BIOGRAPHICAL SKETCH

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NAME: **Vivek M. Rangnekar, PhD**

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

POSITION TITLE: Professor, Department of Radiation Medicine
Associate Director for Strategic Relations, Markey Cancer Center
Co-leader, Cancer Cell Biology and Signaling Program

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	Completion Date	FIELD OF STUDY
University of Bombay, Mumbai, India	BSc	06/1976	Microbiology
University of Bombay, Mumbai, India	MSc	12/1979	Microbiology
University of Bombay, Mumbai, India	PhD	05/1983	Microbiology
University of Chicago, Chicago, IL	Postdoctoral	12/1985	Molecular Genetics

A. Personal Statement

I have a broad background in cancer molecular and cell biology, with specific training and expertise in key research areas related to this application. I have over 20 years of research experience in cancer biology, molecular biology, signal transduction, drug discovery/development and moving compounds to clinical trials. Moreover, I have initiated a number of new projects that test the association of certain biomarkers for breast cancer in individuals from the Appalachian and non-Appalachian regions of Kentucky, as well as the response to therapy resulting in short- or long-term patient survival. I have served on numerous DoD review panels; NCI study sections (including charter membership of Path B study section from 1998-2003); and Program Project P01, U54, and special emphasis panels. I served on the Editorial Board of *Apoptosis* (1998-2008) and as the Associate Editor/Receiving Editor of *Cancer Biology and Therapy* (2002-2012). I currently serve as Senior Editor of *Cancer Biology and Therapy*, and on the Editorial Board of *Genes and Cancer* (2010-present). I also served on the University of Kentucky College of Medicine Dean's Advisory Committee (2008-2011) and became the inaugural holder of the Alfred Cohen Chair in Oncology Research in 2005. I serve as PI of the Cancer Biology T32 grant from NCI for training the next generation of scientists at the NCI-designated Markey Cancer Center for careers in cancer research. This T32 currently trains 3 postdoctoral fellows and 1 graduate student. In the previous funding cycle of the T32, we trained 3 postdoctoral fellows and 5 graduate students, including 2 minority students from the underserved areas of Appalachian Kentucky. I have extensive experience and aptitude in mentoring activities, and have mentored over 45 trainees, including graduate students, postdoctoral fellows, medical residents, and junior basic science faculty and physician-scientists, which are currently well-placed in academia or the private industry. My research projects have received continuous funding from NCI since 1990. I have published over 100 research articles and edited two volumes of a book focused on programmed cell death. I initiated and developed the first cancer biology graduate level course, Biology and Therapy of Cancer in Spring 2005 at the University of Kentucky and have been directing this course since then. As principal investigator or co-investigator on several funded grants, I successfully administered the projects (e.g., staffing, IACUC and IRB requirements, budgeting), collaborated with other researchers, and produced in-depth peer-reviewed publications to advance the field from the bench to the bedside. Moreover, I serve as Co-leader of the Cancer Cell Biology and Signaling Program at the Markey Cancer Center. In summary, I have conducted innovative and productive research projects in an area of high relevance to cancer.

1. Chakraborty M, Qiu SG, Vasudevan K, **Rangnekar VM**. Par-4 drives trafficking and activation of Fas and FasL to induce prostate cancer cell apoptosis and tumor regression. Cancer Res 61:7255-7263, 2001.
2. El-Guendy N, Zhao Y, Gurumurthy S, Burikhanov R, **Rangnekar VM**. Identification of a unique core domain of Par-4 sufficient for selective apoptosis induction in cancer cells. Mol Cell Biol 23:5516-5525, 2003. PMCID: PMC166354

3. Burikhanov R, Zhao Y, Goswami A, Qiu S, Schwarze SR, **Rangnekar VM**. The tumor suppressor Par-4 activates an extrinsic pathway for apoptosis. Cell 138:377-388, 2009. PMCID: PMC2774252
4. Shrestha-Bhattarai T, Hebbar N, **Rangnekar VM**. Par(-4)oxysm in breast cancer. Cancer Cell 24:3-5, 2013. PMCID: PMC3743248

