OMB No. 3145-0279 (Expiration Date 10/31/2026)

NIH BIOGRAPHICAL SKETCH COMMON FORM

Name: Nakshatri, Harikrishna

Persistent Identifier (PID) of the Senior/Key Person: https://orcid.org/0000-0001-8876-0052

Position Title: Marian J. Morrison Professor of Breast Cancer Research

Organization and Location: Indiana University School of Medicine, Indianapolis, Indiana, United States

PROFESSIONAL PREPARATION

INSTITUTION AND LOCATION	DEGREE	Start Date	Completion Date	FIELD OF STUDY
The Picower Institute for Learning and Memory, Cambridge, Massachusetts, United States	Not applicable (N/A)	07/1993	12/1995	Molecular Biology
Louis Pasteur University, Strasbourg, Not Applicable, N/A, France	Not applicable (N/A)	10/1990	06/1993	Molecular Biology
Memorial University of Newfoundland, St. John's, Newfoundland and Labrador, Canada	Doctor of Philosophy (PHD)	09/1986	10/1990	Molecular Biology
University of Agricultural Sciences, Bengaluru, Not Applicable, N/A, India	OTHER DOCTOR OF VETERINARY MEDICINE	09/1977	07/1982	Veterinary Medicine

Appointments and Positions

2008 - present	Marian J. Morrison Professor of Breast Cancer Research, Indiana University School of Medicine, Indianapolis, Indiana, United States
2025 - present	Senior Research Career Scientist, VA Roudebush Medical Center, Indianapolis, Indiana, United States
2022 - present	Director of Translational Cancer Biology PhD Program, Indiana University Simon Comprehensive Cancer Center, Indianapolis, Indiana, United States
2022 - present	Chair, Promotion and Tenure Committee, Indiana University School of Medicine, Indianapolis, Indiana, United States
2020 - 2025	Research Career Scientist, VA Roudebush Medical Center, Indianapolis, Indiana, United States
2019 - present	Co-Leader, Breast Cancer Working Group, Indiana University Simon Comprehensive Cancer Center, Indianapolis, Indiana, United States
2018 - present	Chief Scientific Officer, Komen Normal Tissue Bank at Indiana University, Indianapolis, Indiana, United States
2014 - present	Super-Mentor, Independent Investigator Incubator, Indiana Clinical and Translational Sciences Institute, Indianapolis, Indiana, United States
2009 - present	Associate Director of Education, Indiana University Simon Comprehensive Cancer Center, Indianapolis, Indiana, United States
1996 - present	Professor, Indiana University School of Medicine, Indianapolis, Indiana, United States

Products

Products Closely Related to the Proposed Project

1. Bhat-Nakshatri P, Gao H, Khatpe AS, Adebayo AK, McGuire PC, Erdogan C, Chen D, Jiang G, New F, German R, Emmert L, Sandusky G, Storniolo AM, Liu Y, Nakshatri H. Single-nucleus chromatin accessibility and transcriptomic map of breast tissues of women of diverse genetic ancestry. Nat Med. 2024 Dec;30(12):3482-3494. PubMed Central PMCID: PMC11976273.
2. Adebayo AK, Bhat-Nakshatri P, Davis C, Angus SP, Erdogan C, Gao H, Green N, Kumar B, Liu Y, Nakshatri H. Oxygen tension-dependent variability in the cancer cell kinome impacts signaling pathways and response to targeted therapies. iScience. 2024 Jun 21;27(6):110068. PubMed Central PMCID: PMC11170190.
3. Kumar B, Khatpe AS, Guanglong J, Batic K, Bhat-Nakshatri P, Granatir MM, Addison RJ, Szymanski M, Baldridge LA,

Temm CJ, Sandusky G, Althouse SK, Cote ML, Miller KD, Storniolo AM, Nakshatri H. Stromal heterogeneity may explain increased incidence of metaplastic breast cancer in women of African descent. Nat Commun. 2023 Sep 14;14(1):5683. PubMed Central PMCID: PMC10502140.

