BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Fulton Crews

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

POSITION TITLE: John Andrews Distinguished Professor of Pharmacology and Psychiatry

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
Syracuse University, Syracuse, NY	BS	06/1971	Physiology
University of Michigan, Ann Arbor, MI	PhD	06/1978	Pharmacology
National Institutes of Health, Bethesda, MD Pharmacology-Toxicology Research Fellowship with Nobel Laureate Julius Axelrod, Ph.D	OTH	07/1980	Pharmacology

A. Personal Statement

I have always been excited by science. Throughout my career I have tried to create an environment of discovery for students, fellows, and junior faculty that includes the excitement and fun in science. In 1994, UNC formed the Bowles Center for Alcohol Studies (BCAS) and asked me to become director. There was only one faculty member, but others were recruited and in a few years the BCAS was awarded a P60 Alcohol Research Center Grant and T32 training grant. I led the Center for 28 years, until 2022, when I decided to focus on adolescent alcohol research and transitioned the current P60 Center Grant to Dr. Tom Kash and the T32 to Dr. Donita Robinson. I am proud to have grown the BCAS to a leading alcohol research center with about 100 successful faculty, students, and staff, most of whom I hired. Also I proud of my successful fellows, who include Rueben Gonzales, Judson Chandler, Kim Nixon, Ryan Vetreno, and Leon Coleman in the alcohol field. Also, I have worked for many years with NCCU, a NC historically Black university, to promote diversity in alcohol research. I have received several awards including the Research Society on Alcohol Distinguished Investigator Award, an NIH Merit Award, the RSA Marlatt Mentorship Award, and the John R. Andrews Distinguished Professorship in the UNC School of Medicine. As a Distinguished Professor I plan to continue to focus on models of adolescent alcohol binge drinking-induced changes in adult brains.

I lead the NIAAA-funded Neurobiology of Adolescent Drinking in Adulthood (NADIA) 9-component consortium. The overarching hypothesis is that models of human underage drinking will impact brain maturation, resulting in persistent changes in adult brain function and structure that relate to lasting adult psychopathology. This proposal is an extension of NADIA discoveries that models of adolescent binge drinking (specifically, adolescent intermittent ethanol or AIE) cause lasting changes in brain neuroimmune gene expression, epigenetics, synapses, and brain regional responses to ethanol, as well as increasing risky decisions, impulsivity and anxiety, and alcohol preference and drinking, contributing to risk for adult alcohol use disorder. I plan to continue to determine the impact of AIE on neurodegeneration and neuroimmune activation in brain, particularly the role of toll-like receptors (TLR) and their endogenous agonist, HMGB1, including how this shifts brain glial and neuronal phenotypes and disrupts brain physiology, particularly fMRI networks and behavior. Our recent characterization of rat fMRI large neuronal networks distinguishing salience networks from default networks created the opportunity for the proposed studies on regulation of networks by cholinergic and neuroimmune signaling following AIE. I am excited to test the proposed hypotheses.

Research support that I would like to highlight is listed below.

Neurobiology of Adolescent Drinking in Adulthood (NADIA) NADIA Administrative Core. U24 AA020024-14, NIH-NIAAA, 01/09/2010-08/31/2025; CREWS, FULTON T (PI)

Adolescent Alcohol and Adult Brain Dysfunction (NADIA) NADIA Research. U01 AA020023-14, NIH-NIAAA, 01/09/2010-08/31/2025; CREWS, FULTON T (PI)

Partnerships to Enhance Alcohol Research Across NCCU and UNC (PEAR-NC). U54 AA030463-02. NIH-NIAAA, 09/20/2022 – 08/31//2027; CREWS, FULTON T (Co-PI)

B. Positions, Scientific Appointments, and Honors

Positions

2023 -	Distinguished Professor of Pharmacology and Psychiatry, University of North Carolina School of Medicine, Chapel Hill, NC
1995 - 2022	Director, Bowles Center for Alcohol Studies, Distinguished Professor of Pharmacology and Psychiatry, University of North Carolina School of Medicine, Chapel Hill, NC
1980 - 1994	Professor of Pharmacology, College of Medicine, University of Florida (Asst, 1980-1985, Assoc 1985- 1990), Gainesville, FL
1978 - 1980	Pharmacology Research Associate Program Awardee, Staff Fellow, NIMH, Axelrod Lab Section on Pharmacology Lab of Clinical Science, Bethesda, MD
1973 - 1978	NIH Training Award, Pharm, University of Michigan Rackham Grad School, Ann Arbor, MI

