BIOGRAPHICAL SKETCH

Senior Trainer.

NAME: Manish S. Patankar

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

POSITION TITLE: Professor, Division of Reproductive Sciences

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Bombay	B.Sc.	1987	Chemistry
University of Bombay	M.Sc.	1990	Organic Chemistry
Old Dominion University, Norfolk, VA	M.S.	1993	Chemistry
Old Dominion University and Eastern Virginia Medical School (Joint Program), Norfolk, VA	Ph.D.	1998	Biomedical Sciences

A. Personal Statement

A major focus of my research is in developing biomarkers and therapies for ovarian cancer and preeclampsia. Role of post-doctoral researchers in my lab has been pivotal in my research efforts. I have mentored six postdoctoral candidates (Drs. Chanel Tyler, David Engle, Mian Shahzad, Shitanshu Uppal, Erin Medlin, and Laura Huffman). All six are clinicians who completed their maternal fetal medicine or gynecologic oncology fellowship research under my guidance. All six of my postdoctoral fellows are successful clinicians with four of them in faculty positions at the University of Wisconsin-Madison (UW-Madison), Moffett Cancer Center, University of Michigan, and the University of Arkansas. In addition to these postdoctoral candidates, I have also served as mentor for junior faculty members at my institution (Drs. Bryan Bednarz, Lisa Barroilhet, Derek Boeldt, Aleksandar Stanic-Kostic, and Irene Ong). I am also a trainer for masters and predoctoral candidates. I am currently mentoring three doctoral students and serve on the dissertation committees of four additional mentees.

I am dedicated to mentoring postdoctoral candidates and have also received training in mentoring through the Institute for Clinical and Translational Research (ICTR) at UW-Madison. My mentoring philosophy is based on (a) understanding the strengths and future goals of my mentees, (b) defining clear expectations and (c) providing constructive and objective feedback. I meet with all of my mentees at least once a week on a formal basis and I am available throughout the week for impromptu discussions especially pertaining to designing experiments and analysis of experimental data. I also conduct weekly lab meetings and a journal club which provide further opportunities for mentorship. I am the Associate Director of the Endocrinology and Reproductive Physiology Graduate program and also serve on its steering committee and as the chair of its admissions committee. I also teach in the Responsible Conduct of Research (RCR) course directed by Dr. Ian Bird, the PI of the current T32 application. All of these activities demonstrate my dedication to mentorship and training. My research is interdisciplinary with active collaborations with faculty in basic and clinical science departments as well as in bioengineering. I am therefore confident of providing my future postdoctoral mentees a well-rounded research experience and help them in their career goals as scientists who conduct top-notch biomedical research.

Publications that are most relevant to this proposal:

1. Shahzad MMK, Felder M, Ludwig K, Van Galder HR, Anderson ML, Kim J, Cook ME, Kapur AK, Patankar MS. Trans10,cis12 conjugated linoleic acid inhibits proliferation and migration of ovarian cancer cells by inducing ER stress, autophagy, and modulation of Src. PLoS One. 2018;13(1):e0189524. Epub 2018/01/13. doi: 10.1371/journal.pone.0189524. PubMed PMID: 29324748; PubMed Central PMCID: PMCPMC5764254.

2. Tyler C, Kapur, A., Felder, M., Belisle, JA, Trautman, C, Gubbels JAA, Connor, JP, Patankar, MS. The mucin MUC16 (CA125) binds to NK cells and monocytes from peripheral blood of women with healthy pregnancy and preeclampsia. American Journal of Reproductive Immunology. 2012;68(1):28-37.
3. Engle DB, Belisle JA, Gubbels JA, Petrie SE, Hutson PR, Kushner DM, Patankar MS. Effect of acetyl-l-carnitine on ovarian cancer cells' proliferation, nerve growth factor receptor (Trk-A and p75) expression, and the cytotoxic potential of paclitaxel and carboplatin. Gynecol Oncol. 2009;112(3):631-6. PubMed PMID: 19263582.
4. Liu Y, Whelan RJ, Pattnaik BR, Ludwig K, Subudhi E, Rowland H, Claussen N, Zucker N, Uppal S, Kushner DM, Felder M, Patankar MS, Kapur A. Terpenoids from Zingiber officinale (Ginger) induce apoptosis in endometrial cancer cells through the activation of p53. PLoS One. 2012;7(12):e53178. doi: 10.1371/journal.pone.0053178. PubMed PMID: 23300887; PubMed Central PMCID: PMC3534047.

