

## FREDRICK O. ONONO, M.Sc. (Biochemistry), PhD

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### **EDUCATION AND RESEARCH**

#### **University of Kentucky, Lexington, USA**

- Post Doctoral Research Fellow with Dr. Andrew J. Morris, Department of Internal Medicine, Saha Cardiovascular Research Center. Jan 2014- Present

*Project: Intestinal Phosphatidylcholine as a Link between Diet and Obesity-associated disease risk*

Supported by a T32 training grant, I joined the laboratory of Dr. Andrew Morris to receive training on new skills in animal model and human studies and also learn advanced mass spectrometry approaches to monitor lipid metabolism. Research in his lab concerns lipid metabolism and signaling in cardiovascular and metabolic diseases. Obesity and hyperlipidemia are known risk factors for cardiovascular disease. Given the challenges associated with dietary restriction and physical activity to mitigate these risk factors, a better understanding of the link between diet and cardiovascular disease is warranted for effective intervention. My research program is designed to investigate the possibility that intestinal exposure to the phospholipid phosphatidylcholine (PC), a highly abundant constituent in diet and bile sections, constitute a link between diet and cardiovascular risk by promoting the synthesis of a PC derived bioactive lipid, lysophosphatidic acid (LPA). In my most recent studies, using mass spectrometry we discovered that plasma LPA levels in mice and humans are acutely sensitive to fasting and refeeding and in mice we also showed that dietary PC can be converted to LPA in blood. This project is an effective vehicle for advanced training in research as I have acquire skills and generated data to compete successfully for a career development award as a way of achieving my ultimate goal of becoming an independent investigator.

- Post Doctoral Research Fellow with Dr. H. Peter Spielmann, Department of Molecular and Cellular Biochemistry. Nov 2009 -Dec 2013

*Project: Mechanisms of Exogenous Isoprenol substrate metabolism.*

During my doctoral training we collaborated with Dr. Spielmann using chemical probes his laboratory had developed to complete my studies. Recognizing the power of these approaches for unbiased identification of isoprenylated proteins I was excited to join his group for postdoctoral training to expand and augment my prior training with new expertise in chemical biology and associated analytical approaches. The research I conducted in Dr. Spielmann's lab focused on mechanism of exogenous isoprenol substrate utilization in cancer cells. We discovered that many cancer cells in culture substantially convert exogenous isoprenols to their diphosphate derivatives which are efficient substrates for isoprenylation. Our findings also demonstrated that this is an alternative pathway for the influx/supply or recycling of isoprenoid substrates regulated independently of the classical

mevalonate pathway. Genome-wide expression analysis have identified the mevalonate pathway to be significantly upregulated by mutant p53 and promoting tumor invasiveness in breast cancer cells. Interestingly, we found that mutant p53 depletion or pharmacological inhibition of the mevalonate pathway using statins (HMG-CoA reductase inhibitors) enhances the use of exogenous isoprenols, supporting our findings that regulation of this alternative pathway is independent of the mevalonate pathway. The discovery opens up opportunities for design of cell-directed therapies and provides insights into mechanisms underlying pleiotropic therapeutic benefits and unwanted side effects of mevalonate pathway inhibition. These studies, performed in collaboration with Dr. Andrew Morris, enabled me acquire expertise in tandem mass spectrometry. The research was supported, in part, by a prestigious postdoctoral fellowship award from the American Heart Association and formed the basis of a first author publication in the *Journal of Biological Chemistry* and co-authorship in 2 other articles.

