BIOGRAPHICAL SKETCH

NAME OF APPLICANT: **NILAY SETHI**

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

POSITION TITLE: **ASSISTANT PROFESSOR IN MEDICINE, DANA-FARBER CANCER INSTITUTE 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 (TCNJ) (Ewing, New Jersey)	B.S.	08/2001	05/2004	Biology
Rutgers Robert Wood Johnson Medical School (RWJMS) (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 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.

Today, I am a dedicated physician-scientist who treats patients with gastrointestinal cancer in the hospital 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 enable gastrointestinal cancer initiation 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 determined to improve the outcomes in these patients. By fulfilling my career promise as a gastrointestinal medical oncologist and basic science researcher, I hope that I will come one step closer to this goal.

Ongoing and recently completed projects that I would like to highlight include:

Project Number: W81XWH2110383 Virtual Scholar Career Development Award (Sethi)
Sponsor/Funding Source: Department of Defense
Contact PI: Nilay Sethi; **Effort:** 1.20 CM
Approved Award Period: 09/01/2021-08/31/2025
Annual Direct Costs: $ 191,483**; Project Period Total Costs:** $ 1,363,356
Project Title: Determining the Molecular Basis and Therapeutic Potential of Hyperactive Stem Cell Programs in Colorectal Cancer

Major Goals/Specific Aims: The goal of this proposal to (1) define critical molecular mediators of hyperactive stem cell signaling in colorectal cancer, (2) identify genetic perturbations that block hyperactive stem cell signaling, and (3) generate a genetically engineered mouse model of genome stable colorectal cancer.

Project Number: K08DK120930 Mentored Clinical Scientist Career Development Award (Sethi)
Sponsor/Funding Source: NIDDK/NIH
Contact PI: Nilay Sethi; **Effort:** 10.80 CM
Approved Award Period: 04/01/2019-03/31/2024
Annual Direct Costs: $ 140,200**; Project Period Total Costs:** $ 753,080
Project Title: Integration of Early Genetic Alterations and Inflammation in Gastroesophageal Premalignancy
Major Goals/Specific Aims: 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.

Project Number: Claudia Adams Barr Program in Cancer Research (Sethi)
Sponsor/Funding Source: DFCI Internal Award
Contact PI: Nilay Sethi
Approved Award Period: 07/01/2018 – 06/30/2020
Annual Direct Costs: $ 111,377; **Project Period Total Costs:** $ 281,007
Project Title: Elucidating the Molecular Mechanisms of Mutant Sox9 in Colorectal Cancer
Major Goals/Specific Aims:
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.

B. POSITIONS, SCIENTIFIC APPOINTMENTS, AND HONORS

Research and Professional Experience:

2022-current	Associate Director, Medical Oncology Fellowship, Dana-Farber/Mass General Brigham, Boston, MA
2021-current	Assistant Professor 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
2020-current	Associate Member, Cancer Program, The Broad Institute, Boston, MA
2017-current	Medical Oncologist, Center for Gastrointestinal Oncology, Dana-Farber Cancer Institute, Boston, MA
2017-current	Associate Physician, Brigham and Women's Hospital, Boston, MA
2017-2020	Instructor in Medicine, Harvard Medical School, Boston, MA
2014-2018	Medical Oncology Fellow, Dana-Farber Cancer Institute/MGH/BWH, Boston, MA
2013-2014	Resident in Internal Medicine, UCSF, San Francisco, CA
2012-2013	Intern in Internal Medicine, University of California, San Francisco (UCSF), San Francisco, CA

Professional Memberships

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

Awards and Honors:

2022	Colorectal Cancer Alliance Early Career Investigator Award
2021	DOD Virtual Scholar Award
2020	ASCI Young Physician-Scientist Award
2020	Karin Grunebaum Cancer Research Award
2020	AGA Augustyn Award in Digestive Cancer
2019	AACR Scholar-in-Training Award (Environmental Carcinogenesis Conference)
2019	NIDDK K08 Mentored Clinical Scientist Research Career Development Award
2018	Perry Fellow (DFCI/Division of Gastrointestinal Oncology)
2013	UCSF Favorite Doctor: Staff Holiday Awards
2012	Dean's Research Award: Best Publication by a Medical Student

