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: Director, Bowles Center for Alcohol Studies, Distinguished Professor of Pharmacology and Psychiatry

EDUCATION/TRAINING

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 am enthusiastic about continuing to develop and train alcohol research fellows. I feel student, fellow and young faculty development and research training is one of my most important and rewarding activities. I became director of the UNC Bowles Center for Alcohol Studies in 1994 and developed the NIAAA UNC Alcohol Research Center grant and UNC Alcohol Training grant; both are currently funded in their 4th renewal (i.e., 20+ years of funding). There was 1 faculty member when I joined UNC; that has grown to about 100 alcohol research faculty, staff and trainees at UNC. The BCAS has faculty who lead diverse research areas including pharmacotherapy for alcohol use disorder (AUD), alcohol-induced brain damage, neuroimmune activation, fetal alcohol syndrome, neurobiology of additive behavior, and other areas the cross clinical and preclinical research. The BCAS faculty have trained many successful scientists who continue to make discoveries, and we are proud of their success.

I have mentored students throughout my career – more than 30 postdoctoral fellows and graduate students, in fact. Examples of my students who have become successful independent alcohol researchers include Rueben Gonzales, Judson Chandler, Kim Nixon, Ryan Vetreno and Leon Coleman. I value diversity and have also mentored faculty at North Carolina Central University, an HBCU. Victoria Macht is my current fellow who has a K99 submitted and will emerge as an independent scientist soon. My lab. is active and I plan to continue to train fellows.

My research has focused on alcohol-induced neurodegeneration that more recently includes ethanol activation of innate immune signaling as components of alcohol pathology in multiple tissues, as well as investigating the adolescent brain as a unique neurodevelopmental period of sensitivity to alcohol pathology. Persistent changes appear to be due to cytokines and transcription factors that induce oxidative enzymes and proinflammatory proteins associated with alcohol-induced brain damage and loss of neurogenesis.

I lead the NIAAA-funded, 9-component consortium Neurobiology of Adolescent Drinking in Adulthood (NADIA). 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. Funded for 15 years (2010-2025), NADIA has discovered that adolescent binge drinking causes lasting changes in brain neuroimmune gene expression, epigenetics, synapses, and brain regional responses to ethanol; and increases risky decisions, impulsivity and anxiety, and alcohol preference and drinking, contributing to risk for adult alcohol use disorder. Related to this, I co-wrote a white paper for the State of North Carolina on the impact of underage drinking as part of the state's successful "Talk It Out" campaign to reduce drinking among youth.

I have received numerous lectureship awards, the Research Society on Alcoholism 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.

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

Post-Doctoral Training Grant - Molecular and Cellular Alcohol Research Training Role (This proposal). T32 AA007573-20, NIH-NIAAA, 01/04/1997-03/31/2023; CREWS, FULTON T (Co-PI)

Neurobiology of Adolescent Drinking in Adulthood (NADIA) NADIA Administrative Core. U24 AA020024-11, NIH-NIAAA, 01/09/2010-08/31/2025; CREWS, FULTON T (PI)

Adolescent Alcohol and Adult Brain Dysfunction (NADIA) NADIA Research. U01 AA020023-11, NIH-NIAAA, 01/09/2010-08/31/2025; CREWS, FULTON T (PI)

Alcohol Research Center Grant - Molecular and Cellular Pathogenesis in Alcoholism. P60 AA011605-20, NIH-NIAAA, 01/12/1997-11/30/2022; Kash, T. (new PI)