4. Kumar B, Adebayo AK, Prasad M, Capitano ML, Wang R, Bhat-Nakshatri P, Anjanappa M, Simpson E, Chen D, Liu Y, Schilder JM, Colter AB, Maguire C, Temm CJ, Sandusky G, Doud EH, Wijeratne AB, Mosley AL, Broxmeyer HE, Nakshatri H. Tumor collection/processing under physioxia uncovers highly relevant signaling networks and drug sensitivity. Sci Adv. 2022 Jan 14;8(2):eabh3375. PubMed Central PMCID: PMC8754301.
5. Bhat-Nakshatri P, Gao H, Sheng L, McGuire PC, Xuei X, Wan J, Liu Y, Althouse SK, Colter A, Sandusky G, Storniolo AM, Nakshatri H. A single-cell atlas of the healthy breast tissues reveals clinically relevant clusters of breast epithelial cells. Cell Rep Med. 2021 Mar 16;2(3):100219. PubMed Central PMCID: PMC7974552.

Other Significant Products Highlighting Contributions to Science

1. Keith B, Welch DR, Agarwal N, Blair C, Chukwudozie IB, Shevde LA, Boise LH, Burnstein KL, Antalis TM, O'Connor KL, Dalal SN, Ellis S, Nakshatri H. Challenges and opportunities in training cancer researchers. Nat Cancer. 2025 Feb;6(2):223-225. PubMed Central PMCID: PMC13193226.
2. Prasad M, Kumar B, Bhat-Nakshatri P, Anjanappa M, Sandusky G, Miller KD, Storniolo AM, Nakshatri H. Dual TGFβ/BMP Pathway Inhibition Enables Expansion and Characterization of Multiple Epithelial Cell Types of the Normal and Cancerous Breast. Mol Cancer Res. 2019 Jul;17(7):1556-1570. PubMed Central PMCID: PMC6610652.
3. Nakshatri H, Kumar B, Burney HN, Cox ML, Jacobsen M, Sandusky GE, D'Souza-Schorey C, Storniolo AMV. Genetic Ancestry-dependent Differences in Breast Cancer-induced Field Defects in the Tumor-adjacent Normal Breast. Clin Cancer Res. 2019 May 1;25(9):2848-2859. PubMed Central PMCID: PMC11216537.
4. Kumar B, Prasad M, Bhat-Nakshatri P, Anjanappa M, Kalra M, Marino N, Storniolo AM, Rao X, Liu S, Wan J, Liu Y, Nakshatri H. Normal Breast-Derived Epithelial Cells with Luminal and Intrinsic Subtype-Enriched Gene Expression Document Interindividual Differences in Their Differentiation Cascade. Cancer Res. 2018 Sep 1;78(17):5107-5123. PubMed Central PMCID: PMC6125218.
5. Bhat-Nakshatri P, Goswami CP, Badve S, Magnani L, Lupien M, Nakshatri H. Molecular Insights of Pathways Resulting from Two Common PIK3CA Mutations in Breast Cancer. Cancer Res. 2016 Jul 1;76(13):3989-4001. PubMed PMID: 27197157.

Certification:

I certify that the information provided is current, accurate, and complete. This includes, but is not limited to, information related to current, pending, and other support (both foreign and domestic) as defined in 42 U.S.C. § 6605.

In accordance with Section 10632 of the CHIPS and Science Act of 2022 (42 U.S.C. § 19232), each individual identified as a senior/key person must certify that they are not a party to a malign foreign talent recruitment program.

Research Security Training Requirement for Federal Award Personnel: In accordance with Section 10634 of the CHIPS and Science Act of 2022 (42 U.S.C. § 19234), each individual identified as a senior/key person must certify that they have completed the requisite research security training that meets the requirements specified in Item 2 of Important Notice No. 149 within 12 months prior to proposal submission.

Misrepresentations and/or omissions may be subject to prosecution and liability pursuant to, but not limited to, 18 U.S.C. §§287, 1001, 1031 and 31 U.S.C. §§3729-3733 and 3802.

Certified by Nakshatri, Harikrishna in SciENcv on 2026-07-10 12:08:37

NIH BIOGRAPHICAL SKETCH SUPPLEMENT

Name: Nakshatri, Harikrishna

Persistent Identifier (PID) of the Senior/Key Person: https://orcid.org/0000-0001-8876-0052

Position Title: Marian J. Morrison Professor of Breast Cancer Research

Organization and Location: Indiana University School of Medicine, Indianapolis, Indiana, United States