B. Positions and Honors

Positions and Employment

1986-1987 Research Associate, Rush Presbyterian St. Luke's Medical Center, Chicago, IL
1988-1991 Research Associate-Assistant Professor, Department of Medicine, University of Chicago, Chicago, IL
1992-1996 Assistant Professor of Surgery and Microbiology and Immunology, University of Kentucky, Lexington, KY
1996-1999 Associate Professor of Surgery and Microbiology and Immunology, University of Kentucky, Lexington, KY
1999-present Professor of Radiation Medicine and Microbiology and Immunology, University of Kentucky, Lexington, KY
2004-present Associate Director, Markey Cancer Center, University of Kentucky, Lexington, KY

Other Experience and Professional Memberships

1998-1999 Ad hoc Member, Pathology B Study Section, NCI/NIH
1998-2001 Prostate Cancer Pathobiology Review Panel, Department of Defense
1998-2008 Associate-Editor, Apoptosis
1999-2003 Full Member, Pathology B Study Section, NCI/NIH
2000-2001 Review Panel, Prostate and Breast Cancer Cell Biology, Department of Defense
2001-2004 NIH/NCI Ad hoc Reviewer for P01 grants
2002-2012 Associate-Editor/Receiving Editor, Cancer Biology & Therapy
2004-2005 Review Panel, Prostate Cancer Pathobiology, Department of Defense
2004-2006 Ad hoc Member, TPM Study Section
2004-2013 Associate Director for Translational Research, Markey Cancer Center
2006 Ad hoc Member, U54 TMEN grants
2009 NIH/NCI Ad hoc Reviewer, CE Study Section
2009-present Co-Leader, Cancer Cell Biology and Signaling Program, Markey Cancer Center
2009-present Editorial Board/Receiving Editor, Genes & Cancer
2011 Chair, Markey Cancer Center Pilot Grants Committee
2011-2013 Chair, Markey Cancer Center Biospecimen Steering Committee
2011-present Chair, Markey Cancer Center Membership Committee
2015-2021 NIH/NCI Chartered Member, BMCT Study Section
2013-present Senior Editor, Cancer Biology & Therapy
2013-present Associate Director, Strategic Relations, Markey Cancer Center

Honors

1997 CaPCURE Award, Prostate Cancer Foundation, CA
2005 Alfred Cohen Endowment Chair, University of Kentucky
2007 George Strawbridge Endowment, University of Kentucky
2007-2010 Wethington Award, University of Kentucky
2008 Dean’s Distinguished Lecture, College of Medicine, University of Kentucky
2010 Rotary International Award of Excellence
2013-2014 Wethington Award, University of Kentucky

C. Contributions to Science

1. My laboratory first identified the prostate apoptosis response-4 (Par-4; later also known as PAWR) gene, showed that it is down-modulated or inactivated in tumors, and delineated the mechanism underlying its cancer-selective apoptotic action. We showed that Par-4 is ubiquitously expressed in diverse cell types and tissues, and is required for apoptosis by various cellular insults. By using cell culture models and by generating transgenic mouse models, we showed that upregulation of Par-4 induces apoptosis selectively in cancer cells, not in normal cells. We identified the effector SAC domain (Selective for Apoptosis of

Cancer cells) of Par-4 that is necessary and sufficient to induce apoptosis selectively in cancer cells, and delineated the mechanism underlying Par-4/SAC phosphorylation by protein kinase A, which provides selective induction of apoptosis in cancer cells. Importantly, we first showed that Par-4 is downregulated in renal cell carcinoma or inactivated by Akt1, which binds and phosphorylates Par-4, in prostate cancer. These findings led to a number of new studies by other laboratories on various cancers to demonstrate that Par-4 is downregulated in breast cancer, nasopharyngeal tumors and glioblastoma. Moreover, our work on the Par-4-Akt1 interaction positioned Par-4 in the PI3K/Akt pathway for the design of innovative cancer-selective therapeutics. These findings provided the rationale for the identification of various partner proteins for Par-4 that regulate its pro-apoptotic function and for generating knock-out mice that lacked Par-4/SAC by other laboratories. These knockout mice, as expected from our previous publications, developed spontaneous or inducible tumors at much higher frequency than was found in the control mice. Our recent work on overcoming therapy-resistant tumor growth led to the identification and mechanism of action of a novel amino-terminal domain PAF of Par-4 that induces apoptosis and growth inhibition of therapy-resistant tumors.

