BIOGRAPHICAL SKETCH

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NAME: Urbain Weyemi, M.S./Ph.D.

eRA COMMONS USER NAME (credential, e.g., agency login): SWEYEMI2

POSITION TITLE: Assistant Professor, University of Texas at Austin

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
University of Abomey-Calavi, Benin	B.S.	07/2003	Physiology
University of Paris-Sud XI, Orsay, France	M.S.	07/2006	Physiology & Cell Signaling
University of Paris-Sud XI, Orsay, France	Ph.D.	07/2010	Molecular & Cellular Biology
National Cancer Institute, NIH, Bethesda, MD	Postdoc	12/2015	Molecular Biology
Johns Hopkins University School of Medicine, Baltimore, MD	Postdoc	12/2019	Molecular Neuroscience

A. Personal Statement

Maintaining genome stability is essential for organismal development and survival. Mammalian cells are endowed with multiple pathways that sense and repair genomic DNA lesions. One type of lesion, the DNA double-strand break (DSB), is particularly deleterious. Upon DSB formation, free DNA ends recruit the MRN (MRE11-RAD50-NBS1) complex, leading to the activation of the ATM kinase, which in turn phosphorylates histone variant H2AX on the Ser139 residue (called γH2AX). γH2AX initiates a signaling cascade involving the MDC1 protein, as well as several dozen additional players, such as 53BP1, RNF8, UBC13, RAP80, and BRCA1, which collectively function to activate DNA damage repair (DDR). Compromising this pathway may lead to increased mutation loads, resulting in a broad range of human conditions, including immune deficiency, cancer, and neurological disorders. However, another factor contributing to elevated DNA lesion levels is chronic oxidative stress due to defective mitochondrial energy generation (MEG). My laboratory uses a large range of tools including CRISPR-based screens, mouse models of DNA repair deficiency, as well as several molecular biology approaches, to investigate the interplay between complex regulation of DDR genes and mechanisms of MEG in human diseases. Our disease models include neurological disorders such as Alzheimer's disease and Parkinson's disease, as well as models of cancer progression.

Most recent publications:

1. **Weyemi U**, Paul BD, Bhattacharya D, Malla AP, Boufraqech M, Harraz MM, Bonner WM, Snyder SH. Histone H2AX promotes neuronal health by controlling mitochondrial homeostasis. ***Proc Natl Acad Sci U S A*;** 116:7471-7476, 2019.

2. **Weyemi U**, Paul BD, Snowman AM, Jailwala P, Nussenzweig A, Bonner WM, Snyder SH. Histone H2AX deficiency causes neurobehavioral deficits and impaired redox homeostasis. ***Nature Communications*,** 9:1526, 2018.

3. **Weyemi U***, Redon CE, Aziz T, Choudhuri R, Maeda D, Parekh PR, Bonner MY, Arbiser JL, Bonner WM.

NADPH oxidase 4 is a critical mediator in Ataxia telangiectasia disease. ***Proc Natl Acad Sci U S A.*, 112:2121-6, 2015** (* Corresponding Author)**.**

4. **Weyemi U***, Redon CE, Choudhuri R, Aziz T, Maeda D, Boufraqech M, Parekh PR, Sethi TK, Kasoji M, Abrams N, Merchant A, Rajapakse VN, Bonner WM. The histone variant H2A.X is a regulator of the epithelial-mesenchymal transition. ***Nature Communications*, 7 :10711, 2016** (* Corresponding Author).

B. Positions and Honors

Positions and Employment

2020- Assistant Professor, Department of Molecular Biosciences, University of Texas at Austin, TX, U.S.A.

2015-2019 Research Associate, The Solomon H. Snyder Department of Neuroscience, Johns Hopkins University School of Medicine, Baltimore, MD, U.S.A.
Advisor: Solomon H. Snyder

2010-2015 Postdoctoral Fellow, Developmental Therapeutics Branch, Laboratory of Molecular Pharmacology, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD, U.S.A.
Advisor: William M. Bonner

