BIOGRAPHICAL SKETCH

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NAME: Nakshatri, Harikrishna

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

POSITION TITLE: Marian J. Morrison Chair of Breast Cancer Research, Professor of Surgery, Biochemistry,

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 Agricultural Sciences, Bangalore	BVSc	09/77-07/82	Veterinary Medicine
Memorial University of Newfoundland, Canada	PhD	09/86-10/90	Molecular Biology
LGME, University Louis Pasteur, Strasbourg, France	Post-doc	10/90-06/93	Molecular Biology
Picower Institute for Medical Research, NY	Investigator	07/93-12/95	Molecular Biology

A. Personal Statement: My research focuses on estrogen receptor signaling and metastasis in breast cancer and the effects of cancer at 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 constitutive activation of NF-κB in estrogen receptor negative breast cancer. The current focus is on genomic aspects of anti-estrogen resistance, mechanisms of organ-specific metastasis and heterogeneity in the normal breasts. Using breast tissues from healthy women of different genetic ancestry, we reported ancestry-dependent and ancestry-independent differences in the normal breast biology. Recently, we reported single cell atlas of the healthy breast, which is now part of the human cell atlas. Results of these studies have been published in more than 140 manuscripts and several have been cited 250 - 1200 times. I have received funding from NIH (R01, R21, and R03), VA, DOD, BCRF, Chan-Zuckerberg Initiative, and Susan G. Komen for the Cure for these studies. Additionally, a drug identified from these studies is now in phase I clinical trial. I have co-founded a biotech company and licensed another patent to a diagnostic company for clinical use. 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 am one among the scientists selected from several countries to serve in the Susan G. Komen for the Cure Scholars (2010-2020) and reselected to serve as a scholar (2023-2026). In 2021, I was elected as a Fellow of the American Association for the Advancement of Science (AAAS). In addition, I served as an *Associate Editor of Cancer Research* 2013-2023, and serve as an *Associate Editor of Cancer Research Communications (AACR)* since 2021 and Associate Editor-in-Chief of Cancer Management and Research since 2017. I recently completed my term as a charter member of Cancer Molecular Pathobiology study section of NIH (2012-2018) and currently a regular member of the Cellular and Molecular Medicine study section of the Veteran's Administration (2021-2025).

In this proposal, my laboratory will be involved in establishing PDX for in vivo studies and to generate cell lines and/or organoids from PDXs required for the study. This is a new collaboration with Dr. Kaplan and will help to expand immunology work in breast cancer on campus.

Ongoing projects that I would like to highlight include:

I01 BX002764 (VA)
(Nakshatri, PI)
04/01/2015-08/31/2023
Mechanisms associated with systemic effects of cancer

WH1XWH2010577 (DOD)

(Nakshatri, PI)
07/01/2020-06/20/2023
The influence of adipogenic progenitors and the duffy-null phenotype on the normal breast and breast cancer biology of women of African descent.

Chan-Zuckerberg Initiative
(Nakshatri, PI)
07/01/2019-12/31/2023
Single cell mapping of the normal breast of ethnically diverse population

Department of Defense W81XWH-22-1-0719
(Nakshatri, PI)
07/15/2022-07/14/2025
Genomic determinants of PIK3CA mutation-driven breast cancer initiation

Recent publications from Nakshatri lab:

