist Award
2020	Karin Grunebaum Cancer Research Award

*Early Termination upon Acceptance of NIDDK-K08 Award

C. CONTRIBUTION TO SCIENCE

1. *Early Career: Investigating the Pathogenesis of Infectious Disease*. Under the supervision of Dr. Cadavid, I studied the mechanisms by which the causative agent of Lyme disease engages of the nervous system. We found that the spirochetal bacterium responsible for Lyme disease has the preferential capacity to penetrate nervous system barriers based on their surface protein composition. Select subtypes of these spirochetal bacteria expressing immunodominant variable small proteins had the ability to invade the CNS, while other subtypes caused a more severe systemic disease (***Sethi et al., Infection and Immunity 2006***). These mechanistic investigations improved our understanding of the pathogenesis of Lyme disease and CNS bacterial infections.

   a. **Sethi, NS**; Sondey, M; Bai, Y; Kim, KS; Cadavid, D. Interaction of a neurotropic strain of Borrelia turicatae with the cerebral microcirculation. *Infection and Immunity* (2006) 74(11):6408-18.

b. Gandhi, G[£]; Londoño, D[£]; Whetsine, CR; **Sethi, NS**; Kim, KS; Zückert, WR; Cadavid, D. Association of Variable Small Proteins of the spirochete Borrelia turicatae with human brain endothelial cells. *PLOS One* (2010) 5(10):e13257. [£]*Authors contributed equally*

2. *Early Career: Discovering Regulators of Developmental Pathways.* Using the *Drosophila melanogaster* embryo as a model system, I investigated the role of Hedgehog signaling in germ cell migration while working in the laboratory of Dr. Paul Schedl at Princeton University as an undergraduate student. We showed that genetic manipulation of the Hedgehog pathway disrupted the normal course of germ cell migration, leading to aberrant formation of the primitive gonad (***Despande et al., Genetics 2007***). During graduate school, I engaged in a collaboration with Yan Yan from Dr. Gertrude Schubach's lab to characterize a fundamental regulator of Notch signaling. We showed that Rabconnectin-3 regulated Notch signaling in mammalian cells via actions of a V-ATPase pump (***Sethi et al., Journal of Biological Chemistry 2010***).

   a. **Sethi, NS**; Yan, Y; Quek, D; Schupbach, T; Kang, Y. Rabconnectin-3 is a functional regulator of mammalian notch signaling. *JBC* (2010) 285(45): 34757-64.

   b. Despande, G; **Sethi, NS**; Schedl, P. toutvelu (ttv), a regulator of heparan sulphate proteoglycan biosynthesis, controls guidance cues for germ cell migration. *Genetics* (2007) 176(2): 905-912.

3. *Graduate Career: Elucidating the Role of Notch Signaling in Breast Cancer Progression.* As a graduate student, I studied the molecular basis of cancer metastasis in Yibin Kang's laboratory. With emerging evidence that developmental signaling pathways were inappropriately active in tumor progression (***Sethi and Kang, Bone 2011***), I investigated the role of the Notch pathway in breast cancer metastasis. We made the unexpected observation that the Notch pathway ligand Jagged1 (rather than downstream pathway components) is strongly upregulated in patients with quicker relapse and bone metastasis. Using a well-established mouse model, we showed that enforced expression of Jagged1 in breast cancer cells promotes osteolytic bone metastasis by activating the Notch pathway in the bone microenvironment. Jagged1-mediated activation of Notch signaling in osteoblasts conferred a growth advantage to colonizing tumor cells that was mediated by the inflammatory cytokine IL-6. On the other hand, by directly engaging pre-osteoclasts, tumor-derived Jagged1 stimulated osteoclast maturation and subsequent bone destruction, releasing sequestered growth factors such as the pro-metastasis cytokine TGFβ, which can then feedback onto tumors cells to upregulate Jagged1. Of translational importance, we showed that mice treated with a potent Notch inhibitor reversed Jagged1-mediated bone metastases, implicating Notch pathway inhibitors as therapeutic agents against bone metastasis. These intriguing results suggested a new paradigm for Notch signaling in breast cancer progression, defining a requirement for the pathway in the supporting stroma as opposed to tumor cells in the formation of bone metastasis (***Sethi et al., Cancer Cell 2011***). I am confident that we will continue to discover important regulators of cancer progression, develop innovative approaches to target these mediators, and identify the appropriate patient populations for therapeutic intervention *(**Sethi and Kang, Nature Reviews Cancer 2011**)*.

   a. **Sethi, NS**; Dai, X; Winters, C; Kang, Y. Tumor-derived Jagged1 promotes osteolytic bone metastasis of breast cancer by engaging Notch signaling in bone cells. *Cancer Cell* (2011) 19(2): 192-205 (Cover Article)
      - *Highlighted by Tao, J; Erez, A; Lee, B. One NOTCH Further: Jagged1 in Bone Metastasis. Cancer Cell (2011) 19(2): 159-161*
      - *Highlighted by Cancer Cell's 10th year anniversary as one of the top 5 studies published by the journal in 2011: www.timetoast.com/timelines/cancer-cells-10th-anniversary-celebration-looking-back*

   b. **Sethi, NS** and Kang, Y. Unraveling the complexity of metastasis – molecular understanding and targeted therapies. *Nature Reviews Cancer* (2011) 11(10): 735-748

   c. **Sethi, NS** and Kang, Y. Dysregulation of developmental pathways in bone metastasis. *Bone* (2011) 48(1): 16-22

