OMB No. 0925-0001 (Rev. 08/12 Approved Through 8/31/2015)

**APPLICANT BIOGRAPHICAL SKETCH**

Use only for individual predoctoral and postdoctoral fellowships, dissertation research grants (R36),and Research Supplements to Promote Diversity in Health-Related Research (Admin Suppl). DO NOT EXCEED FIVE PAGES.

NAME OF APPLICANT: Leon Garland Coleman, Jr

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

POSITION TITLE: Research Assistant Professor

EDUCATION/TRAINING (Most applicants will begin with baccalaureate or other initial professional education, such as nursing. Include postdoctoral training and residency training if applicable. High school students should list their current institution and associated information. Add/delete rows as necessary.)

| INSTITUTION AND LOCATION | DEGREE(if applicable) | START DATEMM/YYYY | END DATE (or expected end date)MM/YYYY | FIELD OF STUDY |
| --- | --- | --- | --- | --- |
| University of Virginia, Charlottesville, VA | BS | 9/1999 | 2003 | Chemical Engineering |
| University of North Carolina, Chapel Hill, NC | M.D./PhD | 8/2003 | 5/2012 | PhD in Neurobiology 2010MD 2012 |

1. Personal Statement

My prior clinical experience and research training has led me to a focus on neuroimmune mechanisms and neuron-glial interactions involved in the development of the pathology of alcohol addiction and negative affect. Neuroimmune responses to ethanol contribute to pathology and involve Toll-like receptor (TLR) activation. Recent discoveries I have contributed to suggest that endogenous ligands for TLRs mediate neuroimmune activation in alcohol addiction. We have found that endogenous TLR7 and TLR4 agonists, miRNA let-7b and HMGB1 respectively signal in brain in response to alcohol, leading to neurodegeneration and inflammation. Further, HMGB1 acts as an immune chaperone, binding to miRNA-let-7b and the cytokine IL-1β to modulate immune responses. Neuronal-glial interactions are key in this pathology, as microglia release miRNA let-7 to cause pathology in neurons. TLR7 in neurons seems to be critical. This work has sparked the beginning of a collaboration with Merck, where we are assessing the efficacy of their proprietary TLR7 antagonist in the setting of alcohol-induced neurodegeneration. Thus, we are exploring novel immune mechanisms and potential therapeutic targets in these disease settings. This work contributed to my receiving of a K08 Mentored Clinical Scientist Award from NIAAA (AA024829). This RO1 application builds on our previous discoveries and expands to identify novel signaling interactions between neurons, microglia, and astrocytes that may lead to the progressive development of alcoholic pathology. Using cutting-edge technologies, we will investigate previously unanswerable questions at different stages of disease.

My PhD training and undergraduate research experiences have also given me a broad experience. I completed the MD/PhD program at the University of North Carolina at Chapel Hill. During that time I received and completed an F30 Ruth L. Kirschstein NRSA award for MD/PhD students investigating the effects of alcohol on brain development during the third trimester and adolescence (AA018051). The findings from that award were impactful, resulting in four peer-reviewed first author publications with over 100 citations (listed below), foundational data for the preparation and submission for an NIAAA-NADIA consortium grant, national attention (see below), local and University media coverage, and lectures to middle and high school students using our results to inform them about the risks of binge-drinking. These experiences demonstrate a history of making research discoveries that have a significant impact on health on different levels of society. My clinical training and research experience has uniquely prepared me to have given me a holistic perspective on health and disease that are invaluable for translational research. Having the often merciless effects of critical illness on patients and families I highly motivated to make impactful discoveries.