Awards and Honors

2020 Winner of the University of Texas at Austin internal competition for the Pew-Stewart Scholars Program (2020-2021): Submitted 08/2020
2020 Winner of the University of Texas at Austin internal competition for the Searle Scholars Program (2020-2021): Submission 09/2020
2019 CPRIT First-Time, Tenure-Track Faculty Recruitment Award: CPRIT Scholar
2019 Finalist for the Trans-NIH Earl Stadtman Tenure-Track Investigators search
2019 The American Society for Cell Biology “Accomplishing Career Transition (ACT)” Award (funded by NIH)
2018 The American Society for Cell Biology “Faculty Research and Education Development” Award (funded by NSF)
2014 NIH Fellow Award for Research Excellence (FARE 2014), NIH, Bethesda, MD, USA
2013 NIH Fellow Award for Research Excellence (FARE 2013), NIH, Bethesda, MD, USA
2009 French Foundation for Medical Research Award (FRM), France
2007 First Prize for Poster Presentation, Cancer Institute Gustave Roussy, Villejuif, France
2006 Department of Research and Education (MRT) Graduate Studies Award, France (3 years)
2005 One-Year Master’s degree Fellowship by University of Paris XI, Orsay, France

Other Professional Activities and Mentoring

2008-2010 Mentoring of two students of the University of Paris-Sud, France
2010-2015 Mentoring of six NIH undergraduate students and one graduate student
2013-2014 Judge for NIH Fellow Award for Research Excellence 2014 (FARE 2014)
2013 Reviewer for the *World Journal of Gastroenterology*
2014 Reviewer for the *British Journal of Cancer*
2014-2015 Reviewer for the *Journal of Medicinal Chemistry*
2017 Mentoring of two undergraduate and graduate students at Johns Hopkins University
2017 Reviewer for the *European Journal of Neurology*
2018 Reviewer for *Clinical & Experimental Metastasis*
2020 Reviewer for *Frontiers Oncology*
2020-present Guest Editor for *International Review for Cell and Molecular Biology*

2020-present Mentoring of two Ph.D. students, five undergraduate students, and one Research Assistant at the University of Texas at Austin.

Professional Memberships

2020 Member, LiveStrong Cancer Institute at the Dell Medical School of Texas
2020 Member, American Association for Cancer Research (AACR)
2018 Member, Society for Neuroscience (SfN)
2017 Member, National Research Mentoring Network (NRMN)
2016 Member, Society for Neuroscience (SfN)
2013 Member, Radiation Research Society (RRS)
2009 Member, Endocrine Society
2009 Member, European Thyroid Association (ETA)

C. Contributions to Science

1. Genome Stability and Redox homeostasis in human diseases

My thesis work uncovered the unprecedented role of the NADPH oxidase NOX4 in oncogenic stress and DNA damage response. The NADPH oxidase enzymes are widely described as key players in oxidative stress. For the first time, I described a link between oncogenic activity and DNA damage induced by the ROS-producing enzyme NOX4 in cancer cells. These articles have raised awareness on the emerging role of NADPH oxidases in DNA damage and cancer and have been widely cited (**1a** and **1b**). In pursuit of the link between genomic instability and redox homeostasis in human diseases, I published during my first postdoctoral training a critical role for the ROS-generating NADPH oxidase 4 (NOX4) in cerebellar degeneration and thymic lymphoma associated with Ataxia Telangiectasia (A-T), an autosomal recessive disorder caused by mutations in the ATM gene (**1c**). Many studies have suggested a crucial role for redox homeostasis in the progression of A-T disease, but the sources of the reactive oxygen species (ROS) have remained obscured. For the first time, I showed that several characteristics of A-T cells, including elevated levels of oxidative DNA damage, DNA double-strand breaks and replicative senescence, are all partially abrogated by down-regulation of NOX4 with siRNA. I also observed that NOX4 expression is dependent on a functional ATM. Because cerebellar degeneration is the hallmark of the AT disease in human, I examined human cerebellar and cerebral brain samples from A-T patients and matched normal controls and found NOX4 is highly correlated with DNA damage and apoptosis levels in all A-T samples analyzed. To date, A-T remains incurable. The significance of this finding to the field is that it provides insight into the mechanism of the disease and provides a molecular target for treatment.

a. **Weyemi U**, Caillou B, Talbot M, Ameziane-El-Hassani R, Lacroix L, Lagent-Chevallier O, Al Ghuzlan A, Roos D, Bidart JM, Virion A, Schlumberger M, Dupuy C, Intracellular expression of reactive oxygen species-generating NADPH oxidase NOX4 in normal and cancer thyroid tissues. ***Endocr Relat Cancer*****, 17(1):27-37, 2010.**

b. **Weyemi U**, Lagente-Chevallier O, Boufraqech M, Prenois F, Courtin F, Caillou B, Talbot M, Dardalhon M, Al Ghuzlan A, Bidart JM, Schlumberger M, Dupuy C, ROS-generating NADPH oxidase NOX4 is a critical mediator in oncogenic H-Ras-induced DNA damage and subsequent senescence. ***Oncogene*****. 2012 31(9):1117-29, 2012.**

c. **Weyemi U***, Redon CE, Aziz T, Choudhuri R, Maeda D, Parekh PR, Bonner MY, Arbiser JL, Bonner WM. NADPH oxidase 4 is a critical mediator in Ataxia telangiectasia disease. ***Proc Natl Acad Sci U S A.*****, 112:2121-6, 2015**. (* Corresponding Author)**.**