Scientific Appointments and Professional Memberships

2014 -	Member, N.C. Governor's Substance Abuse and Underage Drinking Prevention and Treatment Task Force
2011 - 2015	Member, NIAAA Advisory Council
2001 - 2011	Chair, NIAAA Council Subcommittee on Strategic Planning (for T.K. Li and Ken Warren)
1998 - 2000	President, Alcohol and Drug Council of North Carolina
1995 - 1999	Board of Directors, Research Society on Alcoholism
1993 -	Member, International Society for Biomedical Research on Alcoholism
1991 - 1995	Member, NIH Study Section: Alcohol Biomedical Research Review Committee (ALCB-2)
1989 - 1991	Member, NIMH Study Section, Psychopathology and Clinical Biology (PCB-2)
1989 -	Member, Research Society on Alcoholism
1986 -	Member, Society for Neuroscience
1980 -	Member, American Society for Pharmacology and Experimental Therapeutics

Honors

2022	Visiting Scholar, University of Louisville
2021	CADRE Distinguished Visiting Scholar, Brown University
2021	Invited Speaker, Scripps Research Institute
2018	Research Society on Alcoholism 2018 Marlatt Mentorship Award
2015	NADIA Progress Report, NIAAA Council
2015	Invited Speaker, Behavioral Sciences Research Institute, University of Puerto Rico
2014	Plenary Speaker, European Pharmacology Society, Sussex England
2014	NIAAA Plenary Speaker, NIH Neuroimmune Workshop
2012	Thomas O'Donohue Memorial Lectureship, Harvard University
2011	ACNP Fellow, American College of Neuropsychopharmacology
2009	Plenary Lecture, Austrian Neuroscience Association, Salzburg, Austria
2009	Okey Memorial Lecture, Psychiatry Research Trust, London, England
2008	John R. Andrews Distinguished Professorship Award, School of Medicine, UNC-Chapel Hill
2007	Guze Lectureship Award, Washington University, St. Louis
2007	Distinguished Investigator Award for Scientific Excellence, Research Society on Alcoholism
2006	Bowles Lectureship Award, School of Medicine, UNC-Chapel Hill
2006	NIAAA Mark Keller Honorary Lecturer, National Institutes of Health Clinical Center
2003	Forbes Lectureship, Grass Foundation Award, Chicago Chapter of Neuroscience

2003 Norbert Kelly Distinguished Award for Contribution to Understanding Addiction as a Mental Disease, Addiction Professionals of NC, NCADC
2002 NIH Grand Rounds Speaker, National Institutes of Health
2001 University of Michigan Outstanding Pharmacology Alumnus Award, University of Michigan

C. Contributions to Science

PERSISTENT ACTIVATION OF NEUROIMMUNE SIGNALING IN BRAIN. How **neuroimmune signaling** alters brain structure and function is among my key contributions to science. In 1999 we discovered ethanol treatment induced cyclo-oxygenase, a proinflammatory gene, across multiple brain regions that persisted long after the ethanol exposure. This led to further studies on ethanol activation of NFkB, a proinflammatory transcription factor, in brain slice cultures and increases in post-mortem human AUD brain microglial markers and CCL2, a proinflammatory chemokine. My most cited paper, and the most cited paper in the journal Glia, was the discovery that a single dose of LPS to adult mice results in long-lasting increases in microglial activation, proinflammatory genes and a slowly developing degeneration of dopamine neurons over 7-10 months (Qin et al. 2007). These studies were extended to show effects in both sexes, and Parkinsonian-like balance loss that was transiently restored by L-DOPA. Other studies found that ethanol pretreatment potentiated LPS-TLR4 (Qin et al. 2008) and PolyIC-TLR3 (Qin et al. 2012) responses that led to the neuroimmune hypothesis of addiction. We also studied proinflammatory signals to HMGB1-TLR signaling, which we discovered is increased by ethanol exposure and is increased in post-mortem human AUD brain. The mechanisms and consequences of brain neuroimmune gene expression are poorly understood, although many human brain diseases show increased levels of expression of innate immune genes. Our studies investigating the mechanism of ethanol induction of brain cytokines led to the discovery that ethanol released HMGB1, a cytokine-like molecule highly expressed in neurons. HMGB1 stimulation increases expression of its receptors including TLR4, RAGE, and others. Chronic ethanol treatment of adult mice was found to induce long-lasting increases in brain HMGB1, TLR receptors and microglial activation markers. Ethanol treatment of mice or rat brain slice cultures increases expression of HMGB1 and release into the media, as well as inducing multiple TLR receptors.