B. Positions, Scientific Appointments, and Honors

Positions

1995 - Present	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
1997 -	Board of Directors, Pavilion Treatment Center
1996 -	Board of Directors, Alcohol and Drug Council of North Carolina
1995 - 1999	Board of Directors, Research Society on Alcoholism
1995 -	Board of Directors, Freedom House Treatment and Recovery Center
1994 -	Board of Directors, NC Governor's Institute on Substance Abuse
1993 - 1994	Chairman, National V.A. Merit-Grant Review Board: Alcoholism and Drug Dependence
1993 -	Awardee, NIH Merit Grant
1993 -	Member, International Society for Biomedical Research on Alcoholism
1991 - 1995	Member, NIH Study Section: Alcohol Biomedical Research Review Committee (ALCB-2)
1991 - 1994	Member, National V.A. Merit-Grant Review Board: Alcoholism and Drug Dependence
1991 - 1994	Board of Directors, Division of Sponsored Research; University of Florida
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
2017	Invited Speaker, Indiana University School of Medicine, 1/5-6
2015	Invited Speaker, International Conference on FASD, the University of British Columbia
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 Alumnus Award, University of Michigan
1999	Editorial Advisory Board, Betty Ford Center quarterly newsletter, Betty Ford Center
1992	NIH Javitts Grant Awardee, National Institutes of Health
1990, 1992	Research Scholar Award, University of Florida
1978	NIH PRAT Fellow, National Institutes of Health
1973	NIH Pre-doctoral Fellow, National Institutes of Health
1968	NY State Regents Scholar, New York State

C. Contributions to Science

1. **NEUROIMMUNE SIGNALING INDUCED BY ETHANOL.** How **neuroimmune signaling** alters brain structure and function is among my key contributions to science. We discovered neuroimmune signaling, particularly HMGB1-TLR signaling, in brain is increased by ethanol 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 induced and released HMGB1, a cytokine- like molecule highly expressed in neurons that is an agonist at TLR4, RAGE and other receptors. Chronic ethanol treatment of adult mice was found to induce long-lasting increases in brain HMGB1, TLR receptors and cytokines and to sensitize to brain cytokine induction by systemic treatment with the TLR4 agonists-lipopolysaccharide (LPS) (Qin et al. 2008) and the TLR3 agonist-PolyIC (Qin et al. 2012). Subsequent studies led to the discovery of ethanol induction of brain TLR and RAGE as well as HMGB1. Ethanol treatment of mice or rat brain slice cultures increases expression of HMGB1 and release, as well as increasing multiple TLR receptors and cytokines. Most recently, we discovered ethanol upregulated signaling of TLR7 and an endogenous miRNA agonist, e.g., 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 a rat model of adolescent binge drinking (NADIA-AIE) was found to be increased by adolescent intermittent ethanol (AIE) treatment and remained elevated during months of abstinent maturation to adulthood. In other studies, we have found adolescent rats are far more sensitive to ethanol-induced neurotoxicity than adults. In mice, we discovered that a single high dose of LPS sensitizes microglial and increase brain neuroimmune gene expression for many months, contributing to delayed neurodegeneration (Qin et al. 2007). Most recently our studies have focused on HMGB1, TLR and RAGE signaling in neurons following ethanol exposure. Examples of recent papers are:

a. Coleman LG, Zou J, **Crews FT**. Microglial depletion and repopulation in brain slice culture normalizes sensitized proinflammatory signaling. *J Neuroinflammation.* 2020 Jan 18;17:27. doi:10.1186/s12974-019-1678-y.
b. Liu W, Vetreno RP, **Crews FT**. Hippocampal TNF-death receptors, caspase cell death cascades and IL-8 in alcohol use disorder. *Molecular Psychiatry,* 26:2254-2262. 2021 June. Preprint 2020 Mar 5.
c. Müller CP…**Crews F**, Schumann G. The cortical neuroimmune regulator TANK affects emotional processing and enhances alcohol drinking: A translational study. *Cereb Cortex.* 2019 Feb 4. doi: 10.1093/cercor/bhy341. PMID: 30721969; PMCID: PMC6430980
d. Randall PA, Vetreno RP, Makhijani VH, **Crews FT**, Besheer J. The Toll-like receptor 3 agonist poly(I:C) induces rapid and lasting changes in gene expression related to glutamatergic function and increases ethanol self-administration in rats. *Alcohol Clin Exp Res*. 2019 Jan;43(1):48-60. doi: 10.1111/acer.13919. Epub 2018 Dec 16. PMID: 30403408; PMCID: PMC6541929

2. 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 risky decisions, impulsivity and anxiety, and alcohol preference and drinking, contributing to risk for adult alcohol use disorder. Adolescent intermittent alcohol (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.