Personal Statement

My research focuses on estrogen receptor signaling, metastasis in breast cancer, and the effects of cancer at a systemic level. In addition, my lab studies the contribution of normal breast genomic heterogeneity on breast cancer incidence and outcome. We were the first to report consitutive activation of NF-KB in estrogen receptor negative breast cancer. Our current focus is on genomic aspects of anti-estrogen resistance, mechanisms of organ-specific metastasis, and heterogeneity in normal breasts. In this process, we have identified a new immortalizing oncogene called TONSL, which confers intrinsic resistance to anti-estrogens and CDK4/6 inhibitors. Using breast tissues from healthy women of different genetic ancestry, we reported ancestry-dependent and ancestry-independent differences in normal breast biology. Recently, we reported single cell atlas of the healthy breast tissues of women of different genetic ancestry which is now part of the human cell atlas. Similar atlas of breast tissues of pregnant, lactating and post-breastfeeding women have just been developed. Results of these studies have been published in more than 190 manuscripts and several have been cited 250-1300 times (>22,000 citations). I have received funding from NIH (R01, U01, R21, and R03), VA, DOD, BCRF, the Chan-Zuckerberg Initiative, Mark Foundation for Cancer Research, Mary Kay Ash Foundation, and Susan G. Komen for the Cure. Additionally, a drug identified from these studies is now in Phase I clinical trial. Our studies have resulted in Phase II clinical trial NCT05846789 which is investigating whether adding IL-6R inhibitor tocilizumab to carboplatin improves response in women with triple negative breast cancer. These outcomes, achieved through extensive collaboration with clinical and basic scientists, demonstrate the translational nature of our research. Based on my scientific contribution to breast cancer, I was selected to serve as a Susan G. Komen for the Cure Scholar in 2010-2020 and reselected in 2023-2026. In 2021, I was elected as a Fellow of the American Association for the Advancement of Science. In addition, I served as an Associate Editor of Cancer Research and serve as the Associate Editor of Cancer Research Communications and the Associate Editor-in-Chief of Cancer Management and Research and Breast cancer Targets and Therapy. I completed my term as a charter member of the Cancer Molecular Pathobiology study section of NIH and the Cellular and Molecular Medicine study section of the Veteran's Administration but continue to provide services to NIH and other organizations by serving as a chair and/or reviewer. I was recently appointed to serve as a Term Member for the American Cancer Society Cancer Cell Biology proposal review committee and on the annual meeting steering committee of the Endocrine Society.

In this proposal, my lab will be responsible for part of the studies proposed in aim 1 and 3. My lab has extensive experience in primary tumor culturing and xenografts (example Molecular Cancer Research 17:1556-1570) and we are confident to complete the proposed studies. Dr. Kolluri's and my labs have been collaborating for a number of years (Cancer Research Communications 4:634-644 and ACS Pharmacy Transl Sci 7:1302-1309) and we will continue with this collaboration.

Honors

2025 - 2028	Chair, National Cancer Institute Biospeciman Science U01 Steering Commitee
2024 - 2025	President-Elect and Secretary (2024) and President (2025), Cancer Biology Training Consortium
2023	1st Place Team Leader, Susan G. Komen for Cure - UT Southwestern Breast Cancer Hackathon
2023 - 2026	Scholar, Susan G. Komen for the Cure
2022	Member, Sigma Xi Scientific Research Honor Society
2021	Fellow, American Association for the Advancement of Sciences
2020	Outstanding Mentor Award, The Indiana Medical Student Program for Research and Scholarship
2014	Prestigious External Award Recognition, Indiana University Purdue University Indianapolis
2013	Oustanding Achievement Award, Society of American Asian Scientists in Cancer Research
2010 - 2020	Scholar, Susan G. Komen for the Cure
2002	Inaugural Michael K. Guest Award for Innovative Research, Walther Cancer Institute
2002	International Cancer Congress Travel Award, American Cancer Society
1989 - 1990	Fellowship, The National Cancer Institute of Canada

1988 Excellence in Research Award, Memoral University of Newfoundland
1988 Fellowship, The Cancer Research Society

Contributions to Science

1. Genetic ancestry, heterogeneity in the normal breast hierarchy and cancer stem cells: Since 2013, laboratory focused on developing model system to understand normal breast biology using breast biopsies collected from healthy women. These efforts led to first demonstration of ethnicity-dependent differences in normal breast composition. Recently, we demonstrated that the normal breasts of women of African Ancestry contain elevated levels of ZEB1+ stem-like cells, whereas the normal breast of women of European ancestry contain elevated number of hormone-responsive GATA3+ cells. We have developed a unique method to grow epithelial cells from normal and cancerous breast and metastasis of various cancers. In addition, using single cell gene expression analyses, we showed that tumors and normal cells needed to be compared at individual level to identify cancer-specific gene expression changes. We developed and published single nucleus chromatin accessibility and transcriptomic atlas of healthy breast tissues of women of different genetic ancestry. Similar atlas of breast tissues of BRCA1 and BRCA2 mutation carriers was also published. We are in the process of completing a manuscript that describes single nucleus chromatin accessibility and transcriptome atlas as well as spatial transcriptome/proteome of breast tissues of pregnant, lactating and post-breastfeeding women.

