COHA Translational Fellowship Opportunity
for residency-trained Veterinary Specialists

Immunoprevention of Breast Cancer

Area of Research: The area of research focuses on the immuprevention of breast cancer in women using the dog as a model

University and Department: Purdue University, Comparative Pathobiology

Primary Mentor: Sulma Mohammed; mohammes@purdue.edu

Mentor Team: Michael Childress; mochildr@purdue.edu

Description of Potential Research Project(s):

Women with genetic mutations or premalignant breast lesions such as ductal carcinoma in situ (DCIS) are at increased risk of developing invasive breast cancer. Currently, these women are clinically identified and are obligatorily treated with surgery that has adverse long-term health effects, as these women suffer weight gain, fatigue, disfiguring, and depression. Hence, new strategies to prevent cancer development with no long-term adverse effects are urgently needed. Recently, the prospect of developing a prophylactic vaccine seems possible. However, the production and testing of such prophylactic cancer vaccines are challenging due to the low cancer incidence rate within the healthy population and the time and cost to run an efficacy trial, and ethical issues. These challenges led researchers to rely heavily on less than perfect cancer models such as rodents to investigate cancer prevention strategies. In the pursuit of identifying an immunocompetent animal model that faithfully represents human breast cancer, we have found that, unlike most studied rodent models, female dogs develop DCIS spontaneously without genetic or chemical manipulation, and that DCIS occurs in about 50% of randomly screened asymptomatic female dogs. We have shown that canine DCIS resembles human DCIS with shared genetic, histopathologic, and molecular features and similar imaging and behavioral characteristics. Dogs with DCIS are at risk of developing invasive mammary cancer within one year. As in women, canine DCIS are heterogeneous and are divided into four subtypes, including triple-negative DCIS (TN-DCIS). Thus, we provide for the first time an immunocompetent animal model for TN-DCIS that will facilitate molecular analysis of pre-invasive triple-negative breast cancer (TNBC) and will provide an invaluable resource for identifying and selecting vaccine targets for TNBC immunoprevention. The work

will evaluate the safety and immunogenicity of α-lactalbumin and mammaglobin A vaccine formulations in healthy female dogs and determine the immunogenicity and efficacy of vaccine formulations in preventing DCIS progression in the dog model

Additional Training Opportunities: the candidate will attend the comparative and clinical sciences seminars and the cancer center seminars and guest speakers. The candidate will mentor in small grant writing and contribute to significant proposals. The candidate will attend and present talks or posters at national and international conferences.

Fellowships are for two years and provide stipend and employee benefits at the NIH post-doctoral pay scale, plus a total of $2500 for travel. Fellows must be U.S. citizens or permanent residents. Fellows may supplement their stipend with up to 25% effort towards clinical work if such work aligns with the research and career development plan and can be financed separately by the training institution.

This cohort of fellows will have a start date of fall 2022.

Biosketch of primary mentor:

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: **Mohammed, Sulma Ibrahim**

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

POSITION TITLE: **Professor of Cancer Biology**

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
Khartoum University, Khartoum, Sudan	DVM	07/1977	Veterinary Medicine
Cornell University, Ithaca, NY	MS	08/1982	Microbiology
Purdue University, West Lafayette, IN	PhD	12/1991	Microbiology and Molecular Biology

A. Personal Statement

I am a Professor of Cancer Biology, Department of Comparative Pathobiology, and Purdue University Center for Cancer Research as well as Indiana University School of Medicine, Indiana, USA.
I have the expertise, leadership, training and motivation necessary to carry successfully out the proposed research project. My DVM degree provided me with a strong background in basic medical sciences and clinical sciences including comparative oncology. I acquired extensive knowledge of basic and applied medical sciences, molecular biology, cell biology, biochemistry, and microbiology through my graduate programs at Cornell University and Purdue University. My eight years of postdoctoral training have given me enormous experience in advanced molecular biology, protein biochemistry, and cell biology. I have gained experience in cancer research from the basic level to pre-clinical research in animal models and human clinical trials. As Director of Purdue Cancer Center Drug Discovery Shared Resource (2002-2007), I have provided high quality service to members of the Cancer Center. I have developed protocols and consulted on the design and implementation of in vitro and in vivo experiments. In collaboration with colleagues at the Purdue College of Veterinary Medicine and Indiana University School of Medicine, I have studied dog mammary intraepithelial lesions and tumors because dogs develop these lesions spontaneously in an intact immune system. I have showed the similarities to human breast cancer and proposed the dog as model for human breast cancer to study cancer progression and treatment. The Department of Defense and Purdue University have supported this project, and I have successfully overseen these projects from staffing and research protections to budget and final manuscripts.