- Wang R, Kumar B, Bhat-Nakshatri P, Khatpe AS, Murphy MP, Wanczyk KE, Simpson E, Chen D, Gao H, Liu Y, Doud EH, Mosley AL, and **Nakshatri H. (2023).** A human skeletal muscle stem/myotube model reveals multiple signaling targets of cancer secretome in skeletal muscle. **iScience (Cell press) 26:106541.**
- Khatpe AS, Dirks R, Bhat-Nakshatri P, Mang H, Batic K, Swiezy S, Olson J, Rao X, Wang Y, Tanaka H, Liu S, Wan J, Chen D, Liu Y, Fang F, Althouse S, Hulsey E, Grantair MM, Addison R, Temm CJ, Sandusky G, Lee-Gosselin A, Nephew KP, Miller KD and **Nakshatri H (2023).** TONSL is an immortalizing oncogene of the chromosome 8q24.3 amplicon and new therapeutic target in breast cancer (**Cancer Research 83:1345-1360**).
- 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 and **Nakshatri H. (2022).** Tumor collection/processing under physioxia uncovers highly relevant signaling networks and drug sensitivity. **Science Advances 8:eabh3375** PMC8754301 (13 citations)
- Bhat-Nakshatri P, Gao H, Sheng L, McGuire PC, Xuei X, Wan J, Liu Y, Althouse SK, Colter A, Sandusky G, Storniolo AM, and **Nakshatri H (2021).** A single cell atlas of the healthy breast tissues reveal clinically relevant clusters of breast epithelial cells. **Cell Reports Medicine 2, 100219.** PMC7974552. (19 citations)

B. Positions, Scientific Appointments, and Honors

Positions

July 2022-	Chair, IU School of Medicine Promotion and Tenure Committee
April 2020-	Research Career Scientist, VA Roudebush Medical Center, Indianapolis
December 2018-	Chief Scientific Officer, Komen Normal Tissue Bank at IU
2017-2019	Research Scientist, VA Roudebush Medical Center, Indianapolis
May 2015-2016	Research Health Scientist, VA Roudebush Medical Center, Indianapolis
July 2014-	Super-mentor, Independent Investigator Incubator, IUSM/CTSI
May 2011-2014	Director, IUPUI Breast Cancer Signature Center
February 2011-19	Co-Program Leader, Breast Cancer Program, IU Simon Cancer Center
September 2009-	Associate Director of Education, IU Simon Cancer Center
September 2008-	Marian J. Morrison Chair in Breast Cancer Research
July 2008-current	Professor, Indiana University School of Medicine
2004- August 2008	Marian J. Morrison Investigator in Breast Cancer Research
2002- June 2008	Associate Professor (Tenure), Indiana University School of Medicine
2000-2008	Adjunct Faculty, Veterinary Clinical Sciences, Purdue University, Indiana
1997-2009	Member, Walther Oncology Center, Indiana University School of Medicine
1996-2002	Assistant Professor, Indiana University School of Medicine, Indianapolis, Indiana.

Honors

2023-	Susan G Komen for Cure-UT Southwestern Breast Cancer Hackathon 1st place winner (Role: team leader)
2023-2026	**Re-appointed as the Susan G Komen for the Cure Scholar**
2022	Elected full member, Sigma Xi, the Scientific Research Honor Society
2021	**Elected Fellow, American Association for the Advancement of Sciences (AAAS)**
2020	Outstanding IMPRS mentor award

2014 Prestigious External Award Recognition, Indiana University-Purdue University, Indianapolis
2013 Outstanding Achievement Award, Society of American Asian Scientists in Cancer Research
2010-2020 Susan G. Komen for the Cure Scholar
2002 Inaugural Michael K. Guest Award for Innovative Research by Walther Cancer Institute
2002 International Cancer Congress Travel Award, American Cancer Society
1989-1990 The National Cancer Institute of Canada fellowship
1988 Excellence in Research Award, Memorial University of Newfoundland.
1988 The Cancer Research Society Inc., Quebec, Canada fellowship
1982 Three gold medals and one state award for obtaining top rank in Veterinary Science
1977-1982: Indian Council of Agricultural Research Studentship.

