BIOGRAPHICAL SKETCH

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NAME: Fulton Crews

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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.

The NADIA Consortium has become my primary focus. Our findings that adolescent ethanol exposure causes persistent increases in adult risky decisions, disinhibition, behavioral inflexibility, and reduces sensitivity to adult ethanol challenge as well as increasing alcohol drinking have convinced me that this is an unexpected discovery that is critically important. As NADIA discoveries were emerging I became increasingly aware of human evidence that adolescent binge drinking and age of drinking onset are associated with a number of lifelong risks, particularly alcohol abuse and alcohol use disorder. Adolescents who start drinking before 15 years of age are four times more likely to develop alcohol dependence in their lifetime than those who start drinking after age 20. Both genetic and environmental factors likely contribute to early drinking and substance use, but the NADIA has found adolescent exposure can cause lasting changes not previously appreciated. Although our NADIA rat AIE model is not a model of alcohol dependence, it causes long-lasting changes in adult brain on molecular, physiological, morphological and histological levels that we have found mimic changes found in post-mortem human AUD brain. These findings increase the importance of NADIA findings, perhaps identifying key factors in AUD. The joint meetings with NCANDA and multiple symposia at research conferences from NADIA faculty have stimulated increasing interest in the impact of alcohol on adolescence. We discovered AIE increases adult brain HMGB1 and its receptors (i.e., Toll-like receptor 4 [TLR4] and receptor for advanced glycation end products [RAGE]). These neuroimmune signals likely contribute to neurodegeneration; however, we discovered they are linked to epigenetic silencing by histone and DNA methylation of cholinergic phenotype genes (i.e., ChAT, VAChT, TrkA). Our findings led to the hypothesis that loss of acetylcholine, which is critical for cortical arousal and integration as well as maturation of neurocircuits, is related to AIE reduced adult ethanol sensitivity. Low response to ethanol is associated with AUD. Thus, I am excited that these studies may find molecular mechanisms contributing to low ethanol responses. It is hypothesized that the adolescent alcohol exposure-induced changes occur through epigenetic mechanisms and are reversible. Identifying reversible molecular mechanisms causing low alcohol response will provide new targets for AUD treatment.

B. POSITIONS AND HONORS

Positions and Employment

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

Other Experience and Professional Memberships

1980 - Member, American Society for Pharmacology and Experimental Therapeutics

1986 -	Member, Society for Neuroscience
1989 -	Member, Research Society on Alcoholism
1989 - 1991	Member, NIMH Study Section, Psychopathology and Clinical Biology (PCB-2)
1991 - 1994	Member, National V.A. Merit-Grant Review Board: Alcoholism and Drug Dependence
1991 - 1995	Member, NIH Study Section: Alcohol Biomedical Research Review Committee (ALCB-2)
1993 -	Awardee, NIH Merit Grant
1993 -	Member, International Society for Biomedical Research on Alcoholism
1993 - 1994	Chairman, National V.A. Merit-Grant Review Board: Alcoholism and Drug Dependence
1994 -	Board of Directors, NC Governor's Institute on Substance Abuse
1995 -	Board of Directors, Freedom House Treatment and Recovery Center
1995 - 1999	Board of Directors, Research Society on Alcoholism
1996 -	Board of Directors, Alcohol and Drug Council of North Carolina
1998 - 2000	President, Alcohol and Drug Council of North Carolina
2001- 2011	Chair, NIAAA Council Subcommittee on Strategic Planning (for T.K. Li and Ken Warren)
2011 - 2015	Member, NIAAA Advisory Council
2014 -	Member, N.C. Governor's Substance Abuse and Underage Drinking Prevention and Treatment Task Force

Honors

1968	NY State Regents Scholar, New York State
1973	NIH Pre-doctoral Fellow, National Institutes of Health
1978	NIH PRAT Fellow, National Institutes of Health
1990	Research Scholar Award, University of Florida
1992	Research Scholar Award, University of Florida
1992	NIH Javitts Grant Awardee, National Institutes of Health
1999	Editorial Advisory Board, Betty Ford Center quarterly newsletter, Betty Ford Center
2001	University of Michigan Outstanding Alumnus Award, University of Michigan
2002	NIH Grand Rounds Speaker, National Institutes of Health
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
2006	Bowles Lectureship Award, School of Medicine, UNC-Chapel Hill
2006	NIAAA Mark Keller Honorary Lecturer, National Institutes of Health Clinical Center
2006	Grass Lectureship Award, U.S. Society for Neuroscience Grant, University of Alaska
2007	Guze Lectureship Award, Washington University, St. Louis
2007	Distinguished Investigator Award for Scientific Excellence, Research Society on Alcoholism
2008	John R. Andrews Distinguished Professorship Award, School of Medicine, UNC-Chapel Hill
2009	Plenary Lecture, Austrian Neuroscience Association, Salzburg, Austria
2009	Okey Memorial Lecture, Psychiatry Research Trust, London, England
2009	Wendy and Stanley Marsh III Endowed Lectureship, University of Texas
2011	ACNP Fellow, American College of Neuropsychopharmacology
2012	Thomas O'Donohue Memorial Lectureship, Harvard University
2014	Plenary Speaker, European Pharmacology Society, Sussex England
2014	NIAAA Plenary Speaker, NIH Neuroimmune Workshop
2015	NADIA Progress Report, NIAAA Council
2015	Invited Speaker, Behavioral Sciences Research Institute, University of Puerto Rico
2015	Invited Speaker, International Conference on FASD, the University of British Columbia
2016	Invited Speaker, University of South Carolina School of Medicine, 10/24-25
2017	Invited Speaker, Indiana University School of Medicine, 1/5-6
2018	Research Society on Alcoholism 2018 Marlatt Mentorship Award

