

AWARD NUMBER: W81XWH-17-1-0273

TITLE: Cyclin-Dependent Kinase 9, A Potential Therapeutic Target in
Gastric Adenocarcinoma: An In Vitro and In Vivo Efficacy Study

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14. ABSTRACT Cyclin dependent kinase 9 (CDK9) is a promising potential therapeutic target in gastric adenocarcinoma (GAC) because of its critical role in transcription of pleiotropic pathways involved in GAC. We hypothesize that CDK9 may be a critical mediator of growth and/or metastatic progression in GAC and functional downregulation of CDK9 will inhibit local growth and/or distant metastasis. Treatment of KKLS, IM95/CMV-luc, MKN-45-luc, KATO-III and AGS cell lines with CDK9 inhibitor (BAY1143572) demonstrated anticancer efficacy by proliferation (MTS), cell cycle, and apoptosis assays (p<0.05). Cell lysates of GAC cell treated with BAY1143572 are prepared to identify candidate CDK9-specific markers indicative of BAY1143572 efficacy by reverse phase protein assay (RPPA) to identify CDK9-dependent molecular targets after CDK9 inhibition. In vivo, BAY1143572 treated IM95/CMV-luc and MKN-45-luc ectopic xenografts inhibited tumor growth in a dose dependent manner compared to control tumors (p<0.05). Drug efficacy of BAY1143572 in a novel orthotopic gastroesophageal junction cancer model is currently being evaluated. Identifying trends in tumor regression (local vs. metastatic) induced by CDK9 inhibition will provide direction in understanding mechanism of action of CDK9 in GAC. Establishing the antitumor efficacy of BAY1143572 in the proposed experiments will pave the way for further exploration of this therapeutic strategy in GAC patients.					
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Title:

Cyclin-Dependent Kinase 9, A Potential Therapeutic Target in Gastric Adenocarcinoma: An *In Vitro* and *In Vivo* Efficacy Study

Abstract (200 words for form SF298):

Cyclin dependent kinase 9 (CDK9) is a promising potential therapeutic target in gastric adenocarcinoma (GAC) because of its critical role in transcription of pleiotropic pathways involved in GAC. We hypothesize that CDK9 may be a critical mediator of growth and/or metastatic progression in GAC and functional downregulation of CDK9 will inhibit local growth and/or distant metastasis. Treatment of KKLS, IM95/CMV-luc, MKN-45-luc, KATO-III and AGS cell lines with CDK9 inhibitor (BAY1143572) demonstrated anticancer efficacy by proliferation (MTS), cell cycle, and apoptosis assays ($p < 0.05$). Cell lysates of GAC cell treated with BAY1143572 are prepared to identify candidate CDK9-specific markers indicative of BAY1143572 efficacy by reverse phase protein assay (RPPA) to identify CDK9-dependent molecular targets after CDK9 inhibition. *In vivo*, BAY1143572 treated IM95/CMV-luc and MKN-45-luc ectopic xenografts inhibited tumor growth in a dose dependent manner compared to control tumors ($p < 0.05$). Drug efficacy of BAY1143572 in a novel orthotopic gastroesophageal junction cancer model is currently being evaluated. Identifying trends in tumor regression (local vs. metastatic) induced by CDK9 inhibition will provide direction in understanding mechanism of action of CDK9 in GAC. Establishing the antitumor efficacy of BAY1143572 in the proposed experiments will pave the way for further exploration of this therapeutic strategy in GAC patients.

Specific Aims: Aim 1: Assess the antitumor effects of CDK9 inhibition by BAY1143572 or shRNA-mediated downregulation on GAC cells and identify CDK9-dependent molecular targets after CDK9 inhibition. Aim 2: Assess the antitumor efficacy of CDK9 inhibition by shCDK9 or BAY1143572 in GAC ectopic xenografts and test markers of response to CDK9 inhibition identified *in vitro*. Aim 3: Assess the efficacy of shCDK9 or BAY1143572 in inhibiting metastases in GEJ orthotopic xenografts and the relevance of markers of CDK9 in the metastatic setting.

Introduction:

Subject: Gastric cancer remains a leading cause of death worldwide. Despite the aggressive standard of care involving gastrectomy with neoadjuvant and/or postoperative chemoradiotherapy, the 5-year survival rate of patients with stage III GAC is 25-35%. Improvements in outcome for patients with advanced disease are limited by tumor heterogeneity and low frequency of predictive markers. Biomarker-driven targeted therapy has very limited success in GAC. **Purpose:** Thus there is an urgent need for new-targeted therapies for GAC patients. CDKs play a multifactorial role in cell cycle progression and transcriptional regulation. CDK9 is one of the “transcriptional” CDKs that promotes initiation and elongation of nascent RNA transcripts by phosphorylating the carboxyl terminal domain of Pol II. Deregulation of CDK9 has been associated with multiple hematologic and solid cancers. The anticancer effects of FDA-approved CDK inhibitors in hematologic malignancies are mediated by targeting MCL-1, a regulator of cell growth in GAC cells. Additionally, CDK9 modifies the transcription of several other proteins critical in cell

processes that are altered in oncogenesis. **Scope:** This wide scope of CDK9 inhibition and ubiquitous expression of CDK9 provide an opportunity to explore CDK9 as a potential new therapeutic target and to identify a CDK9-specific marker as a predictor of response to anti-CDK9 therapy. Our preliminary work indicates overexpression of CDK9 in GAC patient tumors and in GAC cell lines. Prior preclinical studies have shown that CDK inhibitors (with predominant CDK9-inhibitory activity) combined with conventional therapeutic agents have greater efficacy than either agent alone in solid tumors. Our work in esophageal adenocarcinoma (EAC) has shown *in vitro* synergy between flavopiridol (established CDK9 inhibitor) and 5-FU and *in vivo* synergy between flavopiridol and localized radiation, in contrast to modest activity seen with single-agent treatment. The proposed experimental methodology includes both pharmaceutical inhibition by a novel selective CDK9 inhibitor (BAY1143572) and genetic downregulation of CDK9 (shCDK9 or CRISPR/cas9 plasmids) utilizing the resources at MD Anderson as mentioned in Research Strategy.

Keywords:

Stomach cancer, GAC, CDK9, gastro-esophageal junction (GEJ) orthotopic xenografts, invasion, metastasis, BAY1143572, shCDK9, anticancer efficacy, oncogenes, biomarkers

Accomplishments:

1. Demonstrated *in vitro* and *in vivo* efficacy of BAY1143572 in GAC models.
2. Established orthotopic GAC xenograft models with 2 different cell lines (IM95/CMV-luc and MKN-45-luc) characterized by different histology and molecular subtypes of GAC.
3. Completed pre-analytic steps for all samples for RPPA-biomarker analysis.
4. Presented our work titled ‘A novel metastatic orthotopic GEJ mouse model of GAC and EAC’ at “Pathology of mouse models for human disease” workshop organized by Jackson Laboratory.
5. Presented research at the Annual Retreat and at monthly department group meetings and multidisciplinary research meetings in gastric cancer at MD Anderson.
6. Attended institutional workshop on writing and publishing scientific articles.
7. Manuscript focusing on establishing orthotopic GAC mouse models with distinct histological and molecular characteristics and effects of local radiation is in the final stages of submission.

What were the major goals of the project?

Goal 1: Evaluate the *in vitro* efficacy of CDK9 inhibition and identification of CDK9 specific predictive marker of response in various gastric cancer cell lines. **To be accomplished in 1st year.**

Sub goals 1: Generate additional stable shCDK9-knockdown cell lines via transduction with shGFP or shCDK9 by lentivirus. Cell lines used: MKN-45-luc, IM95/CMV-luc

Sub goals 2: Examine the antiproliferative effects of BAY1143572 or shCDK9 in cancer cells using MTS assay. Cell lines used: KKLS, NCI-N87, KATO-III, MKN-45-luc, IM95/CMV-luc.

Sub goals 3: Examine the effects of BAY1143572 and shCDK9 on cancer cells by using invasion and

migration assays. Cell lines used: KKLS, NCI-N87, KATO-III, MKN-45-luc and IM95/CMV-luc.

Sub goals 4: Identify a predictor biomarker of response to anti-CDK9 therapy in cancer cells using Reverse Phase Protein Array [RPPA]. Cell lines used: KKLS, NCI-N87, KATO-III, MKN-45-luc and

Sub goals 5: IM95/CMV-luc. Test the predictive biomarker of response to anti-CDK9 therapy in cancer cells by western blot or immunocytochemistry (IHC). Cell lines used: KKLS, NCI-N87, KATO-III, MKN-45-luc and IM95/CMV-luc.

What was accomplished under these goals?

