

BIOGRAPHICAL SKETCH

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NAME: Nader H. Moniri

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

POSITION TITLE: Professor and Associate Dean for Research

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
Georgia State University, Atlanta, GA	B.S.	03/1997	Biology/Chemistry
University of North Carolina at Chapel Hill, Chapel Hill, NC	Ph.D.	03/2004	Medicinal Chemistry
Duke University Medical Center, Durham, NC	Post-Doc.	10/2005	Pharmacology

A. Personal Statement

My laboratory focuses on studying the molecular pharmacology and biochemistry of G protein-coupled receptors (GPCRs). I have extensive training in biochemical pharmacology of GPCRs, including training in medicinal chemistry and development of novel pharmaceutical agents that target this family of receptors. Additionally, I have extensive experience with the role of GPCRs in the brain, particularly in regard to GPCR-mediated regulation of tyrosine hydroxylase, which controls catecholamine synthesis. My training has included studies on the histamine H1, β 2-adrenergic, α 1-adrenergic, as well as free-fatty acid family of receptors. A central area of study in my lab centers on mechanisms of regulation of the free-fatty acid receptor-4 (FFA4, aka GPR120). This effort seeks to better understand the role that phosphorylation plays in modulating the antidiabetic and anti-inflammatory effects of FFA4, and our lab has contributed to much of the knowledge on regulation of FFA4. We are also studying the role of FFA4 in the brain, and have an ongoing NIH-funded study to determine the effects of FFA4 in Parkinson's Disease. The other major line of study in my lab relates to the role of reactive oxygen species (ROS) on regulation of the β 2-adrenergic receptor (β 2AR). This project seeks to shed light on the relatively recently recognized paradigm of GPCR signaling to, and regulation by, ROS. As the publications below demonstrate, my lab has contributed to much of the recent literature in regard to understanding the biochemical linkage between ROS and β 2AR, and I have extensive experience in biochemical, pharmacological, and molecular biological approaches toward investigating GPCR signaling.

B. Positions and Honors

1999-2004	Research Assistant, Division of Medicinal Chemistry, School of Pharmacy, University of North Carolina at Chapel Hill, Chapel Hill, NC.
2004-2005	Post-Doctoral Fellow, Departments of Surgery, Pharmacology and Cancer Biology, Duke University Medical Center, Durham, NC.
2005-2006	Senior Scientist, Department of Biochemistry and Molecular Pharmacology, Neurogen Corporation, Branford, CT.
7/2006-6/2012	Assistant Professor (tenure-track), Department of Pharmaceutical Sciences, College of Pharmacy and Health Sciences, Mercer University, Atlanta, GA.
7/2012-6/2018	Associate Professor with tenure, Department of Pharmaceutical Sciences, College of Pharmacy, Mercer University, Atlanta, GA.
7/2018-Present	Professor with tenure, Department of Pharmaceutical Sciences, College of Pharmacy, Mercer University, Atlanta, GA.
1/2014-Present	Associate Dean for Research, College of Pharmacy, Mercer University, Atlanta, GA.

Honors

2007	New Professor Recognition Award, 2006-2007, Rho Chi Honor Society, Mercer University Chapter
2008	Teacher of the Year Award, 2007-2008, Rho Chi Honor Society, Mercer University Chapter
2009	Elected Graduation Hooder, Class of 2009, Mercer University College of Pharmacy and Health Sciences
2010	Elected Graduation Hooder, Class of 2010, Mercer University College of Pharmacy and Health Sciences
2011	Elected Graduation Hooder, Class of 2011, Mercer University College of Pharmacy and Health Sciences
2011	Teacher of the Year Award, 2009-2010, Rho Chi Honor Society, Mercer University Chapter
2010-2014	Research Grant Reviewer, American Association of Colleges of Pharmacy
2011-2012	Fellow, American Association of Colleges of Pharmacy, Academic Leadership Fellowship Program
2012	Teacher of the Year Award, 2011-2012, Rho Chi Honor Society, Mercer University Chapter
2012	National Institutes of Health, Molecular and Integrative Signal Transduction (MIST) Study Section Reviewer, Ad hoc. (June, 2012)
2013	Elected Graduation Hooder, Class of 2013, Mercer University College of Pharmacy
2014	Elected Graduation Hooder, Class of 2014, Mercer University College of Pharmacy
2014	Inductee, Rho Chi Pharmacy Honor Society
2014	Award for Excellence in Research, Mercer University College of Pharmacy
2014	National Institutes of Health, Molecular and Integrative Signal Transduction (MIST) Study Section Reviewer, Ad hoc. (June, 2014)
2015	Elected Graduation Hooder, Class of 2015, Mercer University College of Pharmacy
2016	Elected Graduation Hooder, Class of 2016, Mercer University College of Pharmacy
2016	Award for Excellence in Service, Mercer University College of Pharmacy
2016	Distinguished Educator Award, Mercer University College of Pharmacy
2017	Elected Graduation Hooder, Class of 2017, Mercer University College of Pharmacy
2018	Elected Graduation Hooder, Class of 2018, Mercer University College of Pharmacy