Patents (awarded):

2019 US patent # US 10,247,732 B2 Materials and methods for diagnosing and predicting the course of prostate cancer
2015 US patent # 9,200,325 Diagnostic Methods for detection of Cancer
2005 US patent # 6,890,946 Use of parthenolide to inhibit cancer (co-founded Leuchemix, Inc)

Editor: *Associate Editor, Cancer Research (AACR, 2013-April 2023); Associate Editor, Cancer Research Communications (New journal from AACR, October 2021-); Associate Editor-in-Chief, Cancer Management and Research (2017-); Associate Editor-in-Chief, Breast Cancer Targets and Therapy;*

Editorial Boards: Cancer Research (2016-); Nature Scientific Reports (2016-); Cancer Management and Research (2008-); Breast Cancer Targets and Therapy (2009-); Breast Cancer Management (2012-).

Professional Activities:

Florida Department of Health Biomedical Research Program (2001, 2003, 2004, 2007, 2016); Department of Defense Ovarian Cancer Review Panel (2001); Guy's and St. Thomas Charitable Foundation, London, UK (2002); Department of Defense Breast Cancer Concept and/or fellowship Award review panel (2003, 2006-2009); Department of Defense Breakthrough, Idea and Synergy Award study section (2008-2011; 2018-2019); National Institutes of Environmental Health Sciences Special Emphasis Panel (July, 2003); The Canadian Institutes of Health Research Grant Review (2004); NRSA fellowship study section, NIH (2004 – 2007, 2009-2010), Department of Health, Pennsylvania (2004-2006); Ad Hoc Review, MCE Study Section – NIH (2005), BMCT (2007), Cancer Biology ONC-X04 (2008); Manpower & Training grants NCI study section (January 2010); NIH Challenge Grant (June 2009); National Medical Research Council, Singapore, grant review (2009); Association for International Cancer Research, UK (2009) Agency for Science, Technology, and Research's Biomedical research Council, Singapore (2009-11); Louisiana Board of Regents, USA (2009); Susan G. Komen for Cure- study section- 2008-2016, Chair of the study section 2012 and 2016. California Breast Cancer Program 2008-2011, Chair, Tumor Biology Study section, 2011-2014; NIH SPORE review panel (2011-2014), PPG panel 2013, 2016, Provocative questions/Omnibus SEP 2013, 2014, 2015, NCI Physical Sciences Oncology Center review panel 2014; Cancer Molecular Pathobiology Study Section, NIH, June 2011; ***Cancer Molecular and Pathobiology Study section, regular member, 2012-2018***; Board of Director, Cancer Biology Training Consortium (2013-2017); NIH K-series and F99/K00 study section (2017, 2018); NCI Moonshot panel (2018); NCI Site Visits panel, 2018, 2020, METAvivor review panel (2019-) **Department of Veterans Affairs (VA) Joint Biomedical Research and Development (BLRD) and Clinical Science Research and Development (CSRD) Services Scientific Merit Review Board (2021-2025),** NCI R03/R21 Special Emphasis panel (2019-)**,** K22 panel 2022; American Cancer Soceity Cancer Stem cell study section, August 2022, Chair- NCI special emphasis panel, October 2022 and February 2023; Reviewer for ~40 journals.

C. Contributions to Science

Total publications-177, Citations >20,000, H-factor 71, i10 index 151.

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. These cells are suitable for genomic analyses.

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.

- Anjanappa M, Cardoso A, Cheng L, Mohammad S, Gunawan A, Rice S, Dong Y, Li L, Sandusky GE, Srour EF, and **Nakshatri H. (2017).** Individualized breast cancer characterization through single cell analysis of tumor adjacent-normal cells. **Cancer Research 77:2759-2769.** PMC5441682 (17 citations)
- Kumar B, Prasad MS, Bhat-Nakshatri P, Anjanappa M, Kalra M, Marino N, Storniolo AM, Rao X, Liu S, Wan J, Liu Y and **Nakshatri H (2018).** Normal breast-derived epithelial cells with luminal and intrinsic subtype-enriched gene expression document inter-individual differences in their differentiation cascade. **Cancer Research 78:5107-23.** PMC6125218 (46 citations)
- **Nakshatri H,** Kumar B, Burney H, Cox ML, Jacobsen M, Sandusky G, D'Souza-Schorey C and Storniolo AM **(2019).** Genetic ancestry-dependent differences in breast cancer-induced field defects in the tumor-adjacent normal breast. **Clinical Cancer Research 25:2848-2859.** (18 citations)
- Kumar B, Bhat-Nakshatri P, Maguire C, Jacobsen M, Temm CJ, George Sandusky and **Nakshatri H. (2021).** Bidirectional regulatory crosstalk between cell-context and genomic aberrations shapes breast tumorigenesis. **Molecular Cancer Research (19:1802-1817).** PMC8568628