More recently, we discovered ethanol upregulated signaling of TLR7 and an endogenous miRNA agonist, i.e., Let7. In human post-mortem AUD brain, HMGB1, TLR2, TLR3, TLR4, and TLR7 are increased, as well as multiple cytokines, CCL2, TNFα, IL6, IL1B, and the oxidase NOX. Studies in mice and rats discovered that increases in brain innate immune gene expression and microglial responses persist for long periods once increased and are associated with progressive neurodegeneration and cognitive deficits. HMGB1-TLR induction in AIE remains elevated during months of abstinent maturation to adulthood, as do associated cognitive deficits and loss of cholinergic neurons (ChAT). Examples of recent papers are:

1. QIN L, WU X, BLOCK M, LIU YX, BREESE G, HONG JS, KNAPP D, **CREWS FT.** Systemic LPS causes chronic neuroinflammation and progressive neurodegeneration. *Glia*. 2007;55:453-462. **PMID: 17203472; PMCID: PMC2871685.**
2. **CREWS FT,** ZOU J, QIN L. Induction of innate immune genes in brain create the neurobiology of addiction. *Brain Behav Immun.* 2011 Jun;25(Suppl 1:S4-S12). **PMID: 21402143; PMCID: PMC3552373**
3. COLEMAN LG JR, **CREWS FT**, VETRENO RP. The persistent impact of adolescent binge alcohol on adult brain structural, cellular, and behavioral pathology: A role for the neuroimmune system and epigenetics. *Int Rev Neurobiol.* 2021;160:1-44. doi: 10.1016/bs.irn.2021.08.001. Epub 2021 Oct 4. **PMID: 34696871.** Review.
4. **CREWS FT**, VETRENO RP. Cholinergic REST-G9a gene repression through HMGB1-TLR4 neuroimmune signaling regulates basal forebrain cholinergic neuron phenotype. *Front Mol Neurosci*. 2022; 15: 992627. Published online 2022 Aug 22. doi:10.3389/fnmol.2022.992627. **PMID: 36072299; PMCID: PMC944180**

ADOLESCENT ALCOHOL EXPOSURE. I lead the NIAAA consortium Neurobiology of Adolescent Drinking in Adulthood (NADIA). Adolescence, the development of addiction, and neuroplasticity are generally thought to be primarily regulated by synaptic changes. Studies support the overarching hypothesis that models of human underage drinking impact brain maturation, resulting in persistent changes in adult brain function and structure that relate to lasting adult psychopathology risks for addiction. I have contributed to discoveries linking adolescent binge drinking to lasting changes in brain neuroimmune gene expression, epigenetics, synapses,

and brain regional responses to ethanol; increases in risky decisions; impulsivity; anxiety; and alcohol preference and drinking, contributing to risk for adult alcohol use disorder. Adolescent intermittent ethanol (AIE) exposure causes long-lasting changes in adult cognition, anxiety-like behavior, sleep, and rsfMRI connectivity and brain structure. One area of our focus has been AIE-induced loss of adult cholinergic neurons marked by ChAT, VChAT, and TrkA genes. The persistent long-lasting loss of ChAT neurons by AIE likely contributes to neuroimmune gene induction, since acetylcholine is anti-inflammatory, inhibiting microglia. Our current studies suggest adolescent binge drinking models (AIE) lead to epigenetic changes in glia, increasing proinflammatory gene expression in brain that persists following cycles of adolescent alcohol exposure, triggered in part by autocrine-paracrine spread of proinflammatory signals by HMGB1. These signals also alter neuronal gene expression; specifically, we find reduced cholinergic neurons due to silencing mechanisms involving G9a and REST that are reversible.