### **Hannover Medical School, Germany**

- PhD (Molecular Medicine) - Doctoral research with Prof. Dr. Christoph W. Reuter, Department of Hematology, Hemostasis, Oncology and Stem Cell Transplantation. Sep 2004- June 2009

Thesis: "*Elucidation and chemotherapeutic alterations of the farnesylated proteome in leukemia cells.*"

*Project 1: Protein isoprenylation as a cancer therapeutic target.*

*Project 2: Chemotherapeutic potentials of combining farnesyl and dual prenyl transferase inhibitors with anthracycline-induced cytotoxicity in myeloid leukemia.*

My studies focused on targeting protein posttranslational modification to treat hematological malignancies using myeloid leukemia as a model. The goal of my doctoral research was to map isoprenylated (isoprene covalent lipid modified) proteins in cancer cells that might provide cancer-specific targets for therapeutic interventions. Natural lipid substrates for this modification are biosynthesized as intermediates of the mevalonate pathway. Using xenobiotics, we developed a novel cell-based method that accelerates the identification of modified proteins that are therapeutically relevant for cellular resistance to specific treatment strategies. Utilizing unnatural substrates we rapidly and selectively detected the dynamics of isoprenylated proteins following exposure to different classes of targeted pharmacological agents. We also demonstrated that combination of chemically distinct inhibitors targeting prenyltransferase (enzymes that catalyze isoprenylation) can induce synergistic inhibition of myeloid leukemia cells through a mechanism that partially involves disruption of K-Ras oncogene activity. This doctoral training led to publication of four manuscripts - 2 first author articles in *Molecular and Cellular Proteomics* and *Journal of Molecular Medicine*.

## University of Nairobi, Kenya

➤ M.Sc., Biochemistry, Sep 2004

Thesis: *"T-cell responses in cattle immunized with a prototype anti-sporozoite sub-unit vaccine against Theileria parva"*

Project: *Identification and Characterization of Theileria parva candidate vaccine antigens and epitopes.*

## Jomo Kenyatta University of Agriculture and Technology (JKUAT), Juja, Kenya

➤ B.Sc. (Honors) Biochemistry and Chemistry, April 1997

## WORK EXPERIENCE

Assistant Professor (Aug 2015 - Present)

Department of Internal Medicine (Division of Cardiovascular Medicine), University of Kentucky

Research Assistant (Sep 2004-Oct 2009)

Department of Hematology, Hemostasis, Oncology and Stem Cell Transplantation. Hannover Medical School, Germany

Research Technologist (Jan 2002 - Sep 2004)

International Livestock Research Institute (ILRI), Nairobi, Kenya

Student Intern (Mar 1995 - Feb 1997)

Kenya Medical Research Institute, Kisumu, Kenya

## PUBLICATIONS

1. Subramanian T, Ren H, Subramanian KL, Sunkara M, **Onono FO**, Morris AJ and Spielmann HP. **2014** Design and synthesis of non-hydrolyzable homoisoprenoid  $\alpha$ -monofluorophosphonate inhibitors of PPAPDC family integral membrane lipid phosphatases. *Bioorg Med Chem Lett.* 24:4414-7. PMID: 25150376
2. Matveev SV, Spielmann HP, Metts BM, Chen J, **Onono F**, Zhu H, Scheff SW, Walker LC, LeVine H 3rd. **2014** A Distinct Subfraction of A $\beta$  is Responsible for the High-Affinity Pittsburgh Compound B (PIB) Binding Site in Alzheimer's Disease Brain. *J Neurochem.* 131:356-68. PMID: 24995708
3. Reuter CWM\*, Krauter J\*, **Onono FO**, Bunke T, Damm F, Thol F, Wagner K, Göhring G, Schlegelberger B, Heuser M, Ganser A and Morgan MA. **2014**. Lack of non-canonical RAS mutations in cytogenetically normal acute myeloid leukemia. *Ann Hematol.* 93:977-82 PMID: 24737308 \*Equal 1<sup>st</sup> authors

