BIOGRAPHICAL SKETCH

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NAME: Crews, Fulton T.

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

POSITION TITLE: John R. Andrews Distinguished Professor of Pharmacology and Psychiatry; Director, Center for Alcohol Studies UNC School of Medicine

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Syracuse Univ., Syracuse, NY	B.S.	1971	Physiology
Univ. of Michigan, Ann Arbor, MI	Ph.D.	1978	Pharmacology
National Institutes of Health, Bethesda, MD	Post Doc	1980	Pharmacology

NOTE: The Biographical Sketch may not exceed five pages. Follow the formats and instructions below.

A. Personal Statement

Increasing knowledge on the impact of underage drinking and adolescent drug abuse on adult brain is critical to prevention efforts, providing the knowledge for parents and legislators to make better decisions on the long lasting impacts of adolescent alcohol and drug abuse on individuals. I have experience with leading research groups and mentoring. I have worked with Jordan Walter to prepare this application which will provide him with the support needed to develop into a physician-scientist. I became director of the UNC Bowles Center for Alcohol Studies and developed the NIAAA UNC Alcohol Research Center grant and UNC Alcohol Training grant; both are currently funded in their 3rd renewal (e.g. 20 years of funding) that grew from 1 faculty member when I joined UNC to about 100 alcohol research faculty and students at UNC. As PI of the training grant I have been involved in mentoring many students and currently have several student who are leaders in alcohol research. For example, Rueben Gonzales, President of RSA, was my student in the 1980's, Judson Chandler, a current leader at MUSC was my student in the 90's and Kim Nixon, was my student in the 2000's. All are tenured faculty at their current institutions and are successful scientists. I am impressed with Jordan Walter's ability and encourage the review committee to score this proposal within the fundable range.

B. Positions and Honors

Positions and Employment

1973-1978	NIH Training Award, Pharm, U. of Michigan Rackham Grad School. (Advisor: Dr. C.B. Smith)
1978-1980	Pharmacology Research Associate Program Awardee, (Preceptor: Julius Axelrod). Staff Fellow, National Institute of Mental Health, Section on Pharmacology, Lab of Clinical Science.
1980-1994	Prof of Pharm, College of Medicine, U. of Florida. (Assist, 1980-1985, Assoc, 1985-1990).
1995-Present	Director, Bowles Center for Alcohol Studies, Prof. of Pharm and Psychiatry, SOM, UNC-CH.
2008-Present	John Andrews Distinguished Professor of Pharm and Psychiatry, SOM, UNC-CH
2012-Present	Member, National Advisory Council on Alcohol Abuse and Alcoholism

Honors

1968	NY State Regents Scholar
1973	NIH Predoctoral Fellowship
1978	NIH PRAT Fellow

1987	Grass Scientist Award
1989-1991	NIMH Study Section, Psychopathology and Clinical Biology (PCB-2)
1990,1992	Research Scholar Award University of Florida
1991-1994	Member, National V.A. Merit-Grant Review Board: Alcoholism and Drug Dependence
1991-1994	Board of Directors, Division of Sponsored Research, Univ. of Florida
1991-1995	NIH Study Section: Alcohol Biomedical Research Review Committee (ALCB-2)
1992	NIH Javitts Grant Awardee
1993-Present	NIH Merit Grant Awardee
1993-1994	Chairman, National V.A. Merit-Grant Review Board: Alcoholism and Drug Dependence
1994-Present	Board of Directors, N.C. Governor's Institute on Substance Abuse
1995-1999	Research Society on Alcoholism Board of Directors
1995-Present	Board of Directors, Freedom House Treatment and Recovery Center
1996-Present	Board of Directors, Alcohol and Drug Council of North Carolina
1997-Present	Board of Directors, Pavillon Treatment Center
1998-2000	President, Alcohol and Drug Council of North Carolina
1999	Editorial Advisory Board, Betty Ford Center quarterly newsletter *Findings*
2001	Received the University of Michigan Outstanding Alumnus Award
2002	National Institute of Health Grand Rounds Speaker, Bldg. 10
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 North Carolina, NCADC, Pinehurst N.C.
2004-2013	Chair, External Advisory Board for Research Portfolio Review, NIAAA
2006	Grass Lectureship Award, US Society for Neuroscience grant to University of Alaska Fairbanks
2006	Bowles Lectureship Award, CAS, University of North Carolina at Chapel Hill
2006	NIAAA Mark Keller Honorary Lecturer, National Institutes of Health Clinical Center
2007	Guze Lectureship Award – Washington University, St. Louis
2007	Distinguished Investigator Award for Scientific Excellence, Research Society on Alcoholism, Chicago, IL
2008	John R. Andrews Distinguished Professorship Award
2009	Wendy and Stanley Marsh III Endowed Lectureship Univ of Texas 6/16-17/09
2009	Plenary Lecture Austrian Neuroscience Association, Salzburg, Austria, 9/18/09
2009	Okey Memorial Lecture: Psychiatry Research Trust, London England 11/17/09
2011-present	Member NIAAA Advisory Council
2011	ACNP Fellow, American College of Neuropsychopharmacology
2012	Thomas O'Donohue Memorial Lectureship, Harvard University
2014	European Pharmacology Society, Plenary Speaker; Sussex England June 2014
2014	NIH Neuroimmune Workshop, NIAAA Plenary Speaker, Sept. 2014
2015	NIAAA Council NADIA Progress report, February 2015
2015	International Conference on FASD, Vancouver, Canada March 2015

