BIOGRAPHICAL SKETCH

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NAME: Miles, Sarah L.

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

POSITION TITLE: Research Assistant Professor

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)	END DATE MM/YYYY	FIELD OF STUDY
Randolph Macon Woman's College, Lynchburg, VA	BS	05/1998	Biology
Marshall University School of Medicine, Huntington, WV	PHD	12/2004	Biomedical Science
Marshall University School of Medicine, Huntington , WV	Postdoctoral Fellow	12/2012	Biochemistry and Molecular Biology

A. Personal Statement

I am confident that I have the expertise, experience, motivation, and mentor support to successfully fulfill the specific aims in my application titled “Defining molecular mechanisms of paraneoplastic uveal melanocytic proliferation.” I have a broad background in Biomedical Science with specific emphasis on Pharmacology. As a Postdoctoral Fellow and Research Associate I gained extensive experience and expertise in molecular biology techniques, which included cell culture, cell cycle analysis, signal transduction and gene transcription analysis. My main research involves the use of dietary constituents to inhibit the growth and progression of melanoma, and elucidating the molecular mechanisms and pathways involved in melanoma progression and chemotherapeutic resistance. This previous work has encompassed all of the concepts and techniques necessary to successfully complete the studies in this grant proposal. The studies in this proposal will vastly expand our knowledge about the etiology of paraneoplastic Bilateral Diffuse Uveal Melanocytic Proliferation (BDUMP) syndrome. In conjunction with my close collaboration with Dr. Jose Pulido (Mayo Clinic, Rochester MN) and our initial investigations and development of a melanocyte proliferation bioassay for the detection of serum borne BDUMP factor, as PI on a pilot grant funded through the Appalachian Translational Research Network Partnership, I have laid the groundwork for the proposed research by identifying the putative pathway by which the ectopic cancer associated BDUMP serum factor initiates abnormal melanocyte stimulation. The results of these proposed studies will provide novel molecular information to understand how ectopic factors may alter melanocyte biology, with anticipated translation to other melanocytic disorders including ocular and cutaneous melanoma. I am very enthusiastic and committed to seeing this project move forward, to facilitate identifying critical molecular targets for improving diagnosis and treatment options to reverse or prevent the devastating ocular effects of BDUMP syndrome.

1. Jansen JC, Van Calster J, Pulido JS, Miles SL, Vile RG, Van Bergen T, Cassiman C, Spielberg LH, Leys AM. Early diagnosis and successful treatment of paraneoplastic melanocytic proliferation. Br J Ophthalmol. 2015 Jul;99(7):943-8. PubMed PMID: 25908835; PubMed Central PMCID: PMC4501174.
2. Pulido JS, Flotte TJ, Raja H, Miles S, Winters JL, Niles R, Jaben EA, Markovic SN, Davies J, Kalli KR, Vile RG, Garcia JJ, Salomao DR. Dermal and conjunctival melanocytic proliferations in diffuse uveal melanocytic proliferation. Eye (Lond). 2013 Sep;27(9):1058-62. PubMed PMID: 23788206; PubMed Central PMCID: PMC3772365.
3. Miles SL, Niles RM, Pittock S, Vile R, Davies J, Winters JL, Abu-Yaghi NE, Grothey A, Siddiqui M, Kaur J, Hartmann L, Kalli KR, Pease L, Kravitz D, Markovic S, Pulido JS. A factor found in the IgG fraction of serum of patients with paraneoplastic bilateral diffuse uveal melanocytic proliferation causes proliferation of cultured human melanocytes. Retina. 2012 Oct;32(9):1959-66. PubMed PMID: 22791177.

B. Positions and Honors

Positions and Employment

2012 - 2013	Research Associate, Joan C. Edwards School of Medicine, Marshall University, Huntington, WV
2013 –	Research Assistant Professor, Joan C. Edwards School of Medicine, Marshall University, Huntington, WV
2016-	Independent Consultant – Quality System and Laboratory Management, Serucell Corporation, Huntington, WV

Other Experience and Professional Memberships

August 2012	Training: Foundation for Advanced Education in the Sciences (FAES) advanced graduate training: BioTrac 29; Laser Capture Microdissection, Methods for Microgenomic Analysis.
May 2014	Training: Foundation for Advanced Education in the Sciences (FAES) advanced graduate training: BioTrac 23; Flow Cytometry: Principles and Methods.