# B. Positions and Honors

| ACTIVITY/OCCUPATION | STARTDATE (mm/yy) | ENDDATE (mm/yy) | FIELD | INSTITUTION/COMPANY | SUPERVISOR/EMPLOYER |
| --- | --- | --- | --- | --- | --- |
| Quality Improvement Specialist | 2/04 | 11/05 | Data Collection and Analysis | UNC-HospitalsContinuous Quality Improvement | Larry Mandelkehr |
| General Surgery Residency PGY1 – PGY2 | 06/12 | 06/14 | General Surgery | UNC-Hospitals | Chair: Anthony Meyer, MD, PhDResidency Director: Michael Meyers, MD |
| Research Associate Fellow | 07/2014 | **Current** | Alcohol Studies/Neurobiology | UNC-CH Bowles Center for Alcohol Studies | Fulton T. Crews, PhD |

## Academic and Professional Honors

1999 – 2003 University Achievement Award, University of Virginia

1999 - 2003 Rodman Scholar, University of Virginia

2002 – 2003 Virginia Engineering Foundation Award, University of Virginia

2003 BS in Chemical Engineering with Distinction

2004-2005 University of North Carolina Chancellor’s Diversity Task Force

2004-present John B. Graham Research Society

2008-2012 **National Institute on Alcohol Abuse and Alcoholism: Ruth Kirschstein NRSA F30 award for MD/PhD students (1F30A A018051)**

2009 Research selected as one of the *“Hot Topics”* and press release for the Society for

 Neuroscience 2009 annual meeting: *Effects of Adolescent Binge-Drinking on Adult Behavior*

 *and Brain Structure in Mice: Changes in brain volume associated with increased anxiety and*

 *impaired learning*

2009 Local news coverage: <http://www.wral.com/lifestyles/healthteam/story/9385540/>

2009 University of North Carolina news coverage: <http://news.unchealthcare.org/news/2011/april>

2009-2012 Selected for the Neuroscience Scholars Program, the Society for Neuroscience

2010Best Graduate Student Presentation Award, UNC Radiology Research Day: *Models of*

*Binge Drinking During Adolescence Alter the Adult Brain: A Multidisciplinary Approach*

2013 Eskelund Award for Excellence in Pediatric Surgery, UNC-Hospitals, Department of Pediatric

Surgery

2015 Society for Neuroscience, Member

2015 Gubernatorial Appointment to the Minority Health Advisory Committee by NC Governor, Chair

2016 **ISBRA/ESBRA Junior Investigator Award**

2017 **National Institute on Alcohol Abuse and Alcoholism (NIAAA): K08 Mentored Clinical Scientist Research Career Development Award (AA024829)**

2017 **NIAAA/NIDA Early Career Investigator Showcase Travel Award**

# C. Contributions to Science

For a full list of published work visit: <http://www.ncbi.nlm.nih.gov/sites/myncbi/leon.coleman%20jr.1/bibliography/48064712/public/?sort=date&direction=ascending>