2) Constitutive activation of NF-κB 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-κB in breast cancer, which has been reproduced by many groups. We showed the role of stroma in inducing NF-κB in cancer cells, identified signaling network involved in NF-κB activation and developed a drug targeting NF-κB. 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-κB-induced epithelial to mesenchymal transition. Recently, we established a link between NF-κB activation and cancer epigenetics by demonstrating the effects of NF-κB in the expression of epigenetic modulators and tumor suppressors NSD1 and SETD2.

- **Nakshatri H**, Bhat-Nakshatri P, Martin DA, Goulet RJ Jr, and Sledge GW Jr. **(1997).** Constitutive activation of NF-κB during progression of breast cancer to hormone-independent growth. **Mol. Cell. Biol. 17: 3629-3639**. PMC232215 (1072 citations)
- Bhat-Nakshatri P, Newton TR, Goulet RJ Jr., and **Nakshatri H (1998).** NF-κB activation and IL-6 production in fibroblasts by estrogen receptor negative breast cancer cell derived IL-1α. **Proc. Natl. Acad. Sci. USA 95: 6971-6976.** PMC22705 ((110 citations)
- Chua HL, Bhat-Nakshatri P, Clare SE, Morimiya A, Badve S, **Nakshatri H (2007)** NF-κB Represses E-cadherin Expression and Enhances Epithelial to Mesenchymal Transition of Mammary Epithelial Cells: Potential Involvement of ZEB-1 and ZEB-2, **Oncogene 26:711-724.** (692 citations)
- Bhat-Nakshatri P, Kumar B, Simpson E, Ludwig KK, Cox ML, Gao H, Liu Y and **Nakshatri H (2020).** Breast cancer cell detection and characterization from breast milk-derived cells. **Cancer Research 80:4828-4839** PMC7642166.

3) Metastasis and systemic effects of cancer: We first demonstrated a role for NF-κB 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-κB 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.

- Wang R, Bhat-Nakshatri P, Padua MB, Prasad MS, Anjanappa M, Jacobson M, Finnearty C, Sefcsik V, McElyea K, Redmond R, Sandusky G, Penthala N, Crooks PA, Liu J, Zimmers T, and **Nakshatri H. (2017).** Pharmacological dual inhibition of tumor and tumor-induced functional limitations in transgenic model of breast cancer. **Molecular Cancer Therapeutics 16:2747-2758** (18 citations)
- Anjanappa M, Hao Y, Simpson ER, Bhat-Nakshatri P, Nelson JB, Tersey SA, Mirmira RG, Cohen-Gadol A, Saadatzadeh MR, Li L, Fang F, Nephew KP, Miller KD, Liu Y and **Nakshatri. H. (2018).** A system for detecting high impact-low frequency mutations in primary tumors and metastasis. **Oncogene 37:185-198** PMC5764779 (23 citations)
- Wang R, Kumar B, Doud E, Mosley A, Alexander M, Kunkel K, and **Nakshatri H. (2022).** Skeletal muscle-specific overexpression of miR-486 limits mammary tumor-induced skeletal muscle functional limitations. **Molecular Therapy- Nucleic Acids 28:231-248.** PMC8971682 (3 citations)

- Wang R, Bhat-Nakshatri P, Zhong X, Zimmers T, and **Nakshatri H. (2021).** Hormonally regulated myogenic miR-486 is a determinant of sex-specific differences in cancer-induced skeletal muscle defects. **Endocrinology 162:bqab142.** PMC8335968

4) 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.

