BIOGRAPHICAL SKETCH

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NAME: Leon Garland Coleman, Jr

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

POSITION TITLE: 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)*	Completion Date MM/YYYY	FIELD OF STUDY
General Surgery Residency UNC-Hospital PGY1 – PGY2	N/A	06/2014	General Surgery
University of North Carolina, Chapel Hill, NC	M.D./PhD	5/2012	PhD in Neurobiology 2010, MD in 2012
University of Virginia, Charlottesville, VA	BS	05/2003	Chemical Engineering

A. Personal Statement

My prior clinical experience and research training has led me to a focus on how alcohol (i.e. ethanol) causes both central and peripheral immune dysfunction. We have found that alcohol contributes to immune dysregulation both in brain and the periphery that involves the release of immune-modulating extracellular microvesicles and immune complexes. Our findings in brain reveal ethanol causes secretion of microvesicles from glia that contain the miRNA let-7b and activate endosomal TLR7 in neurons that can cause neuronal cell death. This suggests this neuroimmune signaling system contributes to alcohol-induced neurodegeneration. This mechanism could also contribute to neurodegeneration in other contexts. Thus, we are also exploring a role for glial, TLR-mediated neurodegeneration and a contribution of ethanol to neurodegeneration associated with Alzheimer's disease. Our lab is also interested in the role chronic alcohol abuse has in worsening outcomes in other diseases. Persons with alcohol use disorder (AUD) have significantly worse outcomes across many chronic diseases and acute critical illnesses. Further, alcohol use is common in the general population, and its ability to alter peripheral immune function is well known. As such we are exploring the role of alcohol-induced immune dysfunction to worse outcomes in diseases such as severe burn injury and responses to cancer immunotherapy. We find potent immune hetercomplexes induced by ethanol are increased in peripheral blood after severe burn injury. We also find extracellular plasma microvesicles are a key reservoir of immune signaling molecules after burn injury. These novel signaling mechanisms may have significant roles in peripheral immune pathology, and may serve as novel biomarkers to predict response to therapy.

My clinical, PhD training, and undergraduate research experiences have also given me a broad experience. I am a current K08 awardee investigating the roles of central and peripheral immune induction by ethanol. This proposal was birthed from my prior interests in my K08 award and is complementary to those studies. I am also a new recipient of the UNC Simmons Scholar Award, which provides the remainder of my salary support for the next 5 years. Thus, I am able to devote a majority of my funds toward experimentation. 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	START DATE (mm/yy)	END DATE (mm/yy)	FIELD	INSTITUTION/ COMPANY	SUPERVISOR/ EMPLOYER
Quality Improvement Specialist	2/04	11/05	Data Collection and Analysis	UNC-Hospitals Continuous Quality Improvement	Larry Mandelkehr
General Surgery Residency PGY1 – PGY2	06/12	06/14	General Surgery	UNC-Hospitals	Chair: Anthony Meyer, MD, PhD Residency Director: Michael Meyers, MD
Research Associate	07/2014	12/2017	Alcohol Studies/ Neurobiology	UNC-CH Bowles Center for Alcohol Studies	Fulton T. Crews, PhD
Assistant Professor	01/2017	Current	Alcohol Studies/ Neurobiology/ Immunology	UNC-CH School of Medicine, Bowles Center for Alcohol Studies, Department of Pharmacology	Director: Fulton T. Crews, PhD Chair: Henrik Dohlman, 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
2010 Best 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 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**
2018 International Society of Biomedical Research on Alcoholism Travel Award
2018 Research Society on Alcoholism Annual Meeting Program Committee Member
2019 **UNC Simmons Scholar Awardee,** a 5-year salary support institutional award

C. Contributions to Science

For a full list of published work visit: https://www.ncbi.nlm.nih.gov/myncbi/leon.coleman.1/bibliography/public/

(1) *Microvesicle-mediated Neuroimmune Activation via Toll-like Receptor 7 (TLR7) and TRAIL regulate neurodegeneration and immune responses in alcohol use disorders.*