1. Demonstrated *in vitro* efficacy of BAY1143572 in KKLS, KATO-III, IM95/CMV-luc, MKN-45-luc, AGS and NCI-N87 GAC cells on proliferation by MTS, cell cycle and apoptosis assays by flow cytometry (Figures 1, 2 and 3).
2. Invasion and migration assays in KKLS, KATO-III, IM95/CMV-luc, MKN-45-luc, AGS and NCI-N87 GAC cells are established.
3. RPPA lysates of KKLS, KATO-III, IM95/CMV-luc, MKN-45-luc, AGS and NCI-N87 cells treated with BAY1143572 are prepared and sent to the RPPA core lab.

Progress Against Timeline: Ahead of Schedule. Work was performed between project start date, October 1st to June 15th (duration of 7.5 months). I was on leave of absence from June 15th to August 20th due to visa renewal process. Thus except for shCDK9 related work, everything else is ahead of schedule.

Goal 2: To test the antitumor efficacy of anti-CDK9 therapy in GAC ectopic xenografts and to confirm CDK9-dependent molecular targets. **To be accomplished in 2nd year.**

Sub goal 1: Obtain institutional IACUC and DoD ACURO approval for animal use.

Sub goal 3: Evaluate antitumor efficacy of BAY1143572 on GAC xenografts. Cell lines used: 2 cell lines based on results from Specific Aim 1.

What was accomplished under these goals?

1. DoD ACURO approval received on Jan 16th 2018.
2. Demonstrated *in vivo* efficacy of BAY1143572 in dose dependent manner (7.5 and 15 mg/kg body weight) in IM95/CMV-luc and MKN-45-luc subcutaneous xenografts (n=15 per group). (Figures 4, 5, 6 and 7).

Progress Against Timeline: Ahead of Schedule. Work was performed between ACURO approval date, March 1st to June 15th.

Goal 3. To test the antitumor efficacy of anti-CDK9 therapy in orthotopic GEJ cancer mouse model of rapid metastasis and to test CDK9-dependent molecular targets on CDK9 inhibition in the metastatic tumor specimen. **To be accomplished in 2nd year.**

Sub goal 2: Evaluate antitumor and antimetastatic efficacy of BAY1143572 in the orthotopic GEJ cancer model. Cell lines used: 2 cell lines based on results from Specific Aim 1.

What was accomplished under these goals?

1. Successfully established and maintained orthotopic xenograft GAC models utilizing IM95/CMV-luc and MKN-45-luc cells. Successful monitoring of tumors was achieved by bioluminescence imaging. This is an ongoing experiment, thus efficacy of BAY1143572 in the orthotopic GEJ cancer model remains to be demonstrated. (Figures 8 and 9).

Progress Against Timeline: Ahead of Schedule.

What opportunities for training and professional development has the project provided?**Professional Development:**

Developed proficiency in orthotopic GAC models and acquired unique surgical skillsets in implanting tumors via transabdominal approach of stomach, GEJ and lower esophagus. Learnt successful implantation of GAC cells and tumor fragments in developing an orthotopic model which is 1st of a kind in our knowledge. The project also provided an opportunity to learn the best ways of monitoring and maintaining tumors. Differences between imaging techniques such as MRI, CT, PET-CT and BLI and understanding detailed tumor characteristics by each of these imaging techniques.

Workshop and travel scholarships:

2018 AACR Scholar-in-Training Award, the Second AACR International Conference on Translational Cancer Medicine: Cancer Discoveries for Clinical Application, São Paulo, Brazil
2018 Postdoctoral Travel Awards, UT MD Anderson Cancer Center, Houston, TX
2017 Workshop Scholarship, 16th Annual Workshop on the Pathology of Mouse Models for Human Diseases, The Jackson Laboratory, Bar Harbor, ME

Attended “Pathology of mouse models for human disease” workshop held at Bar Harbor, ME and conducted by Jackson Laboratory from Oct 2nd to Oct 7th. This workshop provided a week of intensive training sessions in pathology and histopathology as well as didactic sessions in which particular disease areas and models will be discussed. I had the opportunity to interact with a group of prominent mouse pathologists and geneticists from leading research institutions. Topics and models to be covered: nomenclature, basic mouse genetics, concepts of mouse model generation, approaches to working up mutant mice, role of pathologists at research institutions, systemic, hematopoietic, mammary, gynecologic, cutaneous, infectious and immune system pathology, embryology and cancer models.

Training opportunities: Teaching - Served as a mentor for a high school student awarded Emperor Science Award, PBS Learning Media and Stand Up To Cancer, USA, 3/2018 – Present. Demonstrated the method of orthotopic mouse model implantation to other lab members including a Senior Research Scientist.

Training opportunities: Presentations and accolades–

2018 Certificate of Excellence for Outstanding Performance, Houston, TX

2018 Wunderkind nomination by STAT News, Boston

How were the results disseminated to communities of interest?

Nothing to report

What do you plan to do during the next reporting period to accomplish the goals?

1. Additional stable shCDK9 knockdown cells (IM95/CMV-luc and MKN-45-luc) will be generated by lentivirus or by sgRNA, CRISPR/cas9 technology.
2. Once additional cell lines with stable genetic knockdown of CDK9 are achieved, the antiproliferative effects of shCDK9 (or genetic knockdown) in cancer cells will be performed using MTS assay.
3. The effects of BAY1143572 and shCDK9 (or genetic knockdown) on GAC cells by using invasion and migration assays.
4. Identify a predictor biomarker of response to anti-CDK9 therapy in cancer cells once Reverse Phase Protein Array [RPPA] data is obtained by swift assortment strategy and test the predictive biomarker of response to anti-CDK9 therapy in cancer cells by western blot (WB) or immunocytochemistry (IHC).
5. Evaluate antitumor efficacy of shCDK9 knockdown with shGFP xenografts in 2 cell lines.
6. Test markers of response to CDK9 inhibition chosen from RPPA and tested by WB/IHC (Goal 1) in xenograft tumors by western blot or immunohistochemistry.
7. Evaluate antitumor and antimetastatic efficacy of shCDK9 knockdown with shGFP xenografts in the orthotopic GEJ cancer model.
8. Monitor current antitumor and antimetastatic experiment in IM95/CMV-luc and MKN-45-luc for efficacy of BAY1143572 in the orthotopic GEJ cancer model.
9. Test markers of response to CDK9 inhibition in the orthotopic and metastatic tumors by western blot or immunohistochemistry.

Impact:

Impact on the development of the principal discipline(s) of the project: Orthotopic mouse model is instrumental in advancing our understanding of metastatic GACs. This model is available for investigators to address importance of tumor microenvironment in metastatic and immunological studies, and to develop novel therapeutic approaches for the treatment of GAC cancer. The orthotopic model is a significant step forward in preclinical testing of pharmaceutical agents in GAC.

Impact on other disciplines: Similarly, this model can also be applied to study esophageal adenocarcinoma.

Impact on technology transfer: Nothing to report

Impact on society beyond science and technology: Nothing to report

Changes/Problems:

Changes in approach and reasons for change: Nothing to report

Actual or anticipated problems or delays and actions or plans to resolve them

Project start date was October 1st 2017. Delay in ACURO approval leading to delayed award notice and disbursement of funds. Hence the shCDK9 related experiments were delayed. Since the chartstring is now setup, we do not anticipate any delays in cell and mice work.

Changes that had a significant impact on expenditures: Nothing to report

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents: Nothing to report

Significant changes in use or care of human subjects: Nothing to report

Significant changes in use or care of vertebrate animals: Nothing to report

Significant changes in use of biohazards and/or select agents: Nothing to report

Products:

Publications, conference papers, and presentations

Presentations:

1. Invited for oral talk at 1st Interdisciplinary Education and Training Program for the Next Generation of Translational Scientists (ITERT) Symposium, Houston, TX, 2018
2. 16th Annual Workshop on the Pathology of Mouse Models for Human Disease, Bar Harbor, ME 2017

Journal publications. Manuscript titled ‘Fidelity of Gastro-esophageal Junction Cancer Patient Derived Orthotopic Xenografts: Tool for developing novel therapeutics’ under preparation for submission.

Books or other non-periodical, one-time publications. Nothing to report

Other publications, conference papers, and presentations. Nothing to report

Website(s) or other Internet site(s). Nothing to report

Technologies or techniques. Nothing to report

Inventions, patent applications, and/or licenses. Nothing to report

Other Products. Nothing to report

Participants and other collaborating organizations:

What individuals have worked on the project? No change

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period? The senior key personnel or my mentor's (Dr. Dipen Maru) active support has changed. Received additional funding 1R01CA187238-01, RP180473, and funding from Kadoorie Charitable Foundation. Please see updated funding sources attached.

What other organizations were involved as partners? Nothing to report

Special reporting requirements: Nothing to report

COLLABORATIVE AWARDS: Nothing to report

QUAD CHARTS: Nothing to report

Appendices: CVs, Updated other support for senior personnel, Figures.