C. Contributions to Science

1. Functional Selectivity of GPCR Signaling: Studies early in my career focused on functional selectivity of the histamine H₁ GPCR (H₁R) and coincided with pharmacological characterization of H₁ ligands that were able to selectively activate H₁R-linked pathways coupling to both G $\alpha_{q/11}$ and G α_s . Furthermore, these studies correlated with the role of H₁R functional selectivity in promoting dopamine synthesis in the brain and in bovine adrenal chromaffin cells. These studies were at the core of the larger body of pioneering evidence in the early 2000's that demonstrated a physiological role for the phenomenon of ligand-directed functional selectivity in native tissues, and suggested that functionally selective H₁R agonists could be therapeutically relevant for treatment of neurological disorders such as Parkinson's disease.

- Booth RG, Moniri NH, Bakker RA, Choksi NY, Nix WB, Timmerman H, Leurs R. A novel phenylaminotetralin radioligand reveals a sub-population of histamine H₁ receptors. *J Pharmacol Exp Ther*, 302:328-336, 2002. PMID: 12065734
- Moniri NH, Covington-Strachan DW, Booth RG. Ligand-directed functional heterogeneity of histamine H₁ receptors: Novel agonists selectively activate and block H₁ mediated phospholipase C and adenylyl cyclase signaling in CHO cells. *J Pharmacol Exp Ther*, 311:274-281, 2004. PMID: 15169829
- Moniri NH and Booth RG. Role of PKA and PKC in Histamine H₁ Receptor-Mediated Activation of Catecholamine Neurotransmitter Synthesis. *Neurosci Lett*, 407:249-253, 2006. PMID: 16978782
- Moniri NH and Booth RG. Functional heterogeneity of histamine H₁ receptors. *Inflamm Res*, 53:S71-72, 2004. PMID: 15054625

2. The regulation of the β 2-adrenergic receptor by ROS: As a post-doctoral fellow and into my independent research career, my laboratories work has provided critical insight into a novel dimension of regulation of the β 2-adrenergic receptor (β 2AR). Specifically, we have shown that the agonism of the β 2AR generates reactive oxygen species (ROS) and that ROS generation is required for the ability of the β 2AR to signal through G α_s and β -arrestin, as well as for receptor phosphorylation and internalization. My lab has also shown that the mechanism of ROS-

mediated regulation of β 2AR occurs via oxidant-induced S-sulfenation of the β 2AR on cysteine residues, an effect that occurs in an agonist-dependent manner. Together, these studies have shed light on the linkage between β 2AR and ROS and deduced a novel mechanism of β 2AR regulation via ROS. I serve as principal investigator on all of these studies and * denotes work published as corresponding author while at Mercer University.

- a. Wang G, Moniri NH, Ozawa K, Stamler JS, Daaka Y. Nitric oxide regulates endocytosis by S-nitrosylation of dynamin. *Proc Natl Acad Sci USA*, 103(5):1295-1300, 2006. PMID: 16432212
- b. Moniri NH* and Daaka Y. Agonist-stimulated reactive oxygen species formation regulates β 2-adrenergic receptor signal transduction. *Biochem Pharmacol*, 74: 64-73, 2007. PMID: 17451656
- c. Burns RN and Moniri NH*. Agonist- and H₂O₂- mediated oxidation of the β ₂ adrenergic receptor: evidence of receptor S-sulfenation as detected by a modified biotin switch assay. *J Pharmacol Exp Ther*, 339(3):914-921, 2011. PMID: 21917560
- d. Singh ML and Moniri NH*. Reactive oxygen species are required for β 2-adrenergic receptor- β -arrestin interactions and signaling to ERK1/2. *Biochem Pharmacol*, 84:661-669, 2012. PMID: 22728070
- e. Singh M and Moniri NH. Reactive oxygen species as β 2-adrenergic receptor signal transducers. *J. Pharmaceu Pharmacol*. 2(1): 8-15, 2014.