a. Gurumurthy S, Goswami A, Vasudevan KM, **Rangnekar VM**. Phosphorylation of Par-4 by protein kinase A is critical for apoptosis. Mol Cell Biol 25:1146-1161, 2005. PMCID: PMC544017
b. Goswami A, Burikhanov R, de Thonel A, Fujita N, Goswami M, Zhao Y, Eriksson JE, Tsuruo T, **Rangnekar VM**. Binding and phosphorylation of Par-4 by Akt is essential for cancer cell survival. Mol Cell 20:33-44, 2005.
c. Zhao Y, Burikhanov R, Qiu S, Lele SM, Jennings CD, Bondada S, Spear B, **Rangnekar VM**. Cancer resistance in transgenic mice expressing the SAC module of Par-4. Cancer Res 67:9276-9285, 2007.
d. Hebbar N, Burikhanov R, Shukla Ni, Qiu S, Zhao Y, Elenitoba-Johnson KSJ, and **Rangnekar VM.** A naturally generated decoy of the prostate apoptosis response-4 protein overcomes therapy resistance in tumors. Cancer Res June 16 2017 DOI:10.1158/0008-5472.CAN-16-1970

2. We showed that Par-4 is down-modulated by oncogenes, and identified the role of the Raf-MEK-ERK pathway in Par-4 suppression. Moreover, we showed that Par-4 binds to WT1 and Topoisomerase 1 via its carboxyl-terminal leucine zipper domain and inhibits NF-kB activity as well as Bcl-2 expression. We showed that Par-4 activates the Fas death receptor signaling pathway. These studies indicated co-parallel upregulation of death receptor signaling and downregulation of NF-kB cell survival signaling by Par-4. Our findings formed the basis of further work by other groups showing that oncogenes cause down-regulation of Par-4; that the WT1-Par-4 complex binds to the Bcl-2 promoter to suppress Bcl-2 expression and promote all-trans retinoic acid inducible apoptosis; and that oncogenic Ras activates DNA methylases downstream of ERK activation to inhibit Par-4 expression.
   a. Johnstone RW, See RH, Sells S.F, Wang J, Muthukkumar S, Englert C, Haber DA, Licht J, Sugrue SP, Roberts T, **Rangnekar VM**, Shi Y. A novel repressor par-4 modulates transcription and growth suppression functions of the Wilms' tumor suppressor, WT1. Mol Cell Biol 16:6945-6956, 1996. PMCID: PMC231698
   b. Nalca A, Qiu SG, El-Guendy N, Krishnan S, **Rangnekar VM**. Oncogenic Ras sensitizes cells to apoptosis by Par-4. J Biol Chem 274:29976-29983, 1999.
   c. Qiu G, Ahmed M, Sells SF, Mohiuddin M, Weinstein MH, **Rangnekar VM**. Mutually exclusive expression patterns of Bcl-2 and Par-4 in human prostate tumors consistent with down-regulation of Bcl-2 by Par-4. Oncogene 18:623-631, 1999.
   d. Goswami A, Qiu S, Dexheimer TS, Ranganathan P, Burikhanov R, Pommier Y, **Rangnekar VM**. Par-4 binds to topoisomerase 1 and attenuates its DNA relaxation activity. Cancer Res 68:6190-6198, 2008. PMCID: PMC2562756

3. In addition to the studies on the functional contribution of intracellular Par-4 described above, my laboratory showed that the tumor suppressor Par-4 protein is secreted by normal cells, and that it binds to its cell surface receptor GRP78 to trigger amplification of the endoplasmic stress loop and induce the apoptosis cascade. Importantly, we showed that secreted Par-4 selectively induces apoptosis in cancer cells via this pathway. We also showed that elevation of systemic levels of Par-4 using recombinant Par-4 protein resulted in inhibition of non-autochthonous lung tumors in mice. This finding led to the development of chemical biology approaches by my group to identify novel secretagogues of Par-4, such as Nutlin-3a, Arylquin and the FDA-approved compound chloroquine. In a series of publications that are of critical importance to the field, we identified the targets and mechanism of action of these small molecules in

cancer cells. We also identified the intracellular mechanisms regulating Par-4 secretion. Our findings provide the rationale for the design of new drugs to empower normal cells to secrete Par-4 for paracrine apoptosis of cancer cells and inhibition of tumor growth. Collectively, these findings have resulted in a clinical trial using the FDA-approved Par-4 secretagogue chloroquine in cancer patients at the Markey Cancer Center.