B. Positions and Honors

Positions and Employment

1982-1986 Lecturer, School of Science and Technology, Gezira University, Sudan
1991-1994 Fellow, Department of Biological Sciences, Purdue University, West Lafayette, IN
1994-1998 Fellow, Department of renewable resourced, Purdue University, West Lafayette, IN
1998-2002 Fellow, Walther Cancer Institute, Indianapolis, IN
2000-2002 Fellow, American Association for Cancer Research Cancer Prevention, Purdue University, West Lafayette, IN
2002-2007 Assistant Professor, Department of Comparative Pathobiology, Purdue University, West Lafayette, IN

2002-2007 Assistant Professor, Indiana University School of Medicine, Indianapolis, IN
2002-2007 Directors, Drug Discovery/Animal Model Shared Core Facility, Purdue University Center for Cancer Research, West Lafayette, IN
2007- Associate Professor, Department of Comparative Pathobiology, Purdue University, West Lafayette, IN
2007- Associate Professor, Department of Microbiology and Immunology, Indiana University School of Medicine, Indianapolis, IN
2010-2011 Fellow, National Cancer Institute, Rockville, MD.
2019- Professor, Department of Comparative Pathobiology, Purdue University, West Lafayette, IN
2019- Professor, Department of Microbiology and Immunology, Indiana University School of Medicine, Indianapolis, IN

Other Experience and Professional Memberships

1991- Women in Science
1998- American Association for Cancer Research
2000- Council Member, African Organization of Research and Training in Cancer (AORTIC)
2002- Member, Bindley Bioscience, Discovery Park, Purdue University, West Lafayette, IN
2003-2006 DOD Peer Review Integration Panel
2004- Associate editor, Cancer Chemoprevention Journal
2005-2006 NIH Peer Review, Small Grants Program for Cancer Epidemiology & Cancer Research
2005-2007 Vice President, African Organization of Research and Training in Cancer (AORTIC)
2007- Member, Purdue University Center for Cancer Research, West Lafayette, IN
2007- Member, Indiana University Melvin, and Bern Simon Cancer Center, Indianapolis, IN
2010- Associate editor, International Journal of Women Health
2012- Member, Executive Committee African Union Diaspora Health Initiative
2014- Editor-in-Chief, International Journal of Cancer and Clinical Research
2016- Member of a special emphasis panel Oncology 1 - Basic Translational IRG (OBT)

Honors

1972-77 Merit Scholarship for DVM program from Khartoum University, Sudan
1979-82 Merit Scholarship for MS program from Sudan Government to study at Cornell University
1986-91 The African Graduate Fellowship Program (AFGRAD) Award for Ph.D. study at Purdue University (1 of 5 from the entire continent of Africa offered once every five years)
1991 Student Travel Award to attend 76th American Association of Cereal Chemists National Meeting in Seattle, WA
1991 Midwest Universities Consortium for International Activities, Inc. Award; 1st recipient from Purdue University
1999-01 American Association for Cancer Research Foundation of America Fellowship in Prevention Research
2002 American Association for Cancer Research Minority Scholar Award
2003 American Association for Cancer Research Minority Scholar Award
2004 American Association for Cancer Research Minority Scholar Award
2008 Certificate from Purdue University Graduate School for serving as a research mentor to students participating in the Summer Research Opportunity Program
2010 Excellence and Leadership in the Field of Breast Cancer and Health Awareness Award by University of Medical Sciences and Technology, Khartoum, Sudan
2010 Fellowship from the National Institute of Health/National Cancer Institute, NCI Center to Reduce Cancer Health Disparities
2011 Leading the Way in Breast Cancer Research Award by African Women's Cancer Awareness Association

2012 Outstanding Faculty Mentor Award, Louis Stokes Alliance for Minority Participation Program (LSAMP) program, Purdue University

2013 Fellow of Entrepreneurial Leadership Academy Award, Purdue University

2013 Nominated for American Association for Cancer Research Distinguished Lecture on the Science of Cancer Health Disparities, funded by Susan G. Komen

2014 Nominated for American Association for Cancer Research Distinguished Lecture on the Science of Cancer Health Disparities, funded by Susan G. Komen