C. Contribution to Science (Selected references from over 200 publications).

1. HMGB1-TLR signaling in brain is increased by ethanol and is increased in post-mortem human alcoholic brain. The mechanisms of brain neuroimmune gene expression are poorly understood, although all 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 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) and the TLR3 agonist-PolyIC. 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. In human post-mortem brain HMGB1, TLR2, TLR3 and TLR4 are increased as well as multiple cytokines, CCL2, TNFa, 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, first for 10 months and more recently 20 months that contribute to delayed neurodegeneration supporting the discovery that persistent increases in brain neuroimmune gene expression lead to neurodegeneration and perhaps long lasting alterations in brain circuitry. This led to the discovery that HMGB1 and TLR receptors in post-mortem brain correlate with lifetime alcohol consumption across controls and alcoholics.

a) **CREWS, F.T.**, ZOU, J., QIN L., *Induction of Innate Immune Genes in Brain Create the Neurobiology of Addiction*, Brain, Behavior and Immunity, 2011 Jun; 25 Suppl 1:S4-S12, **PMID: 21402143**

b) **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*, Biological Psychiatry 2013 Apr 1;73(7):602-12. **PMID: 23206318**

c) QIN, L., LIU, Y., HONG, J., **CREWS, FT**. *NADPH oxidase and aging drive microglial activation, oxidative stress and dopaminergic neurodegeneration following systemic LPS administration*, Glia 2013, Jun;61(6):855-68. **PMID: 23536230** ***** listed as "Top 10 Original Articles Published in 2013" in GLIA.

d) 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**

e) VETRENO, RP, QIN, L, **CREWS, FT**. *Increased Receptor for Advanced Glycation End Product Expression in the Human Alcoholic Prefrontal Cortex is Linked to Adolescent Drinking*. Neurobiology of Disease, 2013 Nov; 59:52-62. **PMID: 23867237**

f) WHITMAN BA, KNAPP DJ,WERNER DF, **CREWS FT**, BREESE GR. *The Cytokine mRNA Increase Induced by Withdrawal from Chronic Ethanol in the Sterile Environment of Brian is Mediated by CRF and HMGB1 Release*. Alcohol Clin Exp Res. 2013 37:2086-97. **PMID: 23895427**

g) **CREWS, FT**., VETRENO, RP. *Mechanisms of Neuroimmune Gene Induction in Alcoholism.* Psychopharmacology, 2015 **PMID: 25787746**

h) ZOU, J., **CREWS, F.T.** *Induction of Innate Immune Gene Expression Cascades in Brain Slice Cultures by Ethanol: Key Role of NF-kappaB and Proinflammatory Cytokines.* Alcohol Clin Exp Res. 2010, 34(5):777-89, Epub 2010 Mar. 3 **PMID: 20201932**