1. CREWS FT, COLEMAN LG JR, MACHT VA, VETRENO RP. Targeting Persistent Changes in Neuroimmune and Epigenetic Signaling in Adolescent Drinking to Treat Alcohol Use Disorder in Adulthood. *Pharmacol Rev.* 2023 Mar;75(2):380-396. **PMID: 36781218; PMCID: PMC9969522.**
2. **Crews FT**, Robinson DL, Chandler LJ, Ehlers CL, Mulholland PJ, Pandey SC, Rodd ZA, Spear LP, Swartzwelder HS, Vetreno RP. Mechanisms of persistent neurobiological changes following adolescent alcohol exposure: NADIA consortium findings. *Alcohol Clin Exp Res.* 2019 Sep;43(9):1806-1822. doi: 10.1111/acer.14154. Epub 2019 Aug 14. **PMID: 31335972; PMCID: PMC6758927**.
3. LEE SH, SHNITKO TA, HSU LM, BROADWATER MA, SARDINAS M, WANG TW, ROBINSON DL, VETRENO RP, **CREWS FT**, SHIH YI. Acute alcohol induces greater dose-dependent increase in the lateral cortical network functional connectivity in adult than adolescent rats. *Addiction Neuroscience*. 2023 Sep 7:100105. doi: 10.1016/j.addicn.2023.100105. Epub 2023 Jun 2. **PMID: 37576436; PMCID: PMC 10421607**
4. ROBINSON DL, AMODEO LR, CHANDLER LJ, **CREWS FT**, EHLERS CL, GÓMEZ-A A, HEALEY KL, KUHN CM, MACHT VA, MARSHALL SA, SWARTZWELDER HS, VARLINSKAYA EI, WERNER DF. The role of sex in the persistent effects of adolescent alcohol exposure on behavior and neurobiology in rodents. *Int Rev Neurobiol* 2021; 160: 305–340. Published online 2021 Aug 11. doi: 10.1016/bs.irn.2021.07.007. **PMID: 34696877; PMCID: PMC8672816**

POST-MORTEM HUMAN ALCOHOL USE DISORDER (AUD) BRAIN STUDIES. I have always tried to understand the neurobiology of AUD. In general we include a post-mortem brain figure within a preclinical study on alcohol exposure-induced changes. This approach helps assure preclinical findings are more relavant to AUD pathology. Initial studies on proinflammatory genes were met with skepticism about "inflammation" in brain, prompting more extensive human post-mortem studies. We initially focused on frontal cortex, but later studes on hippocampus (see Coleman et al.) and forebrain ChAT neurons led to studies in those areas. Now it is generally agreed that neuroimmune signaling is involved in regulating alcohol drinking and contributing to AUD. We are currently working on a manuscript about human microglial priming in AUD.

1. HE J, **CREWS FT.** Increased MCP-1 and microglia in various regions of the human alcoholic brain. *Exp Neurol.* 2008;210(2):349-58. **PMID: 18190912; PMCID: PMC2346541**
2. COLEMAN LG Jr, ZOU J, QIN L, **CREWS FT**. HMGB1/IL-1β complexes regulate neuroimmune responses in alcoholism. *Brain Behav Immun*. 2018 Aug;72:61-77. doi:10.1016/j.bbi.2017.10.027. Epub 2017 Nov 2. **PMID: 29102800; PMCID: PMC5932292**.
3. **CREWS FT**, QIN L, SHEEDY D, VETRENO RP, ZOU J. High mobility group box 1/Toll-like receptor danger signaling increases brain neuroimmune activation in alcohol dependence. *Biol Psychiatry.* 2013 Apr 1;73(7):602-12. PMID: 23206318; PMCID: PMC3602398.
4. **CREWS FT**, VETRENO RP. Stress and alcohol priming of brain Toll-like receptor signaling in alcohol use disorder. *Alcohol Alcohol.* 2018 Nov 1;53(6):639-641. doi:10.1093/alcalc/agy061. Epub 19 October 2018. **PMID: 30346466; PMCID: PMC6676785.**

Complete List of Published Work in My Bibliography:
http://www.ncbi.nlm.nih.gov/myncbi/1ZCZoZqJ65o/bibliography/40424694/public/?sort=date&direction=ascending