a. **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
b. Vetreno RP, Bohnsack JP, Kusumo H, Liu W, Pandey SC, **Crews FT.** Neuroimmune and epigenetic involvement in adolescent binge ethanol-induced loss of basal forebrain cholinergic neurons: restoration with voluntary exercise. *Addict Biol.* 2019 Feb 18;1(14). doi: 10.1111/adb.12731. PMID: 30779268; PMCID: PMC6698434
c. Swartzwelder HS, Healey K, Liu W, Dubester K, Miller KM, **Crews FT**. Changes in neuroimmune and neuronal death markers after adolescent alcohol exposure in rats are reversed by donepezil. *Sci Rep (Berlin).* 2019 Aug 20;9(1):12110. doi: 10.1038/s41598-019-47039-1. PMID: 31431637; PMCID: PMC6702347.
d. **Crews FT**, Vetreno RP. Stress and alcohol priming of brain toll-like receptor signaling in alcohol use disorder. *Alcohol Alcohol*. 2018 Nov; 53(6): 639–641. Published online 2018 Oct 19. doi: 10.1093/alcalc/agy061 PMID: 30346466; PMCID: PMC6676785.

3. ETHANOL INHIBITION OF NEUROGENESIS. The adult brain has two neurogenic regions, the hippocampal dentate gyrus and the subventricular zone, which form new neurons that contribute to new neurocircuits. My first study found that acute and chronic binge ethanol exposure of rats inhibited adult neurogenesis in the hippocampus (Nixon, Crews 2002). Exercise was found to create resilience, blocking ethanol inhibition of neurogenesis (Crews et al. 2004). Abstinence-withdrawal from ethanol after a 4-day binge was discovered to lead to bursts of proliferation on new cells: After 2 days, new microglia were formed; 7 days after ethanol, new neuroprogenitors were formed that restore adult neurogenesis to control levels. The subventricular zone was found to be less sensitive to ethanol inhibition of neurogenesis than the hippocampus. Adolescents were found to be more sensitive to ethanol-stress reductions and to have persistent loss of neurogenesis, i.e., they do not recover in abstinence-adulthood. Neuroimmune signaling and epigenetic mechanisms of gene silencing-expression mediate the persistent changes in adulthood following adolescent priming.

a. Macht V, **Crews FT**, & Vetreno RP. Neuroimmune and epigenetic mechanisms underlying persistent loss of hippocampal neurogenesis following adolescent intermittent ethanol exposure. *Curr Opin Pharmacol,* 2019 Nov 25;50:9-16. PMID: 31778865; PMCID: PMC7246179
b. Khatri D, Laroche G, Grant ML, Jones VM, Vetreno RP, **Crews FT**, Mukhopadhyay S. Acute ethanol inhibition of adult hippocampal neurogenesis involves CB1 cannabinoid receptor signaling. *Alcohol Clin Exp Res.* 2018 Apr;42(4):718-726. doi: 10.1111/acer.13608. PMID: 29417597; PMCID: PMC6042509
c. Liu W, **Crews FT**. Persistent decreases in adult subventricular and hippocampal neurogenesis following adolescent intermittent ethanol exposure. *Front Behav Neurosci.* 2017 Aug 14;11:151. doi: 10.3389/fnbeh.2017.00151. PMID: 28855864; PMCID: PMC5557743
d. Sakharkar AJ, Vetreno RP, Zhang H, Kokare DM, **Crews FT**, Pandey SC. A role for histone acetylation mechanisms in adolescent alcohol exposure-induced deficits in hippocampal brain-derived neurotrophic factor expression and neurogenesis markers in adulthood. *Brain Struct Funct.* 2016 Dec;221(9):4691-4703. doi: 10.1007/s00429-016-1196-y. PMID: 26941165; PMCID: PMC5010799