4. **Onono FO**, Subramanian T, Sunkara M, Subramanian KL, Spielmann HP, and Morris AJ. **2013**. Efficient use of exogenous isoprenols for protein isoprenylation by MDA-MB-231 cells is regulated independently of the mevalonate pathway. *J Biol Chem*. 288:27444-55. PMID: 23908355
5. Subramanian T, Subramanian KL, Sunkara M, **Onono FO**, Morris AJ and Spielmann HP. **2013** Synthesis Of Deuterium Labeled Prenyldiphosphate And Prenylcysteine Analogues For in vivo Mass Spectrometric Quantification. *J. Label. Compd. Radiopharm*. 56: 370-375. PMID: 24285475
6. Morgan MA\*, **Onono FO\***, Spielmann HP, Subramanian T, Scherr M, Venturini L, Dallmann I, Ganser A and Reuter CWM. **2012**. Modulation of anthracycline-induced cytotoxicity by targeting the prenylated proteome in myeloid leukemia cells. *J Mol Med* 90:149-61. PMID 21915711 \*Equal 1<sup>st</sup> authors
7. **Onono FO**, Morgan MA, Spielmann HP, Andres DA, Subramanian T, Ganser A, Reuter CW. **2010**. A tagging-via-substrate approach to detect the farnesylated proteome using two-dimensional electrophoresis coupled with Western blotting. *Mol Cell Proteomics*. 9:742-51. PMID: 20103566
8. Divchev D, Grothusen C, Luchtefeld M, Thoenes M, **Onono F**, Koch R, Drexler H, Schieffer B. **2008**. Impact of a combined treatment of angiotensin II type 1 receptor blockade and 3-hydroxy-3-methyl-glutaryl-CoA-reductase inhibition on secretory phospholipase A2-type IIA and low density lipoprotein oxidation in patients with coronary artery disease. *Eur Heart J* 29: 1956-65. PMID: 18565968
9. Graham SP, Pellé R, Yamage M, Mwangi DM, Honda Y, Mwakubambanya RS, de Villiers EP, Abuya E, Awino E, Gachanja J, Mbwika F, Muthiani AM, Muriuki C, Nyanjui JK, **Onono FO**, Osaso J, Riitho V, Saya RM, Ellis SA, McKeever DJ, MacHugh ND, Gilbert SC, Audonnet JC, Morrison WI, van der Bruggen P, Taracha EL. **2008**. Characterization of the fine specificity of bovine CD8 T-cell responses to defined antigens from the protozoan parasite *Theileria parva*. *Infect Immun*. 76: 685-94. PMID: 18070892
10. Graham SP, Pellé R, Honda Y, Mwangi DM, Tonukari NJ, Yamage M, Glew EJ, de Villiers EP, Shah T, Bishop R, Abuya E, Awino E, Gachanja J, Luyai AE, Mbwika F, Muthiani AM, Ndegwa DM, Njahira M, Nyanjui JK, **Onono FO**, Osaso J, Saya RM, Wildmann C, Fraser CM, Maudlin I, Gardner MJ, Morzaria SP, Loosmore S, Gilbert SC, Audonnet JC, van der Bruggen P, Nene V, Taracha EL. **2006**. *Theileria parva* candidate vaccine antigens recognized by immune bovine cytotoxic T lymphocytes. *Proc Natl Acad Sci U S A*. 103, 3286-91. PMID: 16492763

#### **SELECTED ABSTRACTS**

1. **Onono F**, Subramanian T, Sunkara M, Subramanian L, Spielmann HP, Morris AJ. Quantitative Determination of the Alternative Isoprenoid Generation Pathway as a Tool to Exploit the Mevalonate pathway in Cancer Cells. Experimental Biology 2013, Boston