4. *Functional Genomics and Novel Models of Gastrointestinal Cancers:* My postdoctoral training built on previous cancer biology research by expanding experience in functional genomics under the supervision of Dr. Adam Bass. My postdoctoral work yielded (1) a comparative molecular analysis of esophageal, gastric and colorectal adenocarcinomas (***Liu[£], Sethi[£], Hinou[£], Schneider[£] et al., Cancer Cell 2018***); (2) a

functional investigation of mutant p53 and hypoxia in gastroesophageal cancer (***Sethi[£], Kikuchi[£] et al., JCI Insight 2019***); and (3) the development of an integrative mouse model that combines early genetic alterations with exposure to disease-relevant risk factors in order to better study gastrointestinal premalignancy (***Sethi et al., Nature Genetics 2020***).

a. Liu, Y[£]; **Sethi, NS[£]**; Hinou, T[£]; Schneider, B[£]; Cherniack, A; Sanchez-Vega, F; Seoane, J; Farshidfar, F…Thorsson, V[€]; Bass, AJ[€]; Laird, P[€]. Comparative molecular analysis of gastrointestinal adenocarcinomas. *Cancer Cell* (2018) 33(4): 721-735.

b. **Sethi, NS[£]**; Kikuchi, O[£]; McFarland, J; Zhang, Y; Chung, M; Kafker, N; Islam, M; Lampson, B; Chakraborty, A; Kaelin, WG; Bass, AJ. Mutant p53 induces a hypoxia transcriptional program in gastric and esophageal adenocarcinoma. *Journal of Clinical Investigation Insight* (2019) 4(15):1-17.

c. **Sethi, NS**; Kikuchi, O[£]; Duronio, G[£]; Stachler, M[€]; McFarland, J[€]; Ferrer-Luna, F; Bao, C; Bronson, R; Liu, J; Zhang, Y; Sicinska, E; Lazaro, J-B.; Ligon, K; Beroukhim, R; Bass, AJ. Early *TP53* alterations engage environmental exposures to promote gastric premalignancy in an integrative mouse model. *Nature Genetics* (2020) 52(2): 219-230.

- *Highlighted by Ray, K. New markers and models of premalignancy and the early development of gastric cancer. Nature Reviews Gastroenterology and Hepatology* (2020). https://doi-org.ezp-prod1.hul.harvard.edu/10.1038/s41575-020-0280-1

[£, €]Authors contributed equally

5. *Defining Molecular Regulators of Aberrantly Active Stem Cell Programs in Colorectal Cancer:* Disruption of epithelial cell maturation by dysregulating stem cell programs is a hallmark of CRC, which remains the third most common and second most deadly cancer worldwide. In a comparative genomic analysis, we observed an unusually high frequency of heterozygous mutations in the transcription factor SOX9. Ensuing work also revealed a requirement for wildtype SOX9 in CRC. Our focus is to (1) understand the functional significance of heterozygous mutations in essential transcription factors; (2) define the molecular circuitry underlying aberrant stem cell programs **(Liang et al., under review)**; (3) design novel therapeutics aimed at restoring proper intestinal differentiation and eventual death of CRC.

   a. Liang, X; Duronio, G; Xie, Y; Cejas, P; Long, HW; Islam, M, Zhang, Y; Bass, AJ; **Sethi, NS**. A Reinforcing PROM1-SOX9 circuit blocks intestinal differentiation by activating an enhancer-driven stem cell program in colorectal cancer**. *under review***

D. **RESEARCH SUPPORT**

Ongoing Research Support

Claudia Adams Barr Program in Cancer Research	**Sethi (PI)**	**7/1/2018 – 6/30/2020**
Elucidating the molecular mechanisms of mutant SOX9 in colorectal cancer.		
SOX9 is recurrently mutated in the genome stable subtype of colorectal cancer. The goal of this proposal is to study the functional consequence of mutant SOX9 using genome-wide CHIP-sequencing and organoid models		

NIDDK K08 Mentored Clinical Scientist Research Career Development Award	**Sethi (PI)**	**4/1/2019 – 3/30/2024**
Integration of early genetic alterations and inflammation in gastroesophageal premalignancy.		
Intestinal metaplasia is a precursor to gastric and esophageal adenocarcinoma. The goal of this proposal is to study the impact of p53 alterations in intestinal metaplasia using a mouse model of exogenous and endogenous inflammation.		

Karin Grunebaum Cancer Research Award	**Sethi (PI)**	**7/1/2020 – 6/30/2021**
Therapeutic potential of dysregulated stem cell programs in colorectal cancer		
The goal of this proposal is to develop a screening platform to discover therapeutic agents that block stem cell		

activity and promote differentiation in colorectal cancer .

Completed Research Support

American Cancer Society Postdoctoral Fellowship 130392-PF-17-142-01-TBG	**Sethi (PI)**	**07/01/2017 - 06/30/2020** (Terminated 4/2019 due to K08)
Esophageal Adenocarcinoma: where genomics meets inflammation. The goal of this proposal is to generate mouse models of esophageal adenocarcinoma by combining different modes of inflammation with early genomic alterations.		

KL2/ Catalyst Medical Research Investigator Training (CMeRIT)	**Sethi (PI)**	**10/01/2017 - 9/30/2019** (Terminated 4/2019 due to K08)
Esophageal adenocarcinoma as a model to elucidate the interplay between genetic mutations and inflammation in early malignancy. The goal of this proposal to study whether early mutations in p53 can engage inflammatory stress to promote early gastroesophageal lesions using a novel genetically-engineered mouse model.		

Complete List of Published Work in MyBibliography:
https://www.ncbi.nlm.nih.gov/myncbi/nilay.sethi.1/bibliography/public/