B. Positions and Honors

Positions

1990	Research Assistant, Hoechst Research Center, India
1990-1993	Graduate Teaching Assistant, Old Dominion University, Norfolk, VA
1993-1998	Graduate Research Assistant, Eastern Virginia Medical School, Norfolk, VA
1998-1999	Post-Doctoral Fellow, Eastern Virginia Medical School, Norfolk, VA
1999-2002	Instructor, Eastern Virginia Medical School, Norfolk, VA
2002-2004	Research Assistant Professor, Eastern Virginia Medical School, Norfolk, VA
2004-2010	Assistant Professor, Division of Reproductive Sciences, University of Wisconsin School of Madison and Public Health
2004-present	Member, University of Madison Comprehensive Cancer Center
2010-2015	Associate Professor, Division of Reproductive Sciences, University of Wisconsin School of Madison and Public Health
2011-present	Faculty Director, Flow Cytometry Core, University of Wisconsin Comprehensive Cancer Center
2016-present	Professor, Division of Reproductive Sciences, University of Wisconsin School of Madison and Public Health
2016-present	Associate Director, Endocrinology and Reproductive Physiology graduate program at the University of Wisconsin-Madison

Other Experience and Professional Memberships

2001	Member NIH Minority Biomedical Research Support (MBRS) program study section
2007	Member of AACR
2008	Member of Consortium for Functional Glycomics, an NIH Funded consortium for studying and identifying carbohydrate binding proteins in the immune system
2009	Reviewer for NIH RC1 challenge grants
2009	Member of NIH study section (Special Emphasis Panel/Scientific Review Group 2009/10 ZRG1 IMM-G (10) B) to review Immunology-focused STTR and SBIR grants.
2009	Reviewer for grants submitted to the Wellcome Trust, UK
2009	Reviewer for *Journal of Immunology, Disease Markers, Journal of Ovarian Research,* and *Biomaterials*
2010	Member of NIH study section (Special Emphasis Panel/Scientific Review Group) to review Immunology-focused STTR and SBIR grants.
2011	Member of the DoD Cell Biology study section for the Ovarian Cancer Research Program
2012	Member of the DoD Cell and Molecular Biology study section for the Ovarian Cancer Research Program
2013	Member of the Developmental Therapeutics study section of the NIH
2013	Member of NIH study section (Special Emphasis Panel/Scientific Review Group) to review Immunology-focused STTR and SBIR grants.
2014	Member of the DoD Cell and Molecular Biology study section for the Ovarian Cancer Research Program

2015 Member of training grants and P01 study section of the NIH
2016 Member of P01 and SPORE grants study section of the NIH

C. Contribution to Science

***Understanding the importance of MUC16 in ovarian tumor progression*.** Ovarian tumors overexpress MUC16. A major focus of my research effort is to understand the biology of MUC16 and its importance in ovarian cancer progression. To this end we have demonstrated that MUC16 facilitates peritoneal metastasis of ovarian tumors by serving as a binding partner for mesothelin, a GPI-linked glycoprotein expressed on the peritoneal mesothelial cells. Additionally we have also shown that because of MUC16 expression, ovarian tumors exhibit a higher degree of growth. This increase in tumor growth is associated with the ability of MUC16 to inhibit the cytolytic function of natural killer cells.

a. Gubbels JA, Felder M, Horibata S, Belisle JA, Kapur A, Holden H, Petrie S, Migneault M, Rancourt C, Connor JP, Patankar MS. "MUC16 provides immune protection by inhibiting synapse formation between NK and ovarian tumor cells." *Molecular Cancer*. 2010; 9:11. PMCID: PMC2818693.

b. Gubbels JA, Belisle J, Onda M, Rancourt C, Migneault M, Ho M, Bera TK, Connor J, Sathyanarayana BK, Lee B, Pastan I, Patankar MS. "Mesothelin-MUC16 binding is a high affinity, N-glycan dependent interaction that facilitates peritoneal metastasis of ovarian tumors." *Molecular Cancer*. 2006; 5:50. PMCID: PMC1635730.