C. CONTRIBUTION TO SCIENCE

Alcohol and Adolescent Brain Development: I have led the NADIA Consortium for 9 years. Our studies and collaborations established that AIE affects a variety of behaviors in adulthood, including sensitivity of alcohol responses and drinking, anxiety, and cognitive inflexibility, i.e. reversal learning deficits. Adolescent alcohol exposure also increases expression of neuroimmune genes such as in HMGB1, Toll-like receptors, RAGE, proinflammatory chemokines and cytokines. Expression of trophic factors and synaptic genes are decreased by adolescent ethanol exposure, contributing to altered neurocircuitry. HMGB1-TLR signaling in brain is increased

in post-mortem human alcoholic brain and the levels correlate with age of drinking onset. The mechanisms of brain neuroimmune gene expression are poorly understood. 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. This increase in proinflammatory gene expression coupled with reduced BDNF and NGF expression represented a global brain shift in proinflammatory/trophic gene expression which is maintained long after alcohol exposure, along with loss of hippocampal neurogenesis and ChAT+ cholinergic neurons. The shift in proinflammatory/trophic gene expression led to a focus on epigenetic regulation of brain gene expression. We have found adolescent alcohol exposure reduces cholinergic, dopaminergic, and serotonergic neurons as well as hippocampal neurogenesis. We focused on forebrain cholinergic neurons and hippocampal neurogenesis, finding both reduced in adulthood following adolescent ethanol exposure. Further, AIE-induced loss of ChAT and neurogenesis was found to be prevented by anti-inflammatory and epigenetic modifying drugs, supporting neuroimmune-epigenetic mechanisms. Later studies determined that the persistent loss of ChAT and neurogenesis following adolescent ethanol exposure was reversible, with reversal of epigenetic silencing markers. I am excited to continue the proposed studies to further explore these newfound reversible mechanisms.

I have previously included rat brain MRI studies due to the direct translation to human MRI imaging studies. Unlike humans, we found large developmental increases in adolescent rat brain volume that parallel rat increases in body weight. However, in adulthood following adolescent exposure we found a significant, but modest, decrease in volume of adult hippocampus, consistent with our reduced rat hippocampal neurogenesis and findings in adult AUD. In another MRI study, we found AIE caused modest whole brain volume loss with basal forebrain (BF) changes, as well as reductions of BF cholinergic neurons[15]. These findings are consistent with AIE inducing diffuse degeneration associated with AUD. We are currently using functional connectivity MRI to explore neurocircuitry. Our preliminary fcMRI study found that AIE blunts acute ethanol challenge-induced increases in fcMRI connectivity across cortex, striatum, and hippocampus[16]. These findings indicate AIE has unique effects on cortical and subcortical neurocircuits consistent with loss of cholinergic arousal circuitry. This proposal will explore molecular, cellular and fcMRI connectivity mechanisms resulting in low responsivity to ethanol challenge in adulthood.

1. 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: 6758927.
2. 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: Pending.
3. 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.
4. 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. doi: 10.1111/adb.12731. [Epub ahead of print] PMID: 30779268; PMCID: PMC6698434.
5. 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.
6. 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.
7. 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.
8. Vetreno RP, Crews FT. Adolescent binge ethanol-induced loss of basal forebrain cholinergic neurons and neuroimmune activation are prevented by exercise and indomethacin. *PLoS One.* 2018 Oct 8;13(10):e0204500. doi: 10.1371/journal.pone.0204500. eCollection 2018. PMID: 30296276; PMCID: PMC6175501.