- 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.
- Central Findings: We found that binge alcohol causes activation of TLR7 signaling via secretion of its endogenous agonist miRNA let-7b. This involves a novel microvesicle signaling mechanism, whereby let-7b is secreted in microvesicles to activate endosomal TLR7 receptors. We find TLR7 activation causes TRAIL signaling with resultant induction of interferon signaling and neuronal cell death.
- Relevance: These findings are novel in that they identify endogenous TLR and microvesicle signaling systems interact to contribute to alcohol-induced neuropathology. They also identify novel therapeutic targets for neurodegeneration, neuroimmune activation, and alcohol-induced neuropathology.
- Role in work: In conjunction with my collaborators, I helped to develop the hypotheses, plan, and perform the experiments. I analyzed and interpreted data and authored manuscripts.
- Peer-reviewed publications
    - **Coleman,** Zou and Crews. Microglial Repopulation Blunts Toll-like Receptor Signaling and Normalizes Chronic Immune Activation ex-vivo. *Reviews Submitted* 2019
    - Qin**,** Zou, Vetreno, Crews, and **Coleman**. Toll-like Receptor 7 Induces Neurodegeneration via TNFSF10/TRAIL Signaling: A Novel Role in Alcohol Use Disorder. *Under Review 2019*
    - Lawrimore CJ, **Coleman LG**, and Crews FT. Ethanol induces interferon expression in neurons via TRAIL: role of astrocyte-to-neuron signaling. Psychopharmacology (Berl). 2019 Oct;236(10):2881-2897. doi: 10.1007/s00213-018-5153-8. Epub 2019 Jan 4.
    - 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.

(2) *Peripheral Immune Dysregulation via Immune Heterocomplexes in Alcohol Use Disorders and other Immune-Related Pathologies*

- Historical Background: Alcoholics have at least 2-fold worse mortality and morbidity in the setting of critical illness, such as trauma and burn related sepsis. Alcohol causes dysregulation of innate and adaptive immune signaling and may underlie pathologies of alcoholism and alcohol-related diseases. However, the precise immune mediators and therapeutic targets are unknown.
- Central Findings: We found that binge alcohol causes release of the 'master regulator' of immune function, HMGB1. HMGB1 formed synergistic complexes with IL-1β, both in the alcoholic brain and in plasma after burn injuries. Thus, these two disease states (alcoholism and sepsis) share similar immune mechanisms.
- Relevance: These findings are novel in that they identify potent immune heterocomplexes that regulate immune function in alcoholism and burn associated immune dysfunction. Enhanced potency of these heterocomplexes could contribute to the worsened outcomes of alcoholics in the setting of sepsis and critical illness.
- 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 and authored the manuscripts.
- Peer-reviewed publications
    - Garness JA, Khan A, Bixby L, Vincent BG, and **Coleman LG Jr.** Effect of chronic alcohol on responses to immunotherapy: A role for plasma microvesicles. *In Preparation* 2019
    - **Coleman LG Jr**., Crews FT. Innate Immune Signaling and Alcohol Use Disorders. Handb Exp Pharmacol. 2018 Mar 3. doi: 10.1007/164_2018_92. PubMed PMID: 29500721
    - **Coleman LG Jr**, Zou J, Qin L, Crews FT. HMGB1/IL-1β complexes regulate neuroimmune responses in alcoholism. Brain Behav Immun. 2017 Nov 2. pii: S0889-1591(17)30483-X. doi: PubMed PMID: 29102800; PubMed Central PMCID: PMC5932292

- **Coleman LG Jr**, Maile R, Jones SW, Cairns BA, Crews FT. HMGB1/IL-1β complexes in plasma microvesicles modulate immune responses to burn injury. PLoS One. 2018 Mar 30;13(3):e0195335. doi: 10.1371/journal.pone.0195335. eCollection 2018.

(3) *Effect of Alcohol on Brain Development: During Embryonic and Adolescent Development*

- Historical Background: The early embryonic period is associated with heightened vulnerability to ethanol toxicity. Comparably little is known, however, on the effects of ethanol exposure during the third trimester. 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: 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.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 also 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 39 times to date. Adolescent study 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 the adolescent findings have been cited over 119 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
  - **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.

(4) 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.