c. Patankar MS, Jing Y, Morrison JC, Belisle JA, Lattanzio FA, Deng Y, Wong NK, Morris HR, Dell A, Clark GF. "Potent suppression of natural killer cell response mediated by the ovarian tumor marker CA125." *Gynecologic oncology*. 2005; 99:704-13. PMCID exempt

***Developing biomarkers for early detection of Preeclampsia and ovarian cancer*.** Currently, there are no biomarkers available for early detection of ovarian cancer. The only biomarker for this disease is CA125, a repeating peptide epitope present in a large (3-5 million Da) mucin, MUC16. The exact structure of the CA125 epitope that is recognized in a clinically used serum assay for this antigen is not well defined. I therefore undertook a project to define the complex structure of MUC16 with hopes to not only identify the CA125 epitope but also detect other facets of this mucinous molecule that can be exploited to develop a novel bioassay that can be used for early detection of ovarian cancer. With this intent I collaborated with Drs. Anne Dell and Howard Morris, the world's experts on mass spectrometry of oligosaccharides to characterize the N- and O-linked glycans attached to MUC16. This data is now being used in a collaboration with Dr. Ola Blixt (University of Copenhagen) to develop a lectin-based assay for detection of ovarian cancer. My studies also allowed us to determine that the α2,3-sialic acid residues present in MUC16 are recognized by the immune cell receptor Siglec-9 and this interaction leads to binding of the mucin to specific immune cells. Since MUC16 is also expressed during pregnancy, we also explored if binding of this mucin to immune cells in preeclamptic patients also follows a different pattern than that observed in normal pregnancy. This hypothesis was proven to be correct by our work published. These results led us to further hypothesize that monitoring the proteome and transcriptome of circulating immune cells can lead to a novel method for identification of ovarian cancer and preeclampsia biomarkers. We have recently conducted RNASeq analysis of immune cells from preeclamptic women and women with healthy pregnancies as well as ovarian cancer patients and healthy women and have found major differences in their transcriptomes. This data is being mined using bioinformatics tools in collaboration with Dr. Jesus Gonzalez-Bosquet and further analysis of additional samples from human subject and mouse models for preeclampsia ovarian cancer is currently underway to test our hypothesis that circulating immune cells can serve as an important source for biomarker discovery. Although our studies are focused on preeclampsia and ovarian cancer, if proven, this concept can also be applied to other cancers and pathological conditions.

a. Felder M, Kapur A, Gonzalez-Bosquet J, Horibata S, Heintz J, Albrecht R, Fass L, Kaur J, Hu K, Shojaei H, Whelan RJ, Patankar MS. MUC16 "(CA125): tumor biomarker to cancer therapy, a work in progress." *Molecular Cancer*. 2014; 13:129. PMCID: PMC4046138. Highly Accessed.

b. Ma D, Cao W, Kapur A, Felder M, Scarlett CO, Patankar MS, Li L. "Differential expression of proteins in naive and IL-2 stimulated primary human NK cells identified by global proteomic analysis." *Journal of proteomics*. 2013; 91:151-63. PMCID: PMC4326111.

c. Kui Wong N, Easton RL, Panico M, Sutton-Smith M, Morrison JC, Lattanzio FA, Morris HR, Clark GF, Dell A, Patankar MS. "Characterization of the oligosaccharides associated with the human ovarian tumor marker CA125." *The Journal of Biological Chemistry*. 2003; 278:28619-34. PMCID exempt

d. Methods and kits to detect and monitor ovarian cancer and preeclampsia US 8492104 B2

***Developing natural product-based therapies for cancer*.** Over the past three years, I have undertaken a major research initiative to identify natural products found in botanicals and dairy products that inhibit proliferation of ovarian and other tumors. These efforts have led to identification of cis10:trans12 conjugated linoleic acid as a potent inhibitor of tumor cell proliferation through the induction of endoplasmic reticulum stress and autophagy (Shahzad et al, manuscript submitted). In addition to this project, my lab has now also identified that specific monoterpenes present in the rhizomes of the commonly used spice, ginger, are very effective in reducing tumor progression. Research conducted by my lab shows that the monoterpenes that contain an α,β-unsaturated carbonyl compound are potent mediators of cancer cell death. These compounds induce an oxidative response, which causes DNA damage and subsequent activation of apoptotic and autophagic signaling cascades in the cancer cells. In collaboration with Dr. May Xiong's group (College of Pharmacy), we have now developed a nanoparticle-based delivery system that allows us to deliver these monoterpene agents to tumors and reduce the progression of breast tumors in mice.