Figure 1.

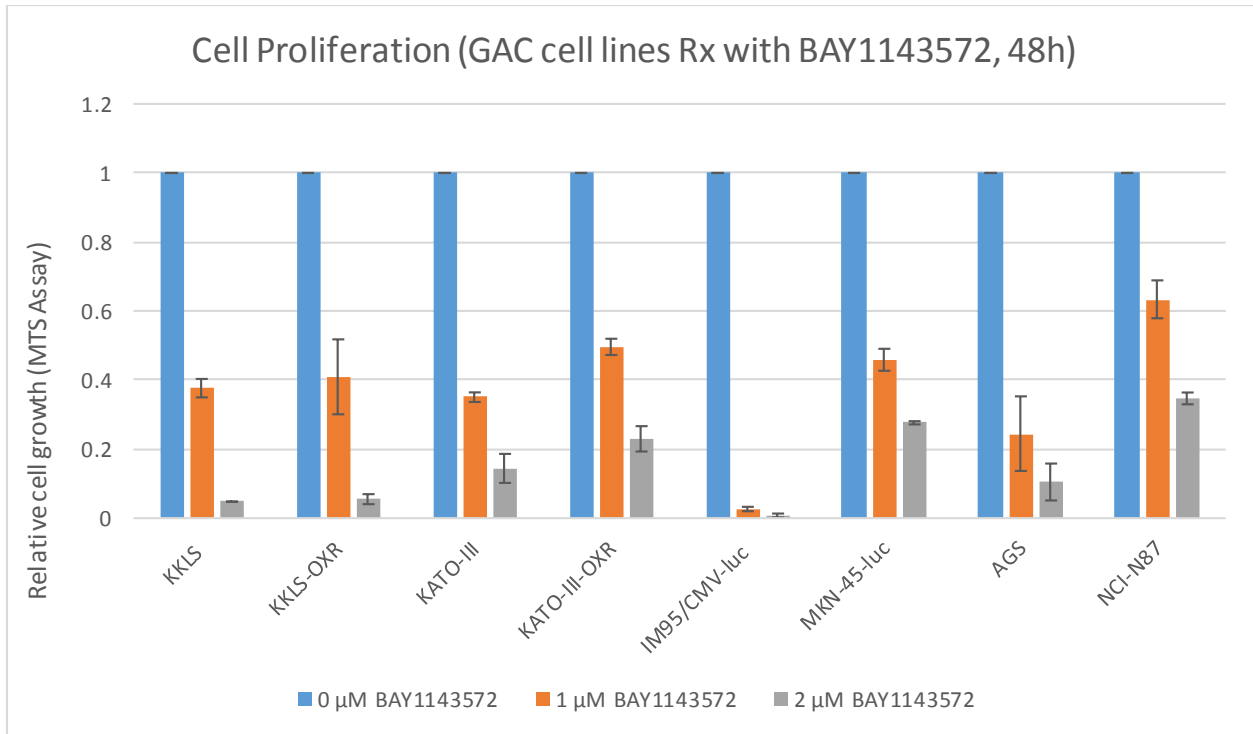


Figure 2.

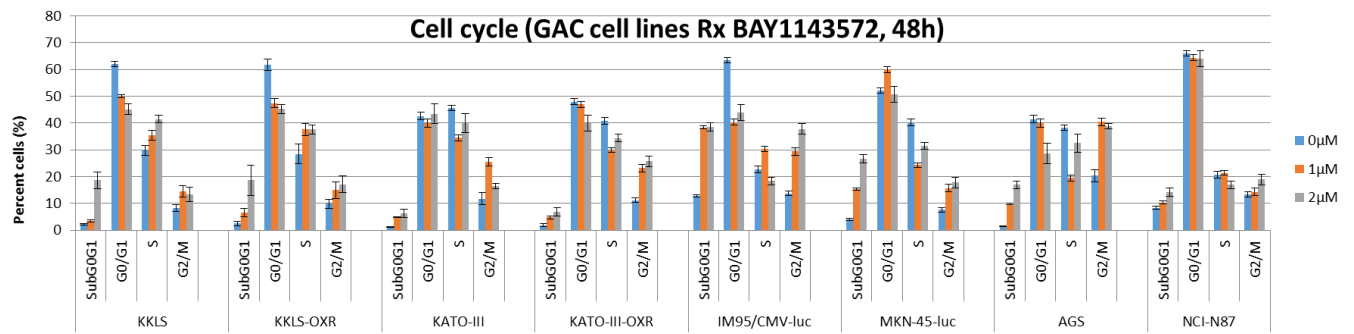


Figure 3.

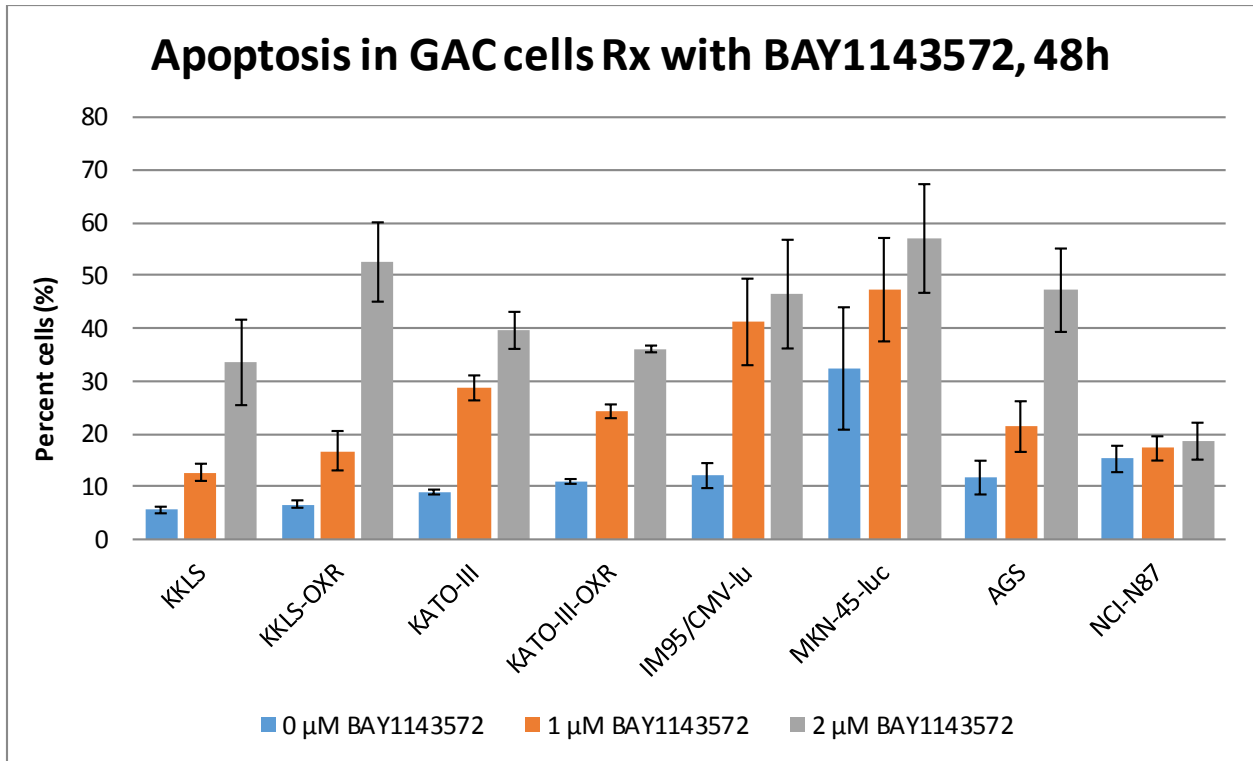


Figure 4.