3. Characterization of phosphoregulation of FFA4 (GPR120): Free-fatty acid receptor-4 has gained considerable attention due to its ability to promote profound anti-inflammatory and anti-diabetic effects, including insulin resensitization, which is an effect that is dependent on β -arrestin signaling. My laboratory has contributed to the understanding of regulation of FFA4 signaling through phosphorylation, which itself drives β -arrestin signaling. We were the first to report on the phosphorylation of both isoforms of the receptor, and have recently revealed that FFA-4 short is phosphorylated heterologously by PKC and homologously by GRK6. We also identified three critical sites of phosphorylation and show that mutation to these sites drastically alters both G protein and β -arrestin signaling. Currently, we are finishing experiments related to mechanisms of phosphoregulation of FFA4-long. Recently, we have also shown that diets rich in omega-3 fatty acids, the endogenous agonists of FFA4, facilitate alterations in FFA4 and TNF- α expression in the rat colon. A recently funded NIH-grant has allowed us to study the role of FFA4 in the brain, including its role in neuroprotection in Parkinson's Disease. These studies entail immunofluorescence colocalization studies of FFA4 with partner proteins in the striatum, as well as pharmacological characterization of FFA4 activity in this region. Together, our work with FFA4 has contributed important knowledge in regard to the molecular pharmacology of the receptor that should be accounted for in drug development efforts which target FFA4. I serve as principal investigator and corresponding author on all of these studies.

- a. Burns RN and Moniri NH. Agonism with the omega-3 fatty acids alpha-linolenic acid and docosahexaenoic acid mediates phosphorylation of both the short and long isoforms of the human GPR120 receptor. *Biochem Biophys Res Commun*, 396: 1030-1035, 2010. PMID: 20471368
- b. Burns RN, Singh M, Senatorov IS, Moniri NH. Mechanisms of homologous and heterologous phosphorylation of FFA receptor 4 (GPR120): GRK6 and PKC mediate phosphorylation of Thr347, Ser350, and Ser357 in the C-terminal tail. *Biochem Pharmacol*, 87:650-659, 2014. PMID: 24412271
- c. Cheshmehkani A, Senatorov IS, Kandi P, Singh M, Britt A, Hayslett R, Moniri NH. Fish oil and flax seed oil supplemented diets increase FFAR4 expression in the rat colon. *Inflamm Res*, 64:809-15, 2015. PMID: 26275932
- d. Moniri NH. Free-fatty acid receptor-4 (GPR120): cellular and molecular function and its role in metabolic disorders. *Biochem Pharmacol*, 110-111:1-15, 2016. PMID: 26827942
- e. Cheshmehkani A, Senatorov IS, Dhuguru J, Ghoneim O, Moniri NH. Free-fatty acid receptor-4 (FFA4) modulates ROS generation and COX-2 expression via the C-terminal β -arrestin phosphosensor in Raw 264.7 macrophages. *Biochem Pharmacol*. 146:139-150, 2017. PMID: 28943238
- f. Senatorov IS and Moniri NH. The role of free-fatty acid receptor-4 (FFA4) in human cancers and cancer cell lines. *Biochem Pharmacol*. 150:170-180, 2018. PMID: 29452095
- g. Chitre NM, Ray A, Wood B, Moniri NH, Murnane KS. The Neuroprotective Effects of Docosahexaenoic Acid in a 6-Hydroxydopamine Rat Model of Parkinsonism is Associated with Reduced Reactive Oxygen Species Formation and Induced Kinase Activity. In preparation, 2019.

Complete List of Published Work:

<http://www.ncbi.nlm.nih.gov/myncbi/browse/collection/42130766/?sort=date&direction=descending>

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

Ongoing Competitive Research Support:

NIH/NHLBI (1R15HL138603), 07/01/2017-06/30/2020

The role of ROS on β 2-adrenergic receptor function in human airway

The major goal of this project is to fully elucidate the linkage between ROS generation and β 2AR function in normal and asthma-diseased human airway.

Role: Principal Investigator

Priority score = 20

Completed Competitive Research Support:

United Soybean Board

Soy Health Research Program

The major goal of this project is to assess the roles of a variety of dietary oils in neuroprotection from Parkinson's Disease.

Role: Principal Investigator

NIH/NINDS (1R03NS095239), 03/01/2016 – 02/28/2019

FFAR4 and nigrostriatal function: A novel target for treatment of PD?

The major goal of this project is to characterize the neuroprotective role of FFAR4 on nigrostriatal neuron function in models of Parkinson's Disease.

Role: Principal Investigator

Priority Score = 25; Percentile = 7

NIH/NIDDK (1R15DK098730), 03/01/2013-02/28/2017

The role of phosphorylation in regulating the antidiabetic effects of O3FAR1 (FFAR4).