1. Toll-like Receptor 7 (TLR7) Signaling and HMGB1 heterocomplexes regulate immune responses in alcoholism and human burn injury
* Historical Background: Alcohol activates immune signaling and may underlie pathologies of alcoholism and alcohol-related diseases. However, the precise immune mediators and therapeutic targets are unknown. Alcoholics have at least 2-fold worse mortality and morbidity in the setting of critical illness, such as trauma and burn related sepsis. Immune mechanisms are involved in the pathology of sepsis, but the immune mediators are unknown.
* Central Findings: We found that binge alcohol causes release of the ‘master regulator’ of immune function, HMGB1. HMGB1 formed complexes with the endogenous agonist for TLR7, miRNA let-7b associated with its secretion in microvesicles. HMGB1 also forms synergistic complexes with IL-1, both in the alcoholic brain and in plasma after burn injuries. Thus, these two disease states (alcoholism and sepsis) share similar immune mechanisms. This could underlie the worsened outcomes of alcoholics in the setting of sepsis and critical illness.
* Relevance: These findings are novel in that they identify endogenous TLR agonists and HMGB1 immune heterocomplexes that regulate immune function in alcoholism and burn associated immune dysfunction. We identify TLR7 activation as critical in ethanol-induced neurotoxicity and are investigating the underlying mechanisms.
* Role in work: In conjunction with my mentor and collaborators, I helped to develop the hypotheses and plan the experiments. I performed the experiments, analyzed the tissues and the data.
* Peer-reviewed publications
	+ **Coleman LG Jr.**, Crews FT. Innate Immune Signaling and Alcohol Use Disorders. March 2018. Handbook of Experimental Pharmacology. Doi:10.1007/164\_2018\_92
	+ **Coleman LG Jr,** Zou, Qin and Crews. HMGB1/IL-1β Complexes Regulate Neuroimmune Responses in Alcoholism. *Brain, Behavior and Immunity* November2017, pii: S0889-1591(17)30483-X, diu 10.1016/j.bbi.2017.10.027
	+ Crews FT, Walter TJ, **Coleman LG Jr**, Vetreno RP. Toll-like receptor signaling and stages of addiction. *Psychopharmacology (Berl)* February 2017, doi: 10.1007/s00213-017-4560-6. (Review)
	+ Crews FT, Lawrimore CJ, Walter TJ, **Coleman LG Jr.** The role of neuroimmune signaling in alcoholism. *Neuropharmacology* February 2017; S0028-3908(17)30037-0. (Review)
	+ **Coleman LG Jr,** Zou J, and Crews FT. Microglial-derived miRNA let-7 and HMGB1 contribute to ethanol-induced neurotoxicity via TLR7. *Journal of Neuroinflammation*  January *2017*; 14(1):22.
	+ **Coleman LG Jr,** Maile, Cairns, and Crews: HMGB1/IL-1β Complexes in Plasma Microvesicles Modulate Immune Responses to Burn Injury. *Under Review* 2017
	+ Qin**, Coleman,** Vetreno, and Crews. Ethanol Neurodegeneration *in vivo* involves Toll-like Receptor 7 Signaling. *In Preparation*
	+ **Coleman,** Zou, and Crews. TLR7-mediated Neurotoxicity to Ethanol Involves Induction of TNF-related apoptosis-inducing ligand (TRAIL) Signaling. *In Preparation*
1. *Effect of Alcohol on Brain Development During Adolescence*
* Historical Background: In humans, alcohol abuse during the adolescent period in particular is associated with and increased risk of developing alcoholism in adulthood. In particular, damage to the prefrontal cortex (PFC) is thought to be involved in the later stages of the pathology of alcoholism, resulting in disinhibition of the limbic system, increased impulsivity, and impaired cognition and decision making.
* Central Findings: Adolescent binge ethanol treatment reduces adult neurotransmitter gene expression, particularly cholinergic genes, reduces basal forebrain and olfactory bulb volumes, and causes a reduction in the density of basal forebrain acetylcholine neurons. Adolescent binge ethanol also caused persistent anxiety like behavior in reversal learning deficits into adulthood. Both of these behaviors are thought to be involved in perseveration and the maintenance of addiction. Loss of cholinergic neurons and forebrain structure could underlie adult reversal learning deficits following adolescent binge drinking. Adolescent binge ethanol also resulted in permanent changes in the brain extracellular matrix, which might contribute cognitive inflexibility. In summary, adolescent binge drinking causes permanent alterations in brain structure and behavior.