2. DNA repair, redox homeostasis, and neurodegeneration

I reported the discovery that the DNA repair histone H2AX plays a prominent role in promoting mitochondrial biogenesis, redox homeostasis (**2a**), and neurobehavioral deficits (**2b**). During my second postdoctoral training, I reported the discovery that mice deficient for the DNA repair histone H2AX exhibit neurobehavioral deficits such as impaired motor balance and reduced locomotion. H2AX knockout cells exhibit pronounced diminution of mitochondrial biogenesis genes and oxidative phosphorylation complexes, findings which are substantiated by a disturbed mitochondrial shape in H2AX mutant cells. Challenging H2AX mutant mice with a drug which selectively targets mitochondrial complexes leads to neuronal cell death, implying a key role for histone H2AX

in promoting neuroprotection. The major significance of these findings is the demonstration that histone H2AX, a classic DNA repair gene, is a key determinant of mitochondrial homeostasis and neuronal fate. To our knowledge, this was the first evidence of a role for a histone variant in mitochondrial homeostasis and neuronal death. The greatest risk factor for aging is the concomitant impairment of mitochondrial function and dysfunction in DNA repair machinery. Our findings that H2AX deficiency leads to mitochondrial damage-associated neuronal death imply a key role for H2AX in aging-associated diseases. Given the importance of mitochondrial homeostasis in neuroprotection, this study has created a new direction to study the interplay between genome repair and mitochondrial homeostasis in neurodegeneration.

a. **Weyemi U**, Paul BD, Bhattacharya D, Malla AP, Boufraqech M, Harraz MM, Bonner WM, Snyder SH. Histone H2AX promotes neuronal health by controlling mitochondrial homeostasis. ***Proc Natl Acad Sci U S A*;** 116:7471-7476, 2019.

b. **Weyemi U**, Paul BD, Snowman AM, Jailwala P, Nussenzweig A, Bonner WM, Snyder SH. Histone H2AX deficiency causes neurobehavioral deficits and impaired redox homeostasis. ***Nature Communications*,** 9:1526, 2018.

3. Reviews on reactive oxygen species (ROS) and DNA damage response

I reflected upon the growing awareness of ROS-producing enzymes NOXs in DNA damage and have written reviews on the role of ROS in inducing genomic instability and DNA-damage signaling (**3a**). I also commented on the consequences of oxidative stress on senescence-associated phenotype in mouse skin tissues (**3b**).

a. **Weyemi U**, Dupuy C, The emerging role of ROS-generating NADPH oxidase NOX4 in DNA-damage responses. ***Mutat Res*, 751(2):77-81, 2012 (Review).** PMID: 22580379.
b. **Weyemi U**, Parekh PR, Redon CE, Bonner WM. SOD2 deficiency promotes aging phenotypes in mouse skin. ***Aging (Albany NY)*, 4(2):116-8, 2012 (Review)**. PMCID: PMC3314173.

Complete List of Published Work in NCBI: https://www.ncbi.nlm.nih.gov/pubmed/?term=Weyemi

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

Active Research Support

CPRIT RR190101 Weyemi, U (PI) 2019-2024
RECRUITMENT OF FIRST-TIME, TENURE-TRACK FACULTY
The goal of this study is to investigate the role of DNA Repair and Redox Biology in aging and cancer.
Role: PI

UT start-up funds Weyemi, U (PI) 2020-2025
Role: PI

ASCB/NIH Weyemi, U (Trainee) 2019-2021
The American Society for Cell Biology “Accomplishing Career Transition (ACT)” Award
Role: Trainee

Completed Research Support

ASCB/NSF Weyemi, U (PI) 2018-2019
The American Society for Cell Biology “Faculty Research and Education Development” Award

Role: Trainee

Foundation for Medical Research (FRM) in France Weyemi, U (PI) 2009-2010
Role of reactive oxygen species in DNA damage response induced by Ras oncogene
Role: Trainee