4. ALCOHOL-INDUCED NEURODEGENERATION INVOLVES ACTIVATION OF BRAIN NFKB TRANSCRIPTION OF NEUROIMMUNE GENES AND EXCITOTOXICITY. Alcohol-induced neurodegeneration is linked to the development of alcohol use disorder. Following the discovery of the glutamate-NMDA receptor, we discovered ethanol treatment of primary neuronal cultures sensitized neurons to NMDA excitotoxicity when alcohol cleared, i.e., during withdrawal, leading to the generally accepted hypothesis that alcohol-induced brain damage occurred during withdrawal (Chandler et al. 2006). We moved to *in vivo* binge drinking models of alcohol-induced brain damage that found damage during intoxication and to brain slice cultures that found glutamate with ethanol and/or TNFalpha potentiated excitotoxicity. In parallel, we discovered binge-like ethanol treatment

of rats increased proinflammatory COX2 in brain (Knapp and Crews, 1999) in association with brain regions showing neurodegeneration (to glutamate excitotoxicity (Zou, Crews 2006)). *In vivo* studies indicated that systemic cytokines enter brain, increasing NFkB transcription that persists for long periods. However, brain slice culture studies indicated ethanol can directly increase brain NFkB transcription, which we later discovered is due to ethanol release of HMGB1 activating NFkB transcription through TLR and other receptors (see above).

a. Walter TJ, **Crews FT**. Microglial depletion alters the brain neuroimmune response to acute binge ethanol withdrawal. *J Neuroinflammation.* 2017 Apr 20;14(1):86. doi: 10.1186/s12974-017-0856-z. PMID: 28427424; PMCID: PMC5439231
b. Lawrimore CJ, Coleman LG, **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. PMID: 30610351; PMCID: PMC6646093
c. 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.b. PMID: 29102800; PMCID: PMC5932292
d. Walter TJ, Vetreno RP, **Crews FT**. Alcohol and stress activation of microglia and neurons: Brain regional effects. *Alcohol Clin Exp Res.* 2017 Dec;41(12):2066-2081. doi: 10.1111/acer.13511. Epub 2017 Nov 8. PMID: 28941277; PMCID: PMC5725687

5. RECEPTOR COUPLING TO PHOSPHOINOSITIDE HYDROLYSIS AND ARACHIDONIC ACID RELEASE.

My first paper was published in Science for the discovery of a delayed increase in norepinephrine release with chronic antidepressant treatment that corresponded with desensitization of presynaptic auto-receptors that inhibit release. The delayed increase in NE release was hypothesized to relate to the delay in antidepressant reversal of depression. At that time, presynaptic autoreceptors had just been discovered and beta-adrenergic receptors were being reported to form multiprotein complexes (G proteins) linked to cyclic AMP. Other receptors acted by stimulating calcium influx. Calcium flux was thought to activate phospholipases, explaining the parallels between lipid metabolism and calcium flux. At NIH with Nobel Laureate Julius Axelrod, I started a decade of studies I continued in my lab on receptor stimulation of phospholipases. Initial studies discovered that phospholipase A activation of arachidonic acid release from phosphatidylcholine formed by phospholipid methyltransferase methylation of phosphatidylethanolamine regulated prostaglandin synthesis. In addition, we characterized multiple receptors activating phospholipase C formation of diacyglycerol, which activates PKC, and inositol triphosphate, which releases intracellular calcium. We were the first to report activation of phospholipase C by guanine nucleotides in isolated brain membranes, a key discovery in establishing the current dogma that receptor-stimulated phosphoinositide hydrolysis stimulates calcium release.

a. **Crews FT**, Smith CB. Presynaptic alpha-receptor subsensitivity after long-term antidepressant treatment. *Science*. 1978 Oct 20;202(4365):322-4. PMID: 211589
b. **Crews FT**, Morita Y, McGivney A, Hirata F, Siraganian RP, Axelrod J. IgE-mediated histamine release in rat basophilic leukemia cells: receptor activation, phospholipid methylation, Ca2+ flux, and release of arachidonic acid. *Arch Biochem Biophys.* 1981 Dec;212(2):561-71. PMID: 6173018
c. Gonzales RA, **Crews FT**. Characterization of the cholinergic stimulation of phosphoinositide hydrolysis in rat brain slices. *J Neurosci.* 1984 Dec;4(12):3120-7. PMID: 6094748; PMCID: PMC6564854
d. Gonzales RA, **Crews FT**. Guanine nucleotides stimulate production of inositol trisphosphate in rat cortical membranes. *Biochem J.* 1985 Dec 15;232(3):799-804. PMID: 3004420; PMCID: PMC1152953

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