The major goal of this project is to fully elucidate the involvement of receptor phosphorylation on regulation of the antidiabetic effects of O3FAR1 (FFAR4).

Role: Principal Investigator

Priority score = 10

Mercer University Seed Grant, 07/01/2012 – 06/30/2013

Omega-3 fatty acid receptor-1 expression and function in the lung.

The major goal of this proposal is to characterize O3FAR1 expression and function in human lung cells.

Role: Principal Investigator

Mercer University Seed Grant, 07/01/2011 – 06/30/2012

The role of ROS on β 2-adrenergic receptor mediated ERK1/2 activation.

The major goal of this proposal is to elucidate the role of ROS on β 2-adrenergic receptor-mediated ERK1/2 signaling.

Role: Principal Investigator

Diabetes Action Research and Education Foundation, 01/01/2011 – 12/31/2011

Uncovering the molecular mechanisms involved in GPR120-mediated GLP-1 secretion.

The major goal of this study is to elucidate the signal transduction cascades involved in GPR120-mediated GLP-1 secretion.

Role: Principal Investigator

American Foundation for Pharmaceutical Education, 08/01/2010 – 07/31/2011

GPR120 intracellular signaling.

The major goal of this project is to assess intracellular signaling of GPR120.

Role: Principal Investigator, (Pre-doctoral fellowship awarded to Rebecca L. Burns, PharmD/PhD student)

Mercer University Seed Grant, 07/01/2010 – 06/30/2011

β 2-Adrenergic receptor oxidation

The major goal of this proposal is to characterize agonist-induced β 2-adrenergic receptor oxidation.

Role: Principal Investigator

Diabetes Action Research and Education Foundation, 01/01/2010 – 12/31/2010

In vivo analysis of the role of omega-3 fatty acids in regulation of GPR120 expression.

The major goal of this study is to examine the role of various omega-3 fatty acids in expression of GPR120 protein in rats.

Role: Principal Investigator

American Foundation for Pharmaceutical Education, 08/01/2009 – 07/31/2010

GPR120 intracellular signaling.

The major goal of this project is to assess intracellular signaling of GPR120.

Role: Principal Investigator, (Pre-doctoral fellowship awarded to Rebecca L. Burns, PharmD/PhD student)

Mercer University Seed Grant, 07/01/2009 – 06/30/2010

GPR120-mediated ERK1/2 phosphorylation.

The major goal of this proposal is to elucidate free fatty acid efficacy and potency with respect to GPR120-mediated ERK1/2 activation.

Role: Principal Investigator

American Association of Colleges of Pharmacy, New Investigators Award, 01/01/2009 – 12/31/2009

β 2-receptor mediated ROS generation.

The major goal of this is to identify the NADPH oxidase isoforms expressed in HEK293 cells and to begin to assess their role in β 2-receptor mediated ROS generation.

Role: Principal Investigator

Diabetes Action Research and Education Foundation, 01/01/2009 – 12/31/2009

The role of omega-3 fatty acids in regulation of GPR120 expression.

The major goal of this study is to examine the role of various omega-3 fatty acids in expression of GPR120 mRNA and protein.

Role: Principal Investigator

American Foundation for Pharmaceutical Education, 08/01/2008 – 07/31/2009

GPR120 intracellular signaling.

The major goal of this project is to assess intracellular signaling of GPR120.

Role: Principal Investigator, (Pre-doctoral fellowship awarded to Rebecca L. Burns, PharmD/PhD student)

Mercer University Seed Grant, 07/01/2008 – 06/30/2009

GPR120 desensitization.

The major goal of this proposal is to characterize free fatty acid mediated desensitization of GPR120.

Role: Principal Investigator

Mercer University Biomedical Scholars Training Initiative, 05/01/2008 – 08/31/2008

β 2-receptor mediated ROS generation.

The major goal of this project is to begin to characterize molecular mechanisms of β 2 adrenergic receptor mediated ROS generation.

Role: Principal Investigator

Grant Review Service:

1. American Association of Colleges of Pharmacy, Invited Grant Reviewer (2010, 2011, 2012, 2013, 2014)
2. National Institutes of Health, Center for Scientific Review, Cell Biology Special Emphasis Panel (ZRG1 CB-T(81)) Study Section Reviewer (June 2016)
3. National Institutes of Health, Center for Scientific Review, Molecular and Integrative Signal Transduction (MIST) Study Section Reviewer, Ad hoc. (June 2012; June 2014)
4. Diabetes U.K., Invited Grant Reviewer (2014)
5. U.K. Biotechnology and Biological Sciences Research Council (BBSRC), Invited Grant Reviewer (2012, 2017)