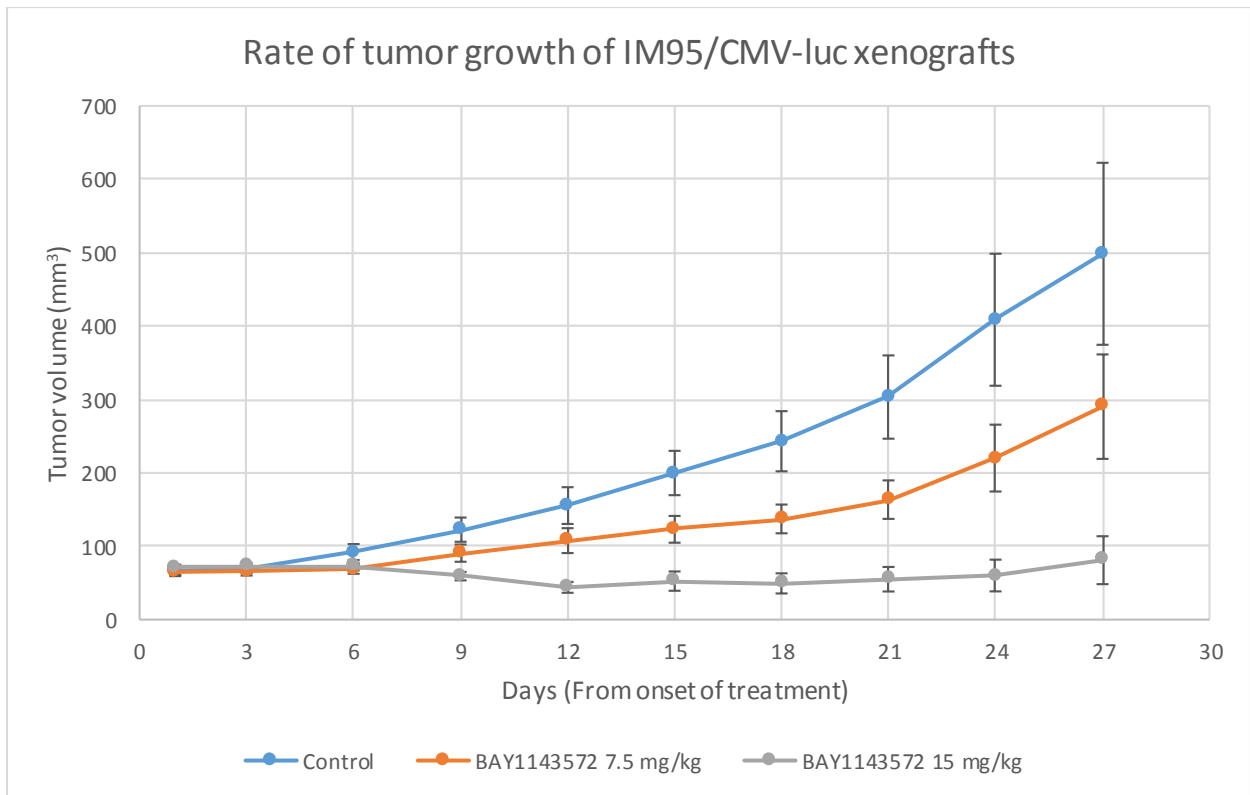


Figure 6.

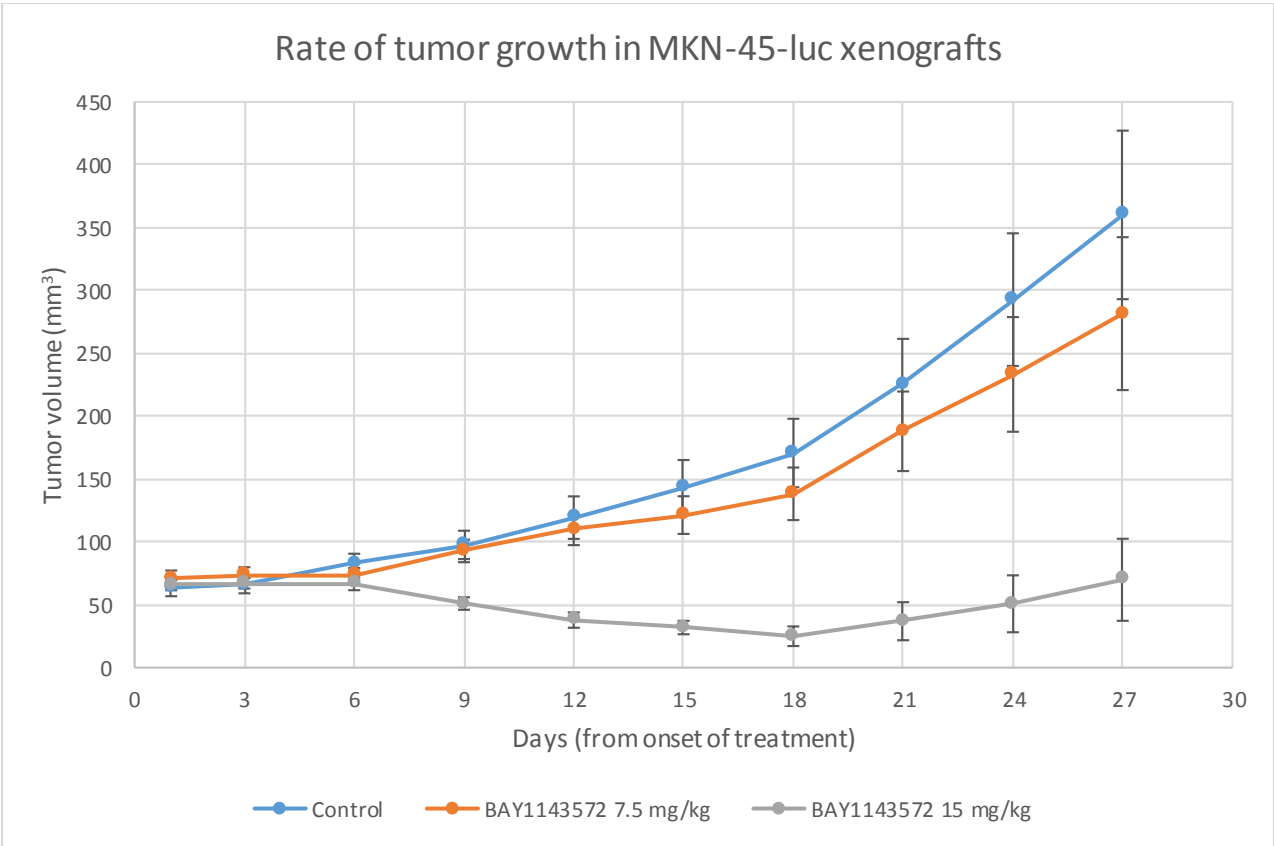


Figure 7.

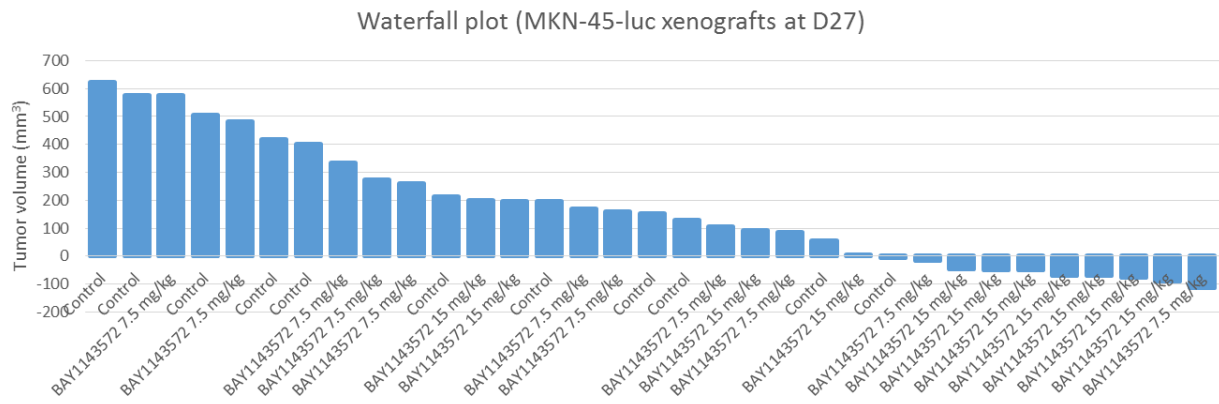


Figure 8.