2012 Outstanding Achievement in the MD-PhD Program (RWJMS/Princeton University)
2011 NJCCR Award for Scientific Excellence
2011 NJCCR Gallo Award for Scientific Excellence
2010 MGH-KI-Cell Press Days of Molecular Medicine Conference Award
2010 AACR Scholar-in-Training Award (Metastasis and the Tumor Microenvironment Conference)
2008 New Jersey Commission on Cancer Research Predoctoral Fellowship
2004 TCNJ Bristol Myers Squibb Senior Award
2003 TCNJ Joseph Vina Junior Award

C. CONTRIBUTION TO SCIENCE

1. *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. 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.*, JBC* 2010**).

   a. **Sethi, NS**; Yan, Y; Quek, D; Schupbach, T; Kang, Y†. Rabconnectin-3 is a functional regulator of mammalian notch signaling. *Journal of Biological Chemistry* (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.

2. *Graduate Career: Elucidating the Role of Notch Signaling in Breast Cancer Progression.* 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 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 led to elaboration of inflammatory cytokine IL-6, which conferred a growth advantage to colonizing tumor cells, and, by directly engaging pre-osteoclasts, stimulated osteoclast maturation and subsequent bone destruction. Of translational importance, we showed that mice treated with a potent Notch inhibitor reversed Jagged1-mediated bone metastases. 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

3. *Functional Genomics and Novel Models of Gastric Cancer:* My postdoctoral training built on previous cancer biology research by pursuing functional genomics in Dr. Adam Bass' laboratory. 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. **[£, €]Authors contributed equally**

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) 17(4) PMID: 32103202.

d. Sahgal, P; Huffman, BM; Patil, DT; Chatila, WK; Yaeger, R; Cleary, JM; **Sethi, NS†**. Early TP53 alterations shape gastric and esophageal cancer development. *Cancers*. 2021; 13(23):5915. PMID: 34885025

e. Prosz, A; Sahgal, P; Morris, CX; Sztupinszki, Z; Borcsok, J; Diossy, M; Tisza, V; Spisak, S; Rusz, O; Csabai, I; Huffman, BM; Singh, H; Lazaro, J-B; Cecchini, M; Cleary, JM; Szallasi, Z†; **Sethi, NS†**. Mutational signature-based identification of DNA repair deficient gastroesophageal adenocarcinomas for therapeutic targeting. *under review*

4. *Defining Molecular Regulators of Differentiation Blocks 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 (**Duronio et al., *Gastro Hep Advances*, 2022**); (2) define the molecular circuitry underlying aberrant stem cell programs (**Liang et al., *Gastroenterology* 2022; Bala*, Rennhack*, *Science Advances*, in revision**); (3) design novel therapeutics aimed at restoring proper intestinal differentiation and eventual death of CRC (Spisak et al., under review).

   a. Liang, X; Duronio, G; Yang, Y; Bala, P; Hebbar, P; Spisak, S; Singh, H; Zhang, Y; Xie, Y; Cejas, P; Long, HW; Bass, AJ; **Sethi, NS†**. An enhancer-driven stem cell-like program mediated by SOX9 blocks intestinal differentiation in colorectal cancer**.** *Gastroenterology* (2022) 162(1): 209-22 PMID: 34571027

   b. Duronio, GN; Liang, X; Hebbar, P; Islam, M; Spisak, S; **Sethi, NS†**. Truncating SOX9 alterations are heterozygous null alleles in genome stable colorectal cancer**.** *Gastro Hep Advances* (2022)

   c. Bala, P*; Rennhack, J*; Aitymbayev, D; Morris, C; Moyer, S; Duronio, GN; Doan, P; Li, Z; Liang, X; Hornick, J; Yurgelun, M.; Hahn, WC; **Sethi, NS†**. Aberrant cell state plasticity mediated by development reprogramming precedes colorectal cancer initiation**.** *Science Advances*, accepted-in-principle

   d. Spisak, S*; Chen, D*; Likasitwatanakul, P*; Doan, P*; Li, Z; Wolpin, B.; Qi, J; **Sethi, NS†**. Utilizing a dual endogenous reporter system to identify functional regulators of aberrant stem cell and differentiation activity in colorectal cancer**.** *under review*

† denotes corresponding author(s)

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