Honors

C. Contribution to Science

1. My research and interest in the field of melanoma has lead to a unique research opportunity, which aims to determine the molecular identity and mechanism behind the development of the paraneoplastic syndrome called bilateral diffuse uveal melanocytic proliferation (BDUMP). BDUMP causes the benign proliferation of melanocytes in the uveal tract of the eye along with exudative retinal detachment and rapid cataract formation, resulting in blindness. My earliest published work involved the development of an in vitro melanocyte bioassay for detecting the presence of BDUMP factor in patient serum. My findings were the first reported in vitro investigations and clearly demonstrated the presences of a circulating melanocyte-selective stimulating factor responsible for BDUMP syndrome. In addition, published collaborative studies have also identified that this syndrome is not limited to ocular melanocytes, but can affect dermal melanocytes as well, which has likely been historically overlooked. The use of this novel bioassay and the continued procurement of deidentified BDUMP patient serum from both national and worldwide sources (through collaboration with Dr. Jose Pulido, and ocular oncologist, Mayo Clinic in Rochester, MN) greatly enhances my ability to pursue discovering the mechanism of this disease. I was recently awarded a pilot grant funded through the Appalachian Translational Research Network Partnership and have made significant preliminary progress in identifying the putative mechanism of the BDUMP factor. By providing evidence that BDUMP syndrome is initiated by a circulating serum factor, my studies have contributed to improving therapy interventions. The implementation of plasmapheresis has proven to have beneficial effects in stabilizing the progression of ocular melanocytic lesions and reversing exudative retinal detachment to improve visual acuity, if the condition is caught early. Unfortunately, combined with typical late-stage diagnosis, plasmapheresis does not provide a long-term solution because of limited patient tolerability as repeated plasmapheresis can have a negative impact on other factors such as the immune system. Thus there is still a considerable need for effective diagnostic and treatment strategies that can only be attained if we can firmly identify the molecular targets of this syndrome. These studies will likely have broader implications in melanocyte biology, which can be translated to several other melanocytic pathologies.

    a. Miles SL, Niles RM, Pittock S, Vile R, Davies J, Winters JL, Abu-Yaghi NE, Grothey A, Siddiqui M, Kaur J, Hartmann L, Kalli KR, Pease L, Kravitz D, Markovic S, Pulido JS. A factor found in the IgG fraction of serum of patients with paraneoplastic bilateral diffuse uveal melanocytic proliferation causes proliferation of cultured human melanocytes. Retina. 2012 Oct;32(9):1959-66. PubMed PMID: 22791177.
    b. Pulido JS, Flotte TJ, Raja H, Miles S, Winters JL, Niles R, Jaben EA, Markovic SN, Davies J, Kalli KR, Vile RG, Garcia JJ, Salomao DR. Dermal and conjunctival melanocytic proliferations in diffuse uveal

melanocytic proliferation. Eye (Lond). 2013 Sep;27(9):1058-62. PubMed PMID: 23788206; PubMed Central PMCID: PMC3772365.

c. Jansen JC, Van Calster J, Pulido JS, Miles SL, Vile RG, Van Bergen T, Cassiman C, Spielberg LH, Leys AM. Early diagnosis and successful treatment of paraneoplastic melanocytic proliferation. Br J Ophthalmol. 2015 Jul;99(7):943-8. PubMed PMID: 25908835; PubMed Central PMCID: PMC4501174.