- Campbell RA, Bhat-Nakshatri P, Patel NM, Constantinidou D, Ali S, and **Nakshatri** H. **(2001).** PI3 kinase/AKT-mediated activation of estrogen receptor alpha: a new model for anti-estrogen resistance. **J. Biol. Chem. 276:9817-9824.** (1237 citations)
- Bhat-Nakshatri P, Wang G, Appaiah H, Luktuke N, Carroll JS, Geistlinger TR, Brown M, Badve S, Liu Y, and **Nakshatri H. (2008).** AKT alters Genome-wide estrogen receptor alpha binding and impacts estrogen signaling in breast cancer. **Molecular and Cellular Biology 28:7487-7503** PMC2593438 (104 citations)
- Bhat-Nakshatri P, Wang G, Collins NR, Thomson MJ, Geistlinger TR, Carroll JS, Brown M, Hammond S, Srour EF, Liu Y, and **Nakshatri H (2009)** Estradiol-regulated microRNAs control estradiol response in breast cancer cells. **Nucleic Acids Research 37:4850-61.** PMC2724297 (481 citations).
- Bhat-Nakshatri P, Goswami CP, Badve S, Magnani L, Lupien M, and **Nakshatri H. (2016).** Molecular insights of pathways resulting from two common PI3KCA mutations in breast cancer. **Cancer Research 76:3989-4001** (23 citations)

5) Pioneer factors as prognostic markers in breast cancer: Genome-wide binding of ER is regulated by another set of transcription factors called Pioneer factors. Pioneer factors include FOXA1, GATA3, AP2gamma, and PBX1. We were the first to demonstrate prognostic utility of FOXA1 in breast cancer (reproduced by others subsequently). ER-positive breast cancers that also express higher levels of FOXA1 were responsive to anti-estrogen therapy. Additionally, we showed that insulin reduces the levels of FOXA1 and GATA3 without having an effect on ER levels. By altering FOXA1 and GATA3 levels, insulin reduced E2-dependent gene expression and rendered cancer cells resistant to anti-estrogens. From these studies, we linked insulin resistance/type II diabetes to resistance to anti-estrogen therapy.

- Badve S, Turbin D, Thorat MA, Morimiya A, Nielsen TO, Perou CM, Dunn S, Huntsman DG, and **Nakshatri H (2007).** FOXA1 expression in breast cancer- correlation with luminal subtype A and survival. **Clinical Cancer Research 13: 4415-4421.** (307 citations).
- Perkins S, Bales C, Vladislav T, Althouse S, Miller KD, Sandusky G, Badve S, and **Nakshatri H. (2015).** TFAP2C expression in breast cancer- correlation with overall survival beyond 10 years of initial diagnosis. **Breast Cancer Research and Treatment 152:519-31.** (30 citations)
- Padua MB, Bhat-Nakshatri P, Anjanappa M, Prasad MS, Hao Y, Liu S, Wan J, Liu Y, McElyea K, Jacobsen M, Sandusky G, Althouse S, Perkins S and **Nakshatri H. (2018).** Dependence receptor UNC5A restricts luminal to basal breast cancer plasticity and metastasis. **Breast Cancer Research 20:35**. PMC5932758 (18 citations)
- Chen D, Parker TM, Bhat-Nakshatri P, Chu X, Liu Y, Wang Y, and **Nakshatri H (2021**). Non-linear relationship between chromatin accessibility and estradiol-regulated gene expression. **Oncogene 40:1332-1346.** (3 citations)

Complete List of Published Work in MYBibliography:
https://www.ncbi.nlm.nih.gov/myncbi/16MHDRkPvDxAs/bibliography/public/