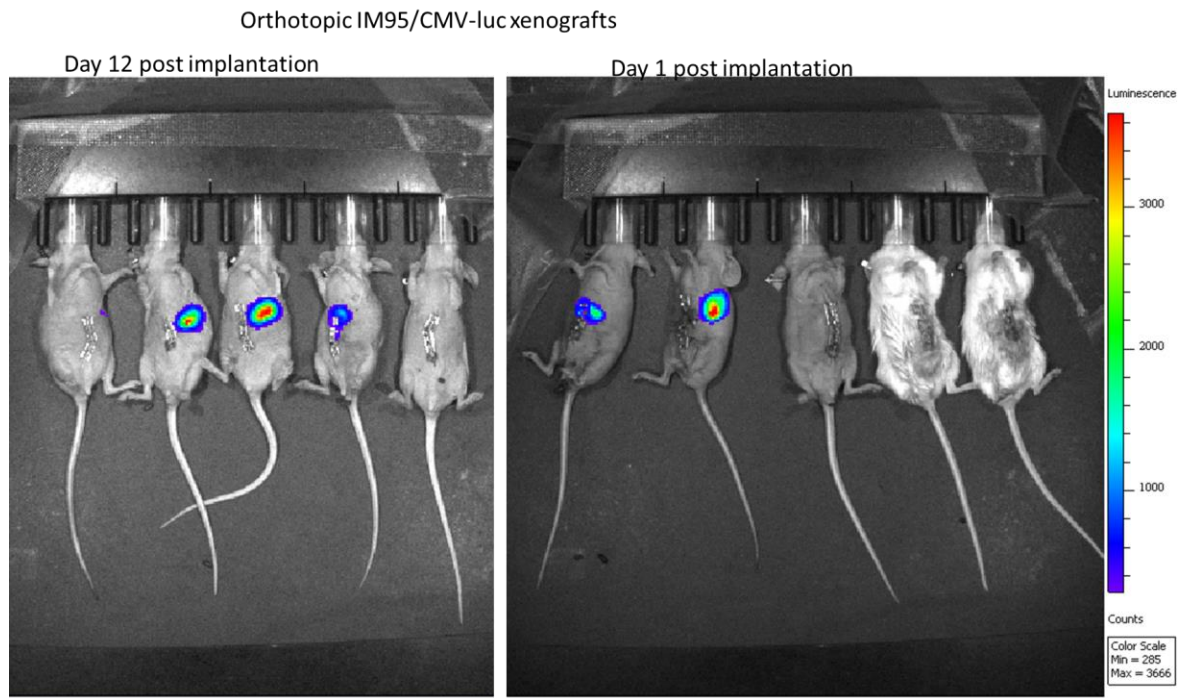
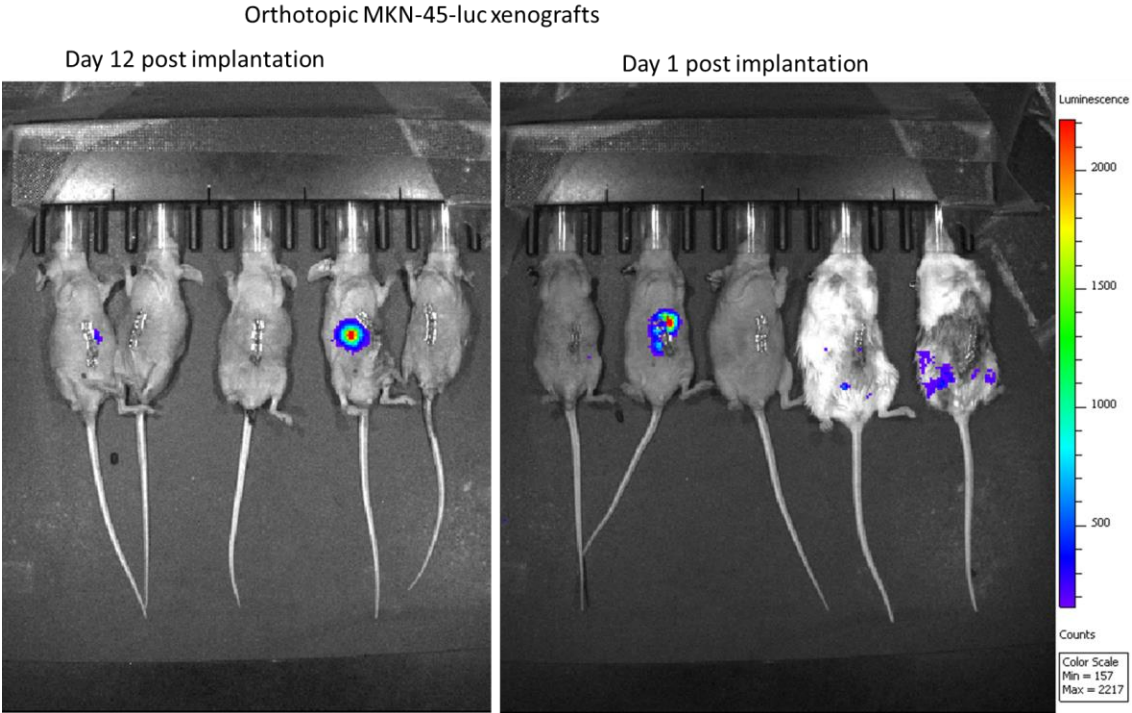


Figure 9.



Biographical Sketch

Provide the following information for each individual included in the Research & Related Senior/Key Person Profile (Expanded) Form.			
NAME: OMKARA LAKSHMI M. VEERANKI		POSITION TITLE: POSTDOCTORAL FELLOW	
EDUCATION/TRAINING (Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training).			
INSTITUTION AND LOCATION	DEGREE (IF APPLICABLE)	YEAR(S)	FIELD OF STUDY
Nagpur Veterinary College, India University at Buffalo, NY, USA Roswell Park Cancer Institute, NY, USA American College of Lab Animal Medicine UT MD Anderson Cancer Center, TX, USA	BVSc & AH (D.V.M) M.S. Ph.D. ACLAM board eligible Postdoctoral fellow	2002-2007 2007-2010 2009-2015 2014-Present 15-Present	Veterinary Medicine Biotechnology Cancer Pathology and Prevention Lab Animal/Comparative Medicine Pathology
RESEARCH AND PROFESSIONAL EXPERIENCE:			
<p>PERSONAL STATEMENT:</p> <p>My long term research interests involve the development of a comprehensive understanding of key molecular targets and how alterations in gene expression contribute to gastrointestinal cancers. My academic training in veterinary medicine and research experience has provided me with an excellent background in multiple disciplines including molecular biology, pharmacology, and in developing new <i>in vivo</i> mouse models for cancer studies and drug development. I studied ‘isothiocyanates (ITCs)– a phytochemical found in cruciferous vegetables’ for bladder cancer (BC) prevention and gained expertise in anticancer efficacy studies and identified COX-2 as a key target of sulforaphane in inhibiting BC progression during my Ph.D. with mentors Drs. James Marshall and Yuesheng Zhang. I was first author in “Organ-Specific exposure and response to sulforaphane, a key chemopreventive ingredient in broccoli: implications for cancer prevention” and was invited to write a review article in a major journal. During my training, I received several academic awards and travel grants. For my postdoctoral training, I will continue to build on my previous training in drug efficacy and target identification that will allow me to address gaps in knowledge in stomach cancer. My mentor Dr. Dipen Maru is an internationally recognized leader in the pathology of gastrointestinal cancers and has an extensive record for training postdoctoral fellows. The proposed research will provide me with new conceptual and technical training in genetic manipulation of targets, evaluation of BAY1143572 in inhibiting tumor growth and metastasis and to optimize a rapid metastatic orthotopic GEJ model. In addition, the proposed training plan outlines a set of career development activities and workshops – e.g. grant writing, presentation skills, lab management, and workshop on mouse models, designed to enhance my ability to be an independent investigator. My choice of sponsors-Drs. S. Kopetz, A. Maitra and J. Morris, research project, and training will give me a solid foundation to reach my goal of developing new treatment options in gastric adenocarcinoma.</p>			

GRANTS:

2018 AACR Scholar-in-Training, Translational Cancer Medicine: Cancer Discoveries for Clinical Application, Sao Paulo, Brazil (\$500)

2018 Travel Award, UT MD Anderson Cancer Center, Houston, Texas (\$1000)

2017 Workshop scholarship grant- 16th Annual Workshop on the Pathology of Mouse Models for Human Disease, March of Dimes, NIH RO13 ODO 10920, and the Howard Hughes Medical Institute, Bar Harbor, ME 10/1/2017-10/6/2017 (\$600)

2016 Principal Investigator, Cyclin Dependent Kinase 9, a potential therapeutic target in Gastric Adenocarcinoma, CA160928, DOD/Congressionally Directed Medical Research Programs (DOD/CDMRP), Mentor – Dr. Dipen Maru, 9/1/2017-8/30/2019 (\$240,000)

2011 ABRF education travel grant, Sacramento, CA (\$500)

2010 NSF travel grant, San Antonio, TX (\$550)

PUBLICATIONS:

In preparation:

1. **Veeranki OL**, Norton W, Kinsley C, Tong Z, Mejia AM, Dokey R, Bhutani M, Maru DM. Establishment of a novel orthotopic gastroesophageal junction (GEJ) cancer mouse model. 2016

Submitted for review:

2. **Veeranki OL**, Tong Z, Dokey R, Mejia AM, , Zhang J, Qiao Y, Singh PK, Katkhuda R, Mino B, Tailor R, Rodriguez-Canales J, Ajani J, Wu JY, Kopetz S, Blum M, Hofstetter W, Krishnan S, Lin SH, Maru DM. Targeting Cyclin-Dependent Kinase 9 Enhances Radiosensitization and Identifies AXL as a Novel Target in Esophageal Adenocarcinoma, 2018.
3. Tong Z, Mejia AM, **Veeranki OL**, Rodriguez-Canales J, Mino B, Dokey R, Hofstetter WL, Lin SH, Krishnan S, Kopetz S, Ajani JA, Maru DM. Preclinical effects of a new CDK9/TEFB inhibitor, BAY1143572 with and without 5-fluorouracil in esophageal adenocarcinoma, 2018.