a. Burikhanov R, Shrestha-Bhattarai T, Qiu S, Shukla N, Hebbar N, Lele SM, Horbinski C, **Rangnekar VM**. Novel mechanism of apoptosis resistance in cancer mediated by extracellular PAR-4. Cancer Res 73:1011-1019, 2013. PMCID: PMC3549021
b. Burikhanov R, Shrestha-Bhattarai T, Hebbar N, Qiu S, Zhao Y, Zambetti G, **Rangnekar VM**. Paracrine apoptotic effect of p53 mediated by tumor suppressor Par-4. Cell Rep 6:271-277, 2014. PMCID: PMC3922895
c. Burikhanov R, Sviripa VM, Hebbar N, Zhang W, Layton WJ, Hamza A, Zhan C-G, Watt DS, Liu C, **Rangnekar VM**. Arylquins target vimentin to trigger Par-4 secretion for tumor cell apoptosis. Nat Chem Biol 10:924-926, 2014. PMCID: PMC4201913
d. Burikhanov R, Hebbar N, Noothi SK, Shukla N, Sledziona J, Araujo N, Kudrimoti M, Wang QJ, Watt DS, Welch DR, Maranchie J, Harada A, **Rangnekar VM.** Chloroquine-inducible Par-4 secretion Is essential for tumor cell apoptosis and inhibition of metastasis. Cell Rep 18:508-519, 2017. PMCID: PMC5264245

Complete List of Published Work in PubMed**:**
http://www.ncbi.nlm.nih.gov/pubmed/?term=Rangnekar+VM

D. Research Support

Ongoing

R01 CA187273 (PI: Rangnekar, VM) 07/01/15-06/30/20
NIH/NCI
"Suppression of Prostate Tumor Growth and Metastasis by Inhibition of Vimentin"
Goals: This study will determine the mechanism of small molecule Arylquin on vimentin inhibition and Par-4 secretion and effects on prostate cancer progression and metastasis.
Role: PI

R01 CA165469 (MPI: Bondada, S; Rangnekar, VM) 02/07/13-01/31/19
NIH/NCI
"Role of Tcl1 and Par-4 in Regulation of Chronic Lymphocytic Leukemia"
Goals: 1) To determine the importance of BCR signaling and the role of specific SFKs in the regulation of Tcl-1 and Par-4 expression using the Eì-Tcl-1 mouse model of CLL. 2) To investigate the importance of Par-4 overexpression for CLL development using a newly generated inducible Par-4 transgenic mice mouse model and the Eì-Tcl-1 mice. 3) Will involve preclinical studies to test the efficacy of extracellular Par-4 and SAC to inhibit CLL growth in the Eì-Tcl-1 mouse model.
Role: MPI

R21 CA179283 (PI: Rangnekar, VM) 04/01/14-03/31/18
NIH/NCI
"Regulation of Par-4 Secretion in Normal Cells for Paracrine Action in Tumor Cells"
Goals: This study will determine the role of p53 in regulation of Par-4 secretion for paracrine apoptotic effects on cancer cells and mouse lung tumor models.
Role: PI

T32 CA165990 (MPI: Rangnekar, VM [contact]; Evers, BM) 04/01/13-03/31/21
NIH/NCI
"Interdisciplinary Research Training in Cancer Biology"
Goals: The ultimate objective is to develop a cadre of future scientists who can become leaders in integrative team approaches to understand the complex issue of cancer as it relates to potential prevention and treatment strategies.
Role: MPI [contact]

P30 CA177558 (PI: Evers, BM) 07/08/13-06/30/18
NIH/NCI
“University of Kentucky Markey Cancer Center – Cancer Center Support Grant”
Goals: To support the ongoing research infrastructure, research programs, shared resources, developmental funds, and administration of the Markey Cancer Center to ensure the development of more effective approaches to cancer prevention, diagnosis, and therapy.
Role: Program Co-leader, Cancer Cell Biology and Signaling