9. Vetreno RP, Lawrimore CJ, Rowsey PJ, Crews FT. Persistent adult neuroimmune activation and loss of hippocampal neurogenesis following adolescent ethanol exposure: blockade by exercise and the anti-inflammatory drug indomethacin. *Front Neurosci.* 2018 Mar 28;12:200. doi: 10.3389/fnins.2018.00200. eCollection 2018. PMID: 29643762; PMCID: PMC5882830.
10. Broadwater MA, Lee SH, Yu Y, Zhu H, Crews FT, Robinson DL, Shih YI. Adolescent alcohol exposure decreases frontostriatal resting-state functional connectivity in adulthood. *Addict Biol*. 2018 Mar;23(2):810-823. doi: 10.1111/adb.12530. Epub 2017 Jul 9. PMID: 28691248; PMCID: PMC5760482.
11. Crews FT, Walter TJ, Coleman LG Jr, Vetreno RP. Toll-like receptor signaling and stages of addiction. *Psychopharmacology (Berl)*. 2017 May;234(9-10):1483-1498. doi: 10.1007/s00213-017-4560-6. Epub 2017 Feb 17. PMID: 28210782; PMCID: PMC5420377.
12. Vetreno RP, Patel Y, Patel U, Walter TJ, Crews FT. Adolescent intermittent ethanol reduces serotonin expression in the adult raphe nucleus and upregulates innate immune expression that is prevented by exercise. *Brain Behav Immun.* 2017 Feb;60:333-345. doi: 10.1016/j.bbi.2016.09.018. Epub 2016 Sep 16. PMID: 27647531; PMCID: PMC5215774.
13. Vetreno RP, Yaxley R, Paniagua B, Johnson GA, Crews FT. Adult rat cortical thickness changes across age and following adolescent intermittent ethanol treatment. *Addict Biol.* 2017 May;22(3):712-723. doi: 10.1111/adb.12364. Epub 2016 Feb 1. PMID: 26833865; PMCID: PMC4969224..
14. 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.
15. Vetreno RP, Yaxley R, Paniagua B, Crews FT. Diffusion tensor imaging reveals adolescent binge ethanol-induced brain structural integrity alterations in adult rats that correlate with behavioral dysfunction. *Addict Biol.* 2016 Jul;21(4):939-53. doi: 10.1111/adb.12232. PMID: 25678360; PMCID: PMC4532660
16. Crews FT, Vetreno RP, Broadwater MA, Robinson DL. Adolescent alcohol exposure persistently impacts adult neurobiology and behavior. *Pharmacol Rev*. 2016 Oct;68(4):1074-1109. doi: 10.1124/pr.115.012138. PMID: 27677720; PMCID: PMC5050442.
17. 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. Epub 2016 Mar 3. PMID: 26941165; PMCID: PMC5010799.

Innate Immune Signaling, Ethanol and TLR. In addition to studies on adolescence, we have investigated adult ethanol brain TLR and neuroimmune responses. 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 agonist-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 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. 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 mice, a single high dose of LPS was discovered to sensitize microglial and increase brain neuroimmune gene expression for many months, contributing to delayed neurodegeneration (Qin et al. 2007). This supports the discovery that persistent increases in brain neuroimmune gene expression lead to changes in neurocircuitry and neurodegeneration.

1. Coleman LG Jr., Crews FT. Innate immune signaling and alcohol use disorders. *Handb Exp Pharmacol.* 2018 Mar 3. doi: 10.1007/164_2018_92. PMID: 29500721; PMCID: PMC61200815.
2. Coleman LG Jr, Zou J, Crews FT. Microglial-derived miRNA let-7 and HMGB1 contribute to ethanol-induced neurotoxicity via TLR7. *J Neuroinflamm.* 2017. 14: 22. Published online 2017 Jan 25. doi: 10.1186/s12974-017-0799-4. PMID: 28118842; PMCID: PMC5264311.
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 F, Nixon K, Kim D, Joseph J, Shukitt-Hale B, Qin L, Zou J. BHT blocks NF-kappaB activation and ethanol-induced brain damage. *Alcohol Clin Exp Res.* 2006 Nov;30(11):1938-49. PMID: 17067360.
5. Zou J, Crews FT. Release of neuronal HMGB1 by ethanol through decreased HDAC activity activates brain neuroimmune signaling. *PLoS One.* 2014 Feb 14;9(2):e87915. PMID: 24551070; PMCID: PMC3925099.

Ethanol Inhibition of Adult 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; however, a chronic relapsing model of alcoholism established by the Heilig lab was found to lead to a persistent loss of forebrain subventricular neuroprogenitors whereas the hippocampal loss was restored as noted above.

1. 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. Epub 2018 Mar 7. PMID: 9417597; PMCID: PMC6042509.
2. Vetreno RP, Crews FT. Binge ethanol exposure during adolescence leads to a persistent loss of neurogenesis in the dorsal and ventral hippocampus that is associated with impaired adult cognitive functioning. *Front Neurosci.* 2015 Feb 12;9:35. doi: 10.3389/fnins.2015.00035. eCollection 2015. PMID: 25729346; PMCID: PMC4325907.
3. Hansson A, Nixon K, Rimondini R, Damadzic R, Sommer W, Eskay R, Crews FT, Heilig M. Long-term suppression of forebrain neurogenesis and loss of neuronal progenitor cells following prolonged alcohol dependence in rats. *Int J Neuropsychopharmacol.* 2010 Jun;13(5):583-93. PMID: 20334723; PMCID: PMC4821191.
4. Crews FT, Nixon K. Mechanisms of neurodegeneration and regeneration in alcoholism. *Alcohol Alcohol.* 2009 Mar-Apr; 44(2):115-27. PMID: 18940959; PMCID: PMC2948812.
5. Stevenson JR, Schroeder JP, Nixon K, Besheer J, Crews FT, Hodge CW. Abstinence following alcohol drinking produces depression-like behavior and reduced hippocampal neurogenesis in mice. *Neuropsychopharmacology.* 2009 Apr; 34(5):1209-22. Epub 2008 Jun 18. PMID: 18563059; PMCID: PMC2844649.

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