a. Zeng S, Kapur A, Patankar MS, Xiong M. "Formulation, characterization, and antitumor properties of trans- and cis-citral in the 4T1 breast cancer xenograft mouse model." 2015; 32:2548-58. PMCID: PMC4490114

b. Liu Y, Whelan RJ, Pattnaik BR, Ludwig K, Subudhi E, Rowland H, Claussen N, Zucker N, Uppal S, Kushner DM, Felder M, Patankar MS, Kapur A. "Terpenoids from *Zingiber officinale* (Ginger) induce apoptosis in endometrial cancer cells through the activation of p53." *PloS ONE*. 2012; 7:e53178. PMCID: PMC3534047.

***Developing immunocytokines to treat ovarian cancer*.** Immunocytokines are antibody-cytokine chimeras that can bind to cancer cells and recruit innate and adaptive immune responses against the tumors. In collaboration with Dr. Paul Sondel (UW-Madison) and Dr. Steve Gillies (Provenance Pharmaceuticals) we are exploring the use of 215-IL2 an immunocytokine that binds to ovarian cancer cells and recruits immune response via its IL-2 chains. We are developing data in preclinical models to demonstrate efficacy of this immunocytokine. This data will be used to develop future clinical trials with the 215-IL2 immunocytokine. Our work has led to the novel observation that the immunocytokines recruit immune cells to the tumor by mediating an immunologic synapse that is formed by clustering of IL-2 Receptor on the immune cells at the junction between tumor target and Natural Killer cells. We are now exploiting this observation to develop methods by which the immune cells can be further attracted to the tumor by developing more efficient and selective ways of displaying IL-2 on the surface of the tumor cells. Representative publications on this topic are listed below.

a. Buhtoiarov IN, Neal ZC, Gan J, Buhtoiarova TN, Patankar MS, Gubbels JA, Hank JA, Yamane B, Rakhmilevich AL, Reisfeld RA, Gillies SD, Sondel PM. "Differential internalization of hu14.18-IL2 immunocytokine by NK and tumor cell: impact on conjugation, cytotoxicity, and targeting." *Journal of Leukocyte Biology*. 2011; 89:625-38. PMCID: PMC3058817.

b. Gubbels JA, Gadbaw B, Buhtoiarov IN, Horibata S, Kapur AK, Patel D, Hank JA, Gillies SD, Sondel PM, Patankar MS, Connor J. "Ab-IL2 fusion proteins mediate NK cell immune synapse formation by polarizing CD25 to the target cell-effector cell interface." *Cancer Immunology Immunotherapy* 2011; 60:1789-800. PMCID: PMC4153733.

Complete List of Published Work in MyBibliography:

http://www.ncbi.nlm.nih.gov/sites/myncbi/manish.patankar.1/bibliography/47617168/public/?sort=date&direction=ascending

D. Research Support

ACTIVE

1R01CA206561-01 Multiple PI: Campagnola, Patankar, Elicieri 5/1/2016-4/30/2021
National Institutes of Health
Title: Quantitative assessment of the role of collagen alterations in ovarian cancer
Goal: This project will examine the altered collagen observed in ovarian cancer and its significance in developing novel imaging diagnostics and cancer progression.

Role: co-PI

1R01CA232517-01 Multiple PI: Campagnola, Kreeger, Masters 07/01/2018-06/30/2023
National Institutes of Health
Title: Engineered ECM platforms to analyze progression in high grade serous ovarian cancer
Goal: Development of 3-D in vitro biomimetic models for ovarian cancer to study the role of the extracellular matrix in the development of primary cancer lesions and metastasized tumors.
Role: Co-I

Intramural Funding PI: Patankar 6/1/2018-5/31/2019
Department of Obstetrics and Gynecology
Title: Fusokine-activated peritoneal innate lymphoid cell therapy for ovarian cancer
Goal: Rhesus and other monkeys develop endometriosis-associated ovarian and peritoneal neoplasms. In this project we will determine if the neoplasms are similar to Clear Cell Ovarian Cancer and if the rhesus can be developed as amodel for Type I ovarian cancer.
Role: PI