Convention and Exhibition Center, April 20 – 24 2013

2. **Onono FO**, Subramanian T, Sunkara M, Troutman JM, Subramanian L, Morris AJ and Spielmann HP. Quantification of the alternative isoprenoid generation flux through the mevalonate pathway. Southeastern Regional Lipid Conference (SERLC) 47th Annual Conference, November 7-9, 2012
3. Morris AJ, Subramanian T, **Onono F**, Sunkara M and Spielmann HP. A chemical biology/mass spectrometry based approach to study isoprenoid diphosphate metabolism in live cells. LIPID MAPS Meeting May 7-8, 2012, La Jolla, CA
4. **Onono F**, Subramanian T, Sunkara M, Morris AJ and Spielmann HP. Functional Characterization of Phosphatidic Acid Phosphatase Domain Containing (PPAPDC) Proteins. 46<sup>th</sup> Annual Southeastern Regional Lipid Conference (SERLC) Cashiers, North Carolina Nov 9-11 2011.
5. **Onono F**, Subramanian T, Sunkara M, Morris AJ and Spielmann HP. Chemical probes reveal the mechanism of incorporation of exogenous isoprenols into proteins. 48<sup>th</sup> Annual Southeastern Regional Lipid Conference (SERLC) Cashiers, North Carolina Nov 10-12 2010.
6. **Onono, FO**, Morgan, MA, Spielmann, HP, Andres, DA, Scherr, M, Venturini, V, Dallman I, Ganser, A and Reuter, CWM. A Novel Proteomic Approach to Define Leukemia Cell Resistance to Farnesyltransferase Inhibitors. *Blood* 114: 1448-1448 Nov 20 2009
7. Morgan MA, **Onono F**, Scherr M, Venturi L, Dallman I, Ganser A and Reuter CWM. K-ras shRNA potentiates farnesyltransferase inhibitor (fti) efficacy in chronic myeloid leukemia. *Hematologica* 94: 308-308 June 2009
8. Morgan MA, Krauter J, **Onono F**, Bunke T, Damm F, Goerhring G, Schegelberger B, Ganser A, and Reuter CWM. K-Ras mutations in cytogenetically normal AML patients. *Hematologica* 94: 26-26 Jun 2009
9. **Onono FO**, Morgan MA, Ganser A and Reuter CWM. The Farnesyltransferase Inhibitor (FTI) L-778,123 Displays Promising Anti-Leukemia Activity. *Blood* 112: 909-909 Nov 2008
10. **Onono FO**, Morgan MA, Wegner J, Ganser A and Reuter CWM. Potentiation of Topoisomerase II Inhibitor-Mediated Myeloid Leukemia Cell Kill by Farnesyltransferase Inhibitor L-744,832 *Blood* 110: 1019A-1019A Nov 2007
11. Reuter CWM, Aydilek E, **Onono FO**, Morgan MA, Henningfeld KA, and Ganser A. Characterization of a Novel R-RAS Mutation Cloned from Primary AML Cells. *Blood* (ASH Annual Meeting Abstracts), Nov 2006; 108: 1439

## **HONORS**

### **Awards**

- Federation of American Societies for Experimental Biology – MARC- Travel Award – 2013
- American Society for Biochemistry and Molecular Biology – Postdoctoral travel Award – 2013
- Southeastern Regional Lipid Conference – Travel Award, 2010
- American Society of Hematology (ASH) – Travel Award, 2009
- Merck Sharp & Dohme Limited GMBH – Travel Grant, 2008

### **Post Doctoral Fellowships**

- NIH Ruth L. Kirschstein National Research Service Award (T32) (July 2014 to June 2015)
- American Heart Association - Great Rivers Affiliate - Postdoctoral fellowship, 2012-2013

### **Doctoral Scholarships**

- German Academic Exchange Program (DAAD) – Merit PhD support funding, 2007-2009
- Hannover Medical School, Germany – Merit PhD fellowship, 2005 – 2009
- International Livestock Research Institute (ILRI) PhD Training Grant, 2004 (Declined in favor of Hannover Medical School fellowship)

### **Pre-Doctoral Scholarships**

- International Livestock Research Institute (ILRI), Nairobi, Kenya – Master's Program fellowship, 2000 – 2002

### **Scholarships**

- Gandhi Smarak Nidhi Fund – Support for undergraduate studies, 1996
- Government of Kenya – Sponsorship for undergraduate studies, 1993 - 1996

## **GRANTS**

### **Career Development Award**

NIH's Mentored Career Development Award (K01). US\$702,000, (July 2015-June 2020)