2. Ethanol inhibition of adult neurogenesis. The adult brain has two neurogenic regions, the hippocampal dentate gyrus and the subventricular zone, that 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. Exercise was found to create resilience, blocking ethanol inhibition of neurogenesis. Abstinence-withdrawal from ethanol after a 4 day binge was discovered to lead to bursts of proliferation on new cells, with the burst after 2 days forming new microglia and the burst 7 days after ethanol forming new neuroprogenitors 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. As noted below, adolescent brain was found to be more sensitive to ethanol inhibition of neurogenesis than adult brain and ethanol treatment was found to cause a persistent loss of adult neurogenesis, different from the adult findings of return to control levels after a prolonged period of abstinence-withdrawal.

a) NIXON, K. AND **CREWS, F.T.:** *Binge ethanol exposure decreases neurogenesis in adult rat hippocampus*. Journal of Neurochem 83: 1087-1093, 2002. **PMID: 12437579**

b) NIXON, K. and **CREWS, F.T.** *Temporally Specific Burst in Cell Proliferation Increases Hippocampal Neurogenesis in Protracted Abstinence from Alcohol*. The Journal of Neuroscience, 24(43): 9714-9722, 2004. **PMID: 15509760**

c) **CREWS, F.T.**, NIXON, K. and WILKIE, MB. *Exercise Reverses Ethanol Inhibition of Adult Neurogenesis*. Alcohol, 33(1): 63-71, 2004. **PMID: 15353174**

d) HE, J, NIXON, K., SHETTY, A., and **CREWS, F.T.** *Chronic alcohol exposure reduces hippocampal neurogenesis and dendritic growth of newborn neurons*. European Journal of Neuroscience, 21(10): 2711-2720, 2005. **PMID: 15926919**

e) NIXON K, KIM D.H., POTTS E.N., HE J., **CREWS, F.T**. *Distinct cell proliferation events during abstinence after alcohol dependence: Microglia proliferation precedes neurogenesis,* Neurobiology of Disease, 2008 Aug; 31(2):218-29. 2008. **PMID: 18585922.**

f) HANSSON, A., NIXON, K., RIMONDINI, R., DAMADZIC, R., SOMMER, W., ESKAY, R, **CREWS, F.T**., 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**

g) ZOU, J., **CREWS, FT**., *Inflammasome IL-1β signaling mediates ethanol inhibition of hippocampal neurogenesis*, Frontiers in Neuroscience, 2012; May 30;6:77 **PMID: 22661925**

h) VETRENO, RP., **CREWS, FT**. *Binge ethanol exposure during adolescence leads to persistent loss of neurogenesis in the dorsal and ventral hippocampus that is associated with impaired adult cognitive functioning.* Frontiers Neurosci. 2015, 12:9:35 **PMID: 25729346**

3. Alcohol induced neurodegeneration involves activation of brain NFkB transcription of neuroimmune genes and excitotoxicity. Alcoholic neurodegeneration is linked to the development of alcoholism. Following the discovery of the glutamate-NMDA receptor we discovered ethanol treatment of primary neuronal cultures sensitized neurons to NMDA excitotoxicity when alcohol cleared, e.g. during withdrawal, leading to the the generally accepted hypotheses that alcoholic brain damage occurred during withdrawal. 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 (necrotic neuronal loss) as well as loss of neurogenesis, loss of new neurons. The ethanol induced neurodegeneration was blocked by an NFkB inhibitor, the proinflammatory transcription factor in vivo, and in vitro in rat brain slice cultures. Further, ethanol treatment of rat brain slice cultures increased NFkB transcription of proinlfammatory cytokines that sensitized to glutamate excitotoxicity. 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). Binge alcohol induced neurodegeneration and increased brain neuroimmune gene expression in frontal cortex was discovered to contribute to long lasting reversal learning deficits, supporting a role for neuroimmune genes and frontal cortical degeneration in the development of alcoholic risk factors. We have currently identified over 14 innate immune and microglial genes increased in post-mortem human alcoholic brain.