Published:

4. Tong Z, Chatterjee D, Deng D, **Veeranki OL**, Mejia AM, Rodriguez J, Ajani J, Hofstetter W, Lin SH, Guha S, Kopetz S, Krishnan S, Maru DM. Antitumor Effects of Cyclin Dependent Kinase 9 Inhibition in Esophageal Adenocarcinoma.
5. **Veeranki OL**, Bhattacharya A, Tang L, Marshall JR, Zhang Y. Cruciferous vegetables, isothiocyanates and prevention bladder cancer recurrence. *Current Pharmacology Reports*, 2015; 1(4):272-282
6. **Veeranki OL**, Bhattacharya A, Marshall JR, Zhang Y. Organ-Specific Exposure and Response to Sulforaphane, a Key Chemopreventive Ingredient in Broccoli: Implications for Cancer Prevention. *British Journal of Nutrition*, 2013; 109(1): 25-32.
7. Masso-Welch PA, Merhige PM, **Veeranki OL**, Kuo SM. Loss of IL-10 decreases mouse post pubertal mammary gland development in the absence of inflammation. *Immunological investigations*, 2012; 41(5): 521-37.

EDITOR:

Journal of Molecular Biology Research, 2015 - Present

EMPLOYMENT, EXPERIENCE, CERTIFICATIONS & HONORS:

EMPLOYMENT:

Postdoctoral fellow, MD Anderson Cancer Center (July 2015 – Present)

Working on understanding the role of CDK9 and beta-catenin in chemoresistant gastric adenocarcinoma

Delineating the driver genes involved in transforming Barrett Esophagus to esophageal adenocarcinoma

Developed a novel orthotopic gastroesophageal junction (GEJ) cancer mouse model

Studied the role of CDK inhibitors as a sensitizer to radiation in esophageal adenocarcinoma

Assisted and contributed technical knowledge in assessing antitumor effects of CDK 9 inhibition in esophageal adenocarcinoma

Research Assistant, Roswell Park Cancer Institute (September 2010 - June 2015)

Coordinated research projects

Developed orthotopic and subcutaneous bladder cancer models

Conducted antitumoral efficacy studies, PK-PD, etc.

Performed bench work as needed

Research and Teaching Assistant, University at Buffalo (August 2008 - May 2009)

Supervised teaching assistant for “Cell and Tissue Culture” course

Course was provided for 30 junior/senior college students

Responsibilities included 2 lab lectures (3 hour), weekly review sessions (1 hour), providing exam questions and grading lab exams

Educational Opportunity Program (EOP) Academic Advisor (May 2008 – August 2008)

University at Buffalo

Advised and taught 20 pre-professional students, helped with curriculum and encouraged academic careers

CERTIFICATIONS:

Certificate of Completion, ITERT Leadership Academy, UT MD Anderson Cancer Center, 2018

Certificate of Completion, Responsible Conduct of Research, UT MD Anderson, 2017

ACLAM Eligible, 2014 - Present

American College of Lab Animal Medicine

Mentor: Dr. Bhupinder Singh, College of Veterinary Medicine, Cornell University, New York

Veterinary Practice Licensing Certificate MSVC-7750, Maharashtra State Veterinary Council

Certificate of Achievement in Leadership (S.O.U.L. Program), University at Buffalo, 2010

Certificate of Completion, Intercultural and Diversity Center, University at Buffalo, 2011

MEMBERSHIPS:

2016-Present American Gastroenterological Association

2011-Present Member of Science Advisory Board

2010- Present Member of American Association for Cancer Research (AACR)

2010- Present Member of Women in Cancer Research, AACR

2009- Present Member of the New York Academy of Sciences

2002-Present Active member of ISAW: Indian Society for Animal-Human Welfare

HONORS:

2018 AACR Scholar-in-Training, 2nd AACR International Conference on Translational Cancer Medicine: Cancer Discoveries for Clinical Application, Sao Paulo, Brazil

2018 Wunderkind nomination by STAT News, Boston

- 2018 Certificate of Excellence for Outstanding Performance and Contribution to ITERT, TX
- 2018 Postdoctoral Travel Awards, UT MD Anderson Cancer Center, Houston, TX
- 2018 The Marion D. Edwards Fellowship Award in Hepatic Oncology for demonstrating potential for excellence in and unique contribution to Hepatic Oncology, Endowed Fellowship Awards, Houston, Texas
- 2017 Workshop Scholarship, Pathology of Mouse Models for Human Diseases, Bar Harbor, ME
- 2017 Bristol Myers Squibb Award finalist in Translational Research, Trainee Research Day, TX
- 2016 Department of Defense CDMRP PRCRP Horizon Award, Fort Detrick, Maryland
- 2016 Second prize, poster presentation at Annual Post-Doc Science Symposium, Houston, TX
- 2016 Elevator Speech Finalist at Trainee Research Day, Houston, TX
- 2015 Academic Excellence in PhD at University at Buffalo, New York
- 2013 Invited for talk on Bladder Cancer for Excellence in Oncology, Ankara, Turkey
- 2011 ABRF education travel grant, Sacramento, CA
- 2010 Selection Panel (grant application review council) for Mark Diamond Research Fund
- 2010 NSF travel grant, San Antonio, TX
- 2009 Academic excellence in MS at University at Buffalo, New York
- 2007 Second rank in B.V.Sc and AH (Doctor of Veterinary Medicine-DVM)
- 2007 LILA Poonawalla Women Scholarship for outstanding students in Pune city, India
- 2003-2007 Awards for highest marks in Microbiology, Preventive Medicine and Epidemiology, Gynecology for 3 consecutive years
- 2004 Student all around award (academics, community, extra-curricular activities)

COMMITTEES AND SCIENTIFIC CONTRIBUTIONS:

- 2018-Present Mentor, Emperor Science Award, PBS Learning Media and Stand Up To Cancer, USA
- 2016-Present Mentor, Association of Minority Biomedical Researchers & GSBS mentoring program
- 2016-Present Career Advancement Leader and Chair of Career Development Committee, MD Anderson Postdoctoral Association Executive Committee, Houston, Texas
- 2016 Elevator speech judge for 1st GSBS Student Research Day, UT Health, Houston, Texas
- 2015-2016 Chair of Career Development Committee, MD Anderson Postdoctoral Association Executive Committee
- 2015-2016 Organizing committee for Annual Presidential Career Symposium by MD Anderson Cancer Center, Houston, Texas
- 2015 Poster judge for 2nd Annual MAPTA Winter Science Symposium by Houston Methodist Research Institute, Houston, Texas
- 2015 Poster judge for 25th Annual Keck Center Research Conference by Gulf-Coast Consortium, Houston, Texas
- 2009-2014 Vice President, Departmental Graduate Student Association, Roswell Park Cancer Institute, Buffalo, New York
- 2010 Selection Panel (grant application review council) for Mark Diamond Research Fund, Buffalo, New York

PRESENTATIONS:

- 2018 Invited to speak at 10th World Congress on Precision and personalized Medicine, Osaka, Japan
- 2018 Invited to speak on a panel with the 1st Generation Student Group, Associations of Minority Biomedical Researchers, Houston, Texas
- 2018 Invited for oral talk at 1st Interdisciplinary Education and Training Program for the Next Generation of Translational Scientists at ITERT Symposium, Houston, Texas
- 2017 Pathology of Mouse Models for Human Disease, Bar Harbor, ME
- 2017 Annual Postdoctoral Science Symposium, Houston, Texas

- 2017 Team Science and Collaboration towards Excellence in Translational Cancer Research, Translational Molecular Pathology Retreat, Houston, Texas
- 2017 Trainee Research Day, MD Anderson Cancer Center, Houston, Texas
- 2016 Poster presentation for the Cancer evolution: Mechanisms of Vulnerability and resistance, Symposia on cancer, Houston, Texas
- 2016 Poster presentation for the Annual Postdoctoral Science Symposium, Houston, Texas
- 2013 Invited for talk on Bladder Cancer for Excellence in Oncology, Ankara, Turkey
- 2009 Sigma Science Poster presentation, Buffalo, New York

SKILLS:

Veterinary Clinical Skills:

Clinical: Physical exams, TPR, catheter care, biopsies, Ultra sound, radiographs, diagnosis, staging and definitive identification of type of malignancy, pain management and prevention of cancer in small animals, lab animal handling and care, anesthesia, analgesia, and euthanasia in experimental animals, maintaining transgenic and knockout mice colonies, drawing blood, developing various in-vivo tumor models, mammary fat pad injections, S/C and orthotopic tumor implantations