2016 African Diaspora Ambassador Award, Harvard Global Health Catalyst, Harvard Medical School

2016 Pillar of Support Award - for Decade of Support and Personal Commitment to Stop Cancer in Africa - awarded by the Forum of African First Ladies/Spouses against Cervical, Breast and Prostate Cancers

2016 Certificate of Recognition for Serving in the Role of Volunteer Faculty Advisor, Indiana University School of Medicine Medical Student Education

2017 College of Veterinary Medicine's 2017 Zoetis Award for Veterinary Research Excellence

2017 American Association for Cancer Research certificate of appreciation in recognition of meritorious service as an honored Judge during the Twelfth Annual AACR Undergraduate Student Caucus and Poster Completion

2017 Appreciation Plaque for Leadership as Course Director 2002-2016 Medical Microbiology, Indiana University School of Medicine - West Lafayette

C. Contributions to Science

http://www.ncbi.nlm.nih.gov/sites/myncbi/1nYgtsGRQLJ/bibliography/48055192/public/?sort=date&direction=ascending.

I am interested in understanding the molecular, genetic, epigenetic, and functional changes involved in the earliest steps of breast disease. The goal of my laboratory is to identify molecules intrinsic to premalignant breast lesions and normal-looking adjacent tissues to typify lesions destined to progress to invasive cancer. Using this information, we plan to elucidate the causative pathways of carcinogenesis and to improve clinical management of patients who at high risk of developing breast cancer. We have devoted much effort to the characterization of a unique animal model that develops spontaneous premalignant lesions very similar to human lesions in all morphological, molecular, and clinical diversity. We have shown that spontaneous canine mammary premalignant lesions such as atypical ductal hyperplasia (ADH) and ductal carcinoma in situ (DCIS) in dogs are similar to those of the human breast in terms of the characteristics of developing spontaneously before mammary tumors, their histologic diversity, and the immunohistochemical profile of ER-α, PR, and HER-2. Also, clustered micro-calcifications and other radiographic lesions, corresponding to BI-RADS criteria for human breast cancer screening, can be detected in the canine mammary glands. This approach allows the non-invasive evaluation of drug efficacy in the prevention of clinical trials. We are using our dog model to shed light on the evolution of ADH and DCIS to malignancy and to identify progression features that distinguish indolent from aggressive disease.

1. Antuofermo E, Miller MA, Pirino S, Xie J, Badve S, Mohammed SI. **Spontaneous mammary intraepithelial lesions in dogs--a model of breast cancer.** Cancer Epidemiol Biomarkers Prev. 2007 Nov;16(11):2247-56. doi: 10.1158/1055-9965.EPI-06-0932. Epub 2007 Nov 2. PMID: 17982119.

2. Mouser P, Miller MA, Antuofermo E, Badve SS, Mohammed SI. **Prevalence and classification of spontaneous mammary intraepithelial lesions in dogs without clinical mammary disease**. Vet Pathol. 2010 Mar;47(2):275-84. doi: 10.1177/0300985809358603. Epub 2010 Jan 22. PMID: 20106771

3. Mohammed SI, Meloni GB, Pinna Parpaglia ML, Marras V, Burrai GP, Meloni F, Pirino S, Antuofermo E. **Mammography and ultrasound imaging of preinvasive and invasive canine spontaneous mammary cancer and their similarities to human breast cancer.** Cancer Prev Res (Phila). 2011 Nov;4(11):1790-8. doi: 10.1158/1940-6207.CAPR-11-0084. Epub 2011 Jul 29. PMID: 21803985

4. Beetch M, Harandi-Zadeh S, Yang T, Boycott C, Chen Y, Stefanska B, Mohammed SI. **DNA methylation landscape of triple-negative ductal carcinoma in situ (DCIS) progressing to the invasive stage in canine breast cancer.** Sci Rep. 2020 Feb 12;10(1):2415. doi: 10.1038/s41598-020-59260-4. PMID: 32051475
5. Mohammed S, Utturkar S, Lee M, Yang HH, Cui Z, Atallah Lanman N, Zhang G, Ramos Cardona XE, Mittal SK, Miller MA. **Ductal Carcinoma In Situ Progression in Dog Model of Breast Cancer**. Cancers (Basel). 2020 Feb 11;12(2):418. doi: 10.3390/cancers12020418. PMID: 32053966

At the international level, I have been involved in issues related to global cancer. With my African colleagues, we reactivated the African Organization for Research and Training in Cancer (AORTIC). AORTIC has become the Pan African Cancer Organization with a membership of ~800 MDs, PhDs, RNs, and others interested in cancer. It has a clear mission: to facilitate research and training and to provide relevant and accurate information on the prevention, early diagnosis, treatment, and palliation of cancer. AORTIC is dedicated to providing all Africans with these benefits, as well as increasing public awareness of cancer and reducing the stigma associated with it. I was the vice president of the North American Chapter and am now a Council Member of AORTIC.