2. Oxygen tension and response to targeted therapies. The majority of preclinical studies are done under ambient air, which is 21% oxygen. However, oxygen tension in various parts of the body varies from 0.5% to 9% but never reaches 21%. By developing a system to collect and process normal and tumor tissues under physiological oxygen levels of 3-5%, we demonstrated that exposing tissues to ambient air causes extra-physiologic oxygen shock/stress and consequently signaling pahway alterations including the levels clinically used biomarkers such as phospho-AKT and epigenetic regulators such as TET2. Several targeted therapies showed differential sensitivity under physiologic and ambient air oxygen levels. We also identified new combination therapies that are effective against cancer cells under physiologic oxygen levels. These results could explain for the limited clinical translation of preclinical studies. Moving forward, we suggest that drugs that are effective against cancer cells under ambient air need to be evaluated under physiologic oxygen to enhance clinical translatability.

3. Constitutive activation of NF-kappaB in breast cancer: Activation of anti-apoptotic signaling network is one of the hallmarks of cancer. We were the first to report constitutive activation of the anti-apoptotic transcription factor NF-kappaB in breast cancer, which has been reproduced by many groups. We showed the role of stroma in inducing NF-kappaB in cancer cells, identified signaling network involved in NF-kappaB activation and developed a drug targeting NF-kappaB. The drug is a derivative of parthenolide and is currently in Phase I clinical trial for leukemia. We subsequently demonstrated the role of ZEB1 in NF-kappaB-induced epithelial to mesenchymal transition. Recently, we established a link between NF-kappaB activation and cancer epigenetics by demonstrating the effects of NF-kappaB in the expression of epigenetic modulators and tumor suppressors NSD1 and SETD2.

4. Metastasis and systemic effects of cancer: We first demonstrated a role for NF-kappaB in metastasis as it induced the expression of the chemokine receptor CXCR4, which is essential for homing of metastatic cells. Subsequently we showed the effect of the NF-kappaB inhibitor in reducing lung metastasis when combined with the chemotherapeutic drug docetaxel. We have generated organ-specific metastatic variants of a breast cancer cell line, which have been distributed worldwide to several investigators. Analysis of these cell lines showed down regulation of miR-22 in metastatic cells compared with parental cells and metastatic cells acquiring gene expression pattern similar to that of the organ to which they have metastasized. We have generated patient derived brain metastasis xenograft models. Recently, we showed that cancer induces systemic effects by deregulating the expression of miR-486 in cardiac and skeletal muscle. Furthermore, we developed an isogenic model of immortalized, ductal carcinoma in situ (DCIS), invasive ductal carcinoma and invasive ductal carcinoma with metastasis of breast cancer starting with breast tissues of healthy women.

5. PI3K-AKT signaling and anti-estrogen resistance in breast cancer: Prior to large-scale genomics studies documenting PI3K and AKT mutations in breast cancer, particularly in ER-positive breast cancer, our group demonstrated the ability of mutant PI3K and AKT to increase phosphorylation of ER-S167 and alter response to anti-estrogens. Subsequently, we demonstrated that AKT alters ER binding to the genome, and affects estrogen-induced mRNA and microRNA expression, and alternative splicing. Contrary to widely held belief, our studies showed that the presence of activated AKT in the nucleus of breast tumor is associated with better outcome in ER-positive breast cancer patients. We recently observed that AKT1 but not AKT2 is the major kinase downstream of PI3K mutation and AKT1 integrates PI3K mutation to ER signaling. We recently identified TONSL, located on chromosome 8q24.3 amplicon, as an immortalizing oncogene and showed that TONSL amplification or overexpression is associated with intrinsic resistance to anti-estrogens and CDK4/6 inhibitors in breast cancer.

Certification:

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