Animal Models: Generating orthotopic bladder cancer rodent models, UM-UC-3 xenografts, syngeneic, primary grafts, genetically engineered mice and transgenics: IL-10 ^{-/-} KO, Nrf2^{-/-} KO and Tg UGT1*1A mice

Imaging: IVIS-BLI, MRI and ultrasound

Laboratory Skills:

Molecular genetic Techniques: CRISPR/cas9 gene editing, PCR, RT-PCR, Multiplex-PCR, Western Blots, Immunoprecipitation, Immunofluorescence, ELISA, SDS-PAGE, Plasmid Profile, enzyme activity assays (GST, NQO1), restriction digestion, RFLP, DNA Fingerprinting, MTT Assay, AST, luciferase activity, flow cytometry, fluorescent microscopy, spheroid assay

Cellular Biology Techniques: Mammalian cell culture, stable and inducible cell line generation, protein expression, protein purification, lentivirus infection, DNA transfection, flow cytometry, fluorescence microscopy

Biomarkers: PD biomarkers: GST, NQO1. Other biomarkers: Cox-2, Bcl-2, pBcl-2, α/β -tubulins, VEGF, EGFR, MMPs

Chemical Biology and proteomics Techniques: HPLC, LC/MS, TLC, Spectroscopy, cell-based assay, PCR (RT, Multiplex), western blots IP:IB

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Maru, Dipen M

eRA COMMONS USER NAME (credential, e.g., agency login): DMARU1

POSITION TITLE: Professor of Pathology and Translational Molecular Pathology

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
M.P. Shah Medical College, Jamnagar, India	MBBS	6/1989	Medicine
M.P. Shah Medical College, Jamnagar, India	MD	6/1993	Pathology
University of Cincinnati Medical Center, Cincinnati, OH	Clinical Residency	7/1998-6/2002	Pathology
The University of Texas MD Anderson Cancer Center, Houston, TX	Clinical Fellowship	7/2002-7/2003	Surgical Pathology
University of Cincinnati Medical Center, Cincinnati, OH	Clinical Fellowship	1/2004-8/2004	Gastrointestinal, Liver and Transplant Pathology

A. Personal Statement

My background in surgical pathology, work in identifying new biomarkers in several cancers, experience with murine models, and translational research from patient material are well suited for the work proposed in this grant. With help from already established laboratory infrastructure to study p-STAT3 and biomarkers in CLIA certified laboratories and other infrastructure in my research laboratory, I will be able support the proposed projects in this DOD grant application.

B. Positions and Honors**Positions and Employment**

2006-2010	Assistant Professor, Department of Pathology, The University of Texas MD Anderson Cancer Center, Houston, TX
2010-2015	Associate Professor, Department of Pathology, The University of Texas MD Anderson Cancer Center, Houston, TX
2015-Present	Professor, Departments of Pathology and Translational Molecular Pathology, The University of Texas MD Anderson Cancer Center, Houston, TX 015-present

Other Experience and Professional Memberships

2006-Present	Principal Investigator, Upper Gastrointestinal Satellite Tissue Bank, Division of Pathology/Lab Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX
2011-Present	Medical Director and Section Chief-Frozen Section and Gross Room, Department of Pathology/lab Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX
2014-Present	Medical Director, Clinical Genomics Banking, Division of Pathology/Lab Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX

- 2016-Present Director, Biobank Informatics Core, The University of Texas MD Anderson Cancer Center, Houston, TX
- 2016 Robert M. Chamberlain Distinguished Mentor Award, Finalist, The University of Texas MD Anderson Cancer Center, Houston, TX

C. Contributions to Science

1. Histologic and Molecular Biomarkers to predict progression of Barrett's esophagus to Esophageal adenocarcinoma: We have demonstrated a role of microRNA (miR) 196a as a potential biomarker for higher grade of dysplasia and carcinoma in setting of Barrett's esophagus. We have also identified in vitro targets of miR196a in esophageal adenocarcinoma. Our laboratory has also demonstrated pHH3 as a promising markers differentially expressed in Barrett's Esophagus, Dysplasia and Carcinoma.
 - a. Maru DM, Singh RR, Hannah C, et al. MicroRNA-196a is a potential marker of progression during Barrett's metaplasia-dysplasia-invasive adenocarcinoma sequence in esophagus. *Am J Pathol* 174(5):1940-8, 5/2009. PMID: PMC2671281.
 - b. Luthra R, Singh RR, Luthra MG, et al. MicroRNA-196a targets annexin A1: a microRNA-mediated mechanism of annexin A1 downregulation in cancers. *Oncogene* 27(52):6667-78, 11/2008. PMID: 18663355
 - c. Goodarzi M, Correa AM, Ajani JA, et al. Anti-phosphorylated histone H3 expression in Barrett's esophagus, low-grade dysplasia, high-grade dysplasia, and adenocarcinoma. *Mod Pathol* 22(12):1612-21, 12/2009. PMID:19734842
2. Histologic and molecular biomarkers as predictor of therapy response and patient outcome in advanced locoregional esophageal adenocarcinoma. Our lab has demonstrated significance of loss of heterozygosity of chromosome 1q21 as a prognostic factor for survival outcome in esophageal adenocarcinoma patients. We have also demonstrated several histopathologic markers as predictors of therapy response to and survival outcome.
 - a. Maru D, Khurana H, Rashid A et al. Retrospective Study of Clinicopathologic Features and Prognosis High-Grade Neuroendocrine Carcinoma of the Esophagus. *American Journal of Surgical Pathology* 32(9):1404-11, 2008. PMID: 18670347
 - b. Maru D, Luthra R, White-Cross J et al. Frequent Loss of Heterozygosity of Chromosome 1q in Esophageal Adenocarcinoma; Loss of Chromosome 1q21.3 is Associated with Shorter Overall Survival. *Cancer* 115(7):1576-85, 4/2009. PMID: 19156915
 - c. Estrella JS, Hofstetter WL, Correa AM et al. Duplicated Muscularis Mucosae Invasion has Similar Risk of Lymph Node Metastasis and Recurrence-Free Survival as Intramucosal Esophageal Adenocarcinoma. *Am J Surg Pathol* 35(7):1045-53, 7/2011. PMID: 21602659
 - d. Viren R Patel, Wayne L Hofstetter, Arlene M Correa et al. Signet Ring Cells in Esophageal Adenocarcinoma Predict Poor Response to Preoperative Chemoradiation. *Annals of Thoracic Surgery*.10/2014. PMID: 25038008
3. Role of CDK9 inhibition in increasing sensitization to chemotherapy and ionizing radiation in esophageal and gastric adenocarcinoma: We have demonstrated efficacy of CDK9 inhibitors as single agent and as an adjuvant to 5-fluorouracil and radiation in preclinical models including patient derived xenografts and identified several candidate markers including AXL as novel CDK9 targets in esophageal and/or gastric adenocarcinoma. Our laboratory is first to identify AXL as the CDK9 target in any tumor and interplay between CDK9 and AXL and study CDK9 inhibitors in patient derived xenografts.
 - a. Tong Z, Chatterjee D, Den D, et al. Antitumor effects of cyclin dependent kinase 9 inhibition in esophageal adenocarcinoma. *Oncotarget*.4/2017. PMID: 28404924
4. Predictive and prognostic biomarkers of response to therapy in colorectal adenocarcinoma: Our group has lead the efforts in validating gene signature for consensus molecular subtypes of colon cancer and I am leading effort in validating gene expression based molecular classification in CLIA certified laboratory.

- a. Guinney J, Dienstmann R, Wang X, et al. The consensus molecular subtypes of colorectal cancer. Nat Med. e-Pub 10/2015. PMID: 26457759
 - b. Brouquet A, Zimmitti G, Kopetz S, et al. Multicenter validation study of pathologic response and tumor thickness at the tumor-normal liver interface as independent predictors of disease-free survival after preoperative chemotherapy and surgery for colorectal liver metastases. Cancer 119(13):1-11, 8/2013. e-Pub 4/2013. PMID: 23868456.
 - c. Agarwal A, Chang GJ, Hu CY, et al. Quantified pathologic response assessed as residual tumor burden is a predictor of recurrence-free survival in patients with rectal cancer who undergo resection after neoadjuvant chemoradiotherapy. Cancer 119(24):4231-41, 12/2013. e-Pub 10/2013. PMID: 24089344.
 - d. Vauthey JN, Zimmitti G, Shindoh J, Chen SS, et al. RAS Mutational Status Predicts Patterns of Recurrence and Survival in Patients Undergoing Hepatectomy Colorectal Liver Metastases. Ann Surg 258 (4):619-27, 10/2013:PMC3856211.
5. Leader of centralized pathology review for a randomized FDA phase 3 clinical trial in diffuse gastric Adenocarcinoma: Digital telepathology based blinded review of biopsy and resection specimens from more than 400 patients of gastric adenocarcinoma enrolled in a trial from Europe, North America and Asia. Confirmation of diffuse histology by two gastrointestinal pathologists required before inclusion of a patient in the trial. Histologic confirmation of diffuse subtype of gastric carcinoma achieved in more than 80% of patients validating the WHO recommended diagnostic criteria of diffuse gastric cancer by digital pathology.