2. In addition to the contributions described above, my other research involves the use of vitamin C (ascorbate) to inhibit the progression of melanoma and potentially augment chemotherapeutic response. The transcription factor Hypoxia Inducible Factor 1-alpha (HIF-1α) has been implicated as a key player in the development and progression of melanoma. Various tumor tissues have been found to be ascorbate depleted when compared to normal surrounding tissue, and in conjunction, often expressed elevated levels of HIF-1α. Providing evidence that vitamin C can be used effectively to regulate aberrant expression and activity of HIF-1α in melanoma cells, this provides further support for investigating its use as an adjuvant therapy to treat not only melanoma but any malignancy where abnormal of HIF-1α may be a sustaining factor. My lab has documented the ability of physiological concentrations of ascorbic acid to reduce the protein expression and activity of HIF-1α and subsequently inhibit the invasiveness of metastatic melanoma cells. By documenting evidence for the efficacy of vitamin C to impede an aggressive malignant phenotype, this work can potentially change the traditional course of therapy for individuals with melanoma. The inclusion of vitamin C as an adjuvant therapy to diminish tumor aggressiveness and augment the therapeutic benefit of chemotherapy merits further investigation. I have served as the primary investigator in the development of these studies and the course of this work is shown in several poster presentations and 3 manuscripts.

   a. Fischer AP, Miles SL. Silencing HIF-1α induces TET2 expression and augments ascorbic acid induced 5-hydroxymethylation of DNA in human metastatic melanoma cells. Biochem Biophys Res Commun. 2017 Aug 19;490(2):176-181. PubMed PMID: 28601635.

   b. Fischer AP, Miles SL. Ascorbic acid, but not dehydroascorbic acid increases intracellular vitamin C content to decrease Hypoxia Inducible Factor -1 alpha activity and reduce malignant potential in human melanoma. Biomed Pharmacother. 2017 Feb;86:502-513. PubMed PMID: 28012930.

   c. Miles SL, Fischer AP, Joshi SJ, Niles RM. Ascorbic acid and ascorbate-2-phosphate decrease HIF activity and malignant properties of human melanoma cells. BMC Cancer. 2015 Nov 7;15:867. PubMed PMID: 26547841; PubMed Central PMCID: PMC4636772.

3. Other significant research that I was directly involved was the development of the West Virginia Cancer Genomics Network (WVCGN). The purpose of this network is to acquire gene expression profiles and other genomic data from consenting patients being treated for either non-solid malignancies (lymphoma, leukemia etc.) or solid tumors such as lung and colon, and is a collaborative effort involving the Joan C. Edwards School of Medicine at Marshall University, West Virginia University and Charleston Area Medical Center. This network provides a rich resource genetic and genomic data on cancers occurring in the Appalachian population. The long-range goal of the WVCGN is to be able to use genomic data for specific tumor types to assist in prognosis and susceptibility to chemotherapeutic interventions. My role as a co-investigator in the WVCGN is the procurement and Laser Capture Microdissection of solid tumors and isolation of genomic DNA and mRNA for downstream genomic analysis. I have attained advanced training at the Foundation for Advanced Education in the Sciences (FAES) graduate school (NIH) through completion of the Bio-Trac course: Laser Capture Microdissection, Methods for Microgenomic Analysis (BioTech 29). My role in the WVCGN is an integral part of its success as I am currently the only individual trained to conduct the LCM studies. The network is a valuable resource for the state of West Virginia with the potential for vast impact on state economics by attracting pharmaceutical interest to fund clinical trials driven by investigator access to genomic data, and potential commercialization of discoveries made by investigators mining the WVCGN database. The patient benefit is also significant. As we move toward personalized medicine, the WVCGN will have a number of direct impacts on patient diagnosis, treatment and care, particularly in our WV population.

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

WV INBRE Cancer Biology
Funding: WV-INBRE
PI: Sarah L. Miles, Ph.D
Title: Defining Molecular Mechanisms of paraneoplastic uveal melanocytic proliferation
Direct Cost: $30,000
Period Funding: August 2019-July 2021

Appalachian Translational Research Network Partnership: University of Kentucky/Marshall University CCTS Collaborative Grant
Funding: Marshall University/UK CTSI
PI: Sarah L. Miles, Ph.D
Title: Characterization and mechanism paraneoplastic ocular/dermal melanocytic proliferation
Direct cost: $25,000
Period of funding: August 1, 2014 – January 1, 2016

Zacharia's Bucks for Brains Award
Funding: Marshall University
PI: Sarah L. Miles Ph.D, Co-PI; Nadim Bou Zgheib, MD
Title: Molecular signature of platinum resistance in ovarian cancer stem cells
Direct cost: $33,733
Period of funding: January 1, 2015 – December 31, 2015