* Relevance: These findings have informed the public regarding the dangers of underage drinking. Both local and national media covered the findings. Presentations to middle and high school students were given to inform them regarding the risks of binge drinking. The manuscripts prepared from this work have been cited over 70 times to date. In addition, these studies were the basis of a subsequently funded NIAAA-NADIA consortium.
* Role in work: In conjunction with my PhD advisor, I developed the hypotheses and planned the experiments. I performed the experiments, analyzed the tissues and the data. I prepared first author manuscripts and presentations under the supervision of my mentor.
* Peer-reviewed publications
	+ **Coleman LG, Jr,** Liu W, Oguz I, Styner M, Crews FT. Adolescent binge ethanol treatment alters adult brain regional volumes, cortical extracellular matrix protein and behavioral flexibility. *Pharmacology, Biochemistry and Behavior 2013*.
	+ **Coleman LG Jr,** He J, Lee J, Styner M, Crews FT. Adolescent binge drinking alters adult brain neurotransmitter gene expression, behavior, brain regional volumes and neurochemistry in mice. Alcoholism: Clinical and Experimental Research April 2011; 35(4):671-88
1. *Effect of Alcohol on Brain Development During the Third Trimester of Pregnancy*
* Historical Background: The early postnatal period is associated with heightened vulnerability to ethanol toxicity. Little is known, however, on the effects of ethanol exposure during the third trimester.
* Central Findings: We found that ethanol treatment during the analog of the human third trimester causes persistent reductions in adult brain volume, frontal cortical neuron number and adult neurogenesis. This may proceed through the NMDA antagonism effect of ethanol.
* Relevance: These findings show that the third trimester of pregnancy is also a ‘danger period’ for alcohol use. This informs debate regarding alcohol consumption during pregnancy. The manuscripts prepared from this work have been cited 29 times to date.
* Role in work: In conjunction with my PhD advisor, I developed the hypotheses and planned the experiments. I performed the experiments, analyzed the tissues and the data. I prepared first author manuscripts and presentations under the supervision of my mentor.
* Peer-reviewed publications
	+ **Coleman LG Jr,** Oguz I, Styner M, and Fulton T. Crews. Persistent effects of P7 ethanol treatment on adult mouse brain: reduced brain volume, frontal cortical neuron reductions and altered adult hippocampal neurogenesis. *Alcohol* September 2012; 46(6):603-12
	+ **Coleman LG Jr**, Jarskog LF, Moy SS, Crews FT. Deficits in adult prefrontal cortex neurons and behavior following early post-natal NMDA antagonist treatment. *Pharmacology, Biochemistry and Behavior* 2009; 93(3):322-30.
1. Oxidized low density lipoprotein activates blood platelets:
* Historical Background: Elevated plasma levels of low-density lipoprotein are a well-recognized risk factor for stroke, heart attack, and atherosclerosis. This relationship has been linked to increased amounts of oxidized low-density lipoprotein (ox-LDL) present in atherosclerotic plaques.
* Central Findings: Oxidized-LDL is highly effective at inducing platelet function, causing stable aggregation and alpha-granule secretion dependent on p38 MAPK activation.
* Role in work: In conjunction with my mentor and collaborators, I developed the hypotheses and planned the experiments. I performed the experiments and analyzed the data. I prepared a first author manuscript under the supervision of my mentor.
* Relevance: This data supported the hypothesis that ox-LDL stimulates platelets and is involved in the pathogenesis of stroke and heart attack. Further, it identified the p38 MAPK pathway as critical for this activation, identifying a potential drug target for platelet protection.
* Peer reviewed Publications:
	+ **Coleman LG Jr**, Polanowska-Grabowska RK, Marcinkiewicz M, and Gear AR: LDL oxidized by hypochlorous acid causes irreversible platelet aggregation when combined with low levels of ADP, thrombin, epinephrine, or macrophage-derived chemokine (CCL22). *Blood*. 2004; 104(2):380-9.

# D. RESEARCH SUPPORT

Independent Investigator Award R01 AA026659 -**–** Under Review, NIH-NIAAA

CREWS, FULTON T (PI) Mechanisms of Ethanol Induction of Neuroimmune Signaling

COLEMAN, LEON (INVESTIGATOR)

Clinician Scientist Research Career Development AwardK08 AA024829, 9/8/2017-9/8/2022 NIH-NIAAA

COLEMAN, LEON (PI) Ethanol modulates central and peripheral immune responses via HMGB1, IL-1β and other Immune Signaling Molecules

Ruth L. Kirschstein National Research Service Award for MD/PhD F30 AA018051, 2008-2012, NIH-NIAAA

COLEMAN, LEON (PI) Alcohol and Development of the Prefrontal Cortex