Complete List of Published Work in MyBibliography: <https://www.ncbi.nlm.nih.gov/sites/myncbi/12Sj-8tHbFskC/bibliography/40996093/public/?sort=date&direction=ascending>

D. Additional Information: Research Support and/or Scholastic Performance

Ongoing Research Support

<p>1R01CA187238-01 Kopetz (PI) NIH/NCI Therapeutic Strategies for Patients With BRAF Mutant Colorectal Cancer Find therapeutic strategies for patients with BRAF Mutant Colorectal Cancer Role: Collaborator</p> <p>Colorectal Cancer Moon Shoot, Kopetz, Hamilton, Hawk (PI) MD Anderson Cancer Center Assay Development and Validation for Novel Consensus Classification of Colorectal Cancer Role: Project Leader</p> <p>CA160928, Veeranki Omkara (PI) Department of Defense. Peer Reviewed Cancer Horizon Award, Cyclin Dependent Kinase 9, a potential therapeutic target in Gastric Adenocarcinoma. Major Goals: Role of genetic and pharmaceutical inhibition of CDK9 in gastric adenocarcinoma in vitro & in xenograft models Role: Mentor</p> <p>RP180473 Tweardy (PI) Cancer Prevention & Research Institute of Texas (CPRIT) Clinical trials of C188-9, an oral inhibitor of signal transducer and activator of transcription (STAT) 3, in patients with hepatocellular carcinoma (HCC) Project Goal: To establish the efficacy of C188-9 in Hepatocellular Carcinoma as single agent or in combination with Sorafenib. Role: Collaborator</p> <p>KADOORIE CHARITABLE FOUNDATION Futreal (PI)</p>	<p>08/01/2014-07/01/2019</p> <p>09/01/2014-08/31/2019</p> <p>09/01/2017-08/30/2019</p> <p>03/01/2018-02/28/2022</p> <p>03/01/2018 - 02/28/2021</p>
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Differential topological accumulation of somatic mutations in normal and cancerous gastric stem cells, and their association with gastric carcinogenesis and anti-tumor immune response

Project Goals: To examine the clonal diversity of T cells and to analyze for regional phylogenetic evolution and the relationship between mutational burden and signature and immune cells profile.

Role: Collaborator

EMD-Serono Inc. Morris (PI)

12/01/2017 - 11/30/2019

Phase I/II clinical trial of a TGF-beta inhibitor, M7824 in microsatellite instability (MSI) or Consensus Molecular Subtype (CMS) 4 metastatic colorectal cancer

Project Goals: Assess efficacy and toxicity of M7824 in MSI-H or CMS 4 colorectal adenocarcinoma

Role: Coinvestigator

Completed Research Support

LS2011-00034580 Ajani (PI)

01/01/2010-12/31/2015

Taiho Pharma Inc. USA and Food and Drug Administration

Central Pathology Review-An Open-Label, Multicenter, Randomized, Phase 3 Study of S-1 and Cisplatin Compared to 5-FU and Cisplatin in Patients with Metastatic Diffuse Gastric Cancer Previously Untreated with Chemotherapy

Major Goals: Double blinded central pathology review of tissue samples for sub-typing the gastric carcinoma.

Role: Project Leader

1R01CA157880003 Ellis, LM (PI)

05/01/2012-3/31/2017

NIH/NCI

Paracrine role of endothelial cells on the Colorectal Cancer Stem Cell Phenotype

Explore the Paracrine role of endothelial cells on the Colorectal Cancer Stem Cell Phenotype

Role: Collaborator

RP140515 Maru (PI)

08/01/2014-2/28/2018

Cancer Prevention & Research Institute of Texas (CPRIT)

CDK Inhibitors as Adjunctive to 5-FU and/or Radiation in Esophageal Adenocarcinoma- Assessment of Efficacy and Predictive Biomarkers

Major Goals: In vitro and in vivo efficacy including patient derived xenografts experiments to assess efficacy clinically used CDK 9 inhibitors as adjunct to neoadjuvant chemoradiation in locoregional esophageal adenocarcinoma and study CDK9 targets as predictors of response to neoadjuvant chemoradiation.

Role: Principal Investigator

1R01CA172741 Ajani, Jaffer (PI)

09/01/2013-06/30/2018

NIH/NCI

Inhibition of Hedgehog Signaling in Gli-1+Ad carcinoma of Esophagus or GE Junction.

Role: Co-Investigator

Current and Pending Support

List all current and pending grant support for each PI and collaborator. If an individual has no current or pending support, indicate as such.

MARU, DIPEN M.

ACTIVE

1R01CA187238-01(Hong, Kopetz) NIH	08/01/2014-07/01/2019 \$207,500	0.6 calendar
Therapeutic Strategies for Patients with BRAF Mutant Colorectal Cancer Project Goal: Combination therapies and strategies to increase the efficacy of existing agents including evaluating BRAF and EGFR inhibitors Role: Collaborator		
CA160928 Veeranki (PI) Department of Defense	09/01/2017-08/30/2019 \$149,999	0.12 calendar
Peer Reviewed Cancer Horizon Award Cyclin Dependent Kinase 9, a potential therapeutic target in Gastric Adenocarcinoma Major Goals: Role of genetic and pharmaceutical inhibition of CDK9 in gastric adenocarcinoma in vitro & in xenograft models Role: Mentor		
RP180473 (Tweardy) CPRIT	03/01/2018-02/28/2022 \$570,001	0.12 calendar
Clinical trials of C188-9, an oral inhibitor of signal transducer and activator of transcription (STAT) 3, in patients with hepatocellular carcinoma (HCC) Project Goal: To establish the efficacy of C188-9 in hepatocellular carcinoma as single agent or in combination with Sorafenib. Role: Collaborator		
Differential topological accumulation of somatic mutations in normal and cancerous gastric stem cells, and their association with gastric carcinogenesis and anti-tumor immune response		
PI (Futreal) KADOORIE CHARITABLE FOUNDATION	3/1/2018 - 2/28/2021 \$174,615	1.2 Calendar
Project Goals: To perform multi-region sequencing of matching primary and metastatic gastric cancer and to perform immune cell profiling through multiplex immunofluorescence panels and automated quantitative image processing, to examine for clonal diversity of T cells and to analyze for regional phylogenetic evolution and the relationship between mutational burden and signature with immune cell profile Role: Collaborator		
Phase I/II clinical trial of a TGF-beta inhibitor, M7824 in microsatellite instability (MSI) or Consensus Molecular Subtype (CMS) 4 metastatic colorectal cancer, Morris (PI) EMD-Serono Inc.	12/1/2017 - 11/30/2019 \$484,000	0.6 Calendar
Project Goals: Assess efficacy and toxicity of M7824 in MSI-H or CMS 4 colorectal adenocarcinoma Role: Coinvestigator		

Principal Investigator: Veeranki, Omkara L.

PENDING

UH2CA207101 (Maru, Kopetz, Morris, Luthra) 12/01/2017-11/30/2022 0.6 calendar
NIH \$153,754

Colorectal Cancer Molecular Subtype Assay Development and Validation

Major Goal: Establishment of an analytically validated clinical assay based on RNA expression signature for consensus molecular subtyping of colon cancer.

Role: Principle Investigator

P50 CA221707-01 (Kopetz, Maitra) 04/01/2018 – 03/31/2023 1.2 calendar
NIH/NCI \$154,930

MD Anderson Cancer Center SPORE in Gastrointestinal Cancer

Major Goal: The overall goal of the UT MD Anderson Cancer Center SPORE in Gastrointestinal Cancer is to reduce mortality and morbidity rates from colorectal cancer and pancreatic ductal adenocarcinoma and to improve the quality of life of patients afflicted by these diseases.

Role: Biospecimen and Pathology Core Leader

1R01CA234273-01 (Maru) 09/01/2018-08/31/2023 1.08 calendar
NIH/NCI \$248,000

Targeting Cyclin Dependent Kinase 9 Mediated MCL-1 Regulation to Enhance Chemoradiation Efficacy in Esophageal Adenocarcinoma

Project Goal: To establish efficacy and understand mechanisms of pharmaceutical inhibition of CDK 9 in enhancing chemoradiation effects in esophageal adenocarcinoma and determine relevance of a novel mechanism of transcription regulation of MCL-1 by CDK 9 inhibitors in enhancing chemoradiation efficacy.

Role: Principle Investigator

OVERLAP

None