- **Mohammed SI**, Williams CK, Ndom P, Holland JF. The African Organization for Research and Training in Cancer: a historical perspective. **Curr Oncol**. 2012;19(5):272-6. PMID: 23144576.
- Abuidris DO, Elsheikh A, Ali M, Musa H, Elgaili E, Ahmed AO, Sulieman I, **Mohammed SI**. Breast cancer screening with trained volunteers in the rural areas of Sudan: a pilot study. **Lancet Oncol.** 2013; 14(4):363-70. PMID: 23375833
- **Mohammed SI,** Harford JB. Sorting reality from what we think we know about breast cancer in Africa. **PLoS Med.** 2014 9;11(9):e1001721. PMID: 25203049
- Elgaili EM, Abuidris DO, Rahman M, Michalek AM, **Mohammed SI**. Breast cancer burden in central Sudan. **Int J Women's Health**. 2010;2:77-82. PMID: 21072300

In an ongoing project in collaboration with Dr. Flowers at Emory University and Dr. Parham at the University of North Carline Chapel Hill as well as Dr. J Irudayaraj and Dr. Linnes, a major focus of my laboratory is to develop a point of care test for early cervical cancer detection. Cervical cancer claims the lives of many women in low and middle-income countries. Cervical cancer screening using Papanicolaou's smear test has been highly effective in reducing death from this disease. However, this test is unaffordable in low- and middle-income countries, and its complexity has limited wide-scale uptake. Alternative tests, such as visual inspection with acetic acid or Lugol's iodine and human papillomavirus DNA, are sub-optimal in terms of specificity and sensitivity; thus, sensitive and affordable tests with high specificity for on-site reporting are needed. Using proteomics and bioinformatics, we have identified a valosin-containing protein (VCP) as differentially expressed between normal specimens and those with cervical intraepithelial neoplasia grade 2/3 (CIN2/CIN3+) or worse. VCP-specific immunohistochemical staining (validated by a point-of-care technology) provided sensitivity (93%) and specific (88%) identification of CIN2/CIN3+ and may serve as a critical biomarker for cervical cancer screening. Through this application, we plan to focus on further refinements to enhance analytic sensitivity and specificity of our proposed test, as well as on prototype development

- **Mohammed SI**, Ren W, Flowers L, et al. Point-of-care test for cervical cancer in LMICs. Oncotarget. 2016;7(14):18787–18797. doi:10.18632/oncotarget.7709
- **Ren W**, Mohammed SI, Wereley S, Irudayaraj J. Magnetic Focus Lateral Flow Sensor for Detection of Cervical Cancer Biomarkers. Anal Chem. 2019;91(4):2876–2884. doi:10.1021/acs.analchem.8b04848

In another ongoing study in collaboration with Indiana University School of Medicine to collect lymph from women with metastatic breast cancer, a major recent focus of my laboratory is the identification and characterization in terms of receptors expression of stem cell-like properties and the pathway analysis of lymph tumor circulating cells compared to blood tumor circulating cells in humans. We have successfully grown lymph tumor circulating cells isolated from lymph collected from an animal model in vitro. This study has the

potential to identify metastasis-specific molecules that helps to stratify women with breast cancer according to the risk of developing metastasis, to provide targets to treat and prevent metastasis, and to determine therapeutic efficacy.

- Rahman M and **Mohammed SI**. Breast cancer metastasis and the lymphatic system. Oncol Lett. 2015 Sep; 10(3): 1233–1239.
- **Mohammed SI,** Torres-Luquis O, Walls E, Lloyd F. Lymph-Circulating Tumor Cells show distinct properties to Blood Circulating Tumor Cells and constitute extraordinary efficient metastatic precursors. Mol Oncol. 209 Jun; 13(6):1400-1418
- **Mohammed SI**, Torres-Luquis O, Zhou W, Lanman NA, Espina V, and Liotta L. Tumor-draining Lymph Secretome en Route to the Regional Lymph Node in Breast Cancer Metastasis. Breast cancer: Target and Therapy. Accepted in Press, 2020.