a) CHANDLER, L.J., NEWSOME, H., SUMNERS, C. and **CREWS, F.T.**: Chronic Ethanol Exposure Potentiates NMDA Excitotoxicity in Cerebral Cortical Neurons. *J. Neurochem.* 60:1578-1581, 1993**. PMID: 8455043**

b) OBERNIER, J.A., WHITE, A.M., SWARTZWELDER H.S., and **CREWS, F.T**.: *Cognitive deficits and CNS damage after a 4-day binge ethanol exposure in rats.* Pharmacol Biochem Behav 72:521-532, 2002. **PMID: 12175448**

c) **CREWS, F.T**., NIXON, KIM, KIM, DANIEL, JOSEPH, JAMES, SHUKITT-HALE, BARBARA, QIN, LIYA, ZOU, JIAN. *BHT blocks NF-κB activation and Ethanol-Induced Brain Damage.* Alcohol Clin Exp Res, 30(11): 1938-1949, 2006. **PMID: 17067360**

d) ZOU, J. and **CREWS, F.T.** *CREB and NFκB transcription factors regulate sensitivity to excitotoxic and oxidative stress induced neuronal cell death*. Cellular and Molecular Neurobiology, 2006 26(4-6):385-405. **PMID: 16633891**

e) QIN, L., WU, X., BLOCK, M., LIU, Y. X., BREESE, G., HONG, J.S., KNAPP, D., **CREWS, F.T.** *Systemic LPS Causes Chronic Neuroinflammation and Progressive Neurodegeneration*, GLIA 55: 453-462, 2007**. PMID: 17203472**

f) HE, J., **CREWS, F.T.** *Increased MCP-1 and microglia in various regions of the human alcoholic brain*, Experimental Neurology 210(2): 349-58, 2008. **PMID: 18190912**

4. Adolescent Brain is Uniquely Sensitive to Alcohol Pathology. Little is known about how adolescent brain differs from adult brain. Emerging epidemiology studies indicated individuals who begin drinking in the early teen years are about 4 times more likely to become alcohol dependent within their lifetime than those who begin regular drinking at 21 years of age. Our hypothesis that alcohol induced brain damage led to increased risks for alcoholism prompted direct comparisons of adult and adolescent rats on sensitivity to

alcohol induced pathology. We first discovered that the adolescent brain was uniquely sensitive to binge ethanol induced neuronal death as well as ethanol inhibition of neurogenesis. These studies were extended.

a) **CREWS, F.T.**, BRAUN, C.J., HOPLIGHT B., SWITZER, III, R.C., and KNAPP, D.J.: *Binge ethanol consumption causes differential brain damage in young-adolescent compared to adult rats*. Alcohol Clin Exp Res 24(11):1712-1723, 2000. **PMID: 11104119**

b) **CREWS, F.T.,** MDZINARISHVILI A., HE, J., KIM, D., and NIXON, K. *Neurogenesis in adolescent brain is potently inhibited by ethanol*. Neuroscience 137: 437-445, 2006. **PMID: 16289890**

c) HE, JUN, and **CREWS, F.T.** *Neurogenesis decreases during brain maturation from adolescence to adulthood*. Pharmacology, Biochemistry and Behavior, Special Issue, 86(2): 327-333, 2007. **PMID: 17169417**

d) **CREWS, F.**, HE, JUN, and HODGE, CLYDE. *Adolescent cortical development: a critical period of vulnerability for addiction*, Pharmacology, Biochemistry and Behavior, Special Issue, 86(2): 189-199, 2007. **PMID: 17222895**

e) STEVENSON, J.R., SCHROEDER, J.P., NIXON, K., BESHEER, J., **CREWS, F.T.**, HODGE, C.W. *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**

f) COLEMAN, L.G., HE, J., LEE, J. STYNER, M. and **CREWS, F.T**., *Adolescent Binge Drinking Alters Adult Brain Neurotransmitter Gene Expression, Behavior, Brain Regional Volumes, and Neurochemistry in Mice*, Alcoholism: Clinical and Experimental Research, 2011, Jan 11.doi:10.1111/j.1530-0277.2010.01385x. [Epub ahead of print] **PMID: 2122304**

g) BROADWATER, MA, LIU, W, **CREWS, FT** AND SPEAR, LP. *Persistent loss of hippocampal neurogenesis and increased cell death following adolescent, but not adult, chronic ethanol exposure*. Developmental Neuroscience. 2014;36(3-4):297-305. **PMID: 24993092**

h) VETRENO, RP., BROADWATER, M., LIU, W., SPEAR, LP., **CREWS, FT**. *Adolescent, but not adult, binge ethanol exposure leads to persistent global reductions of choline acetyltransferase expressing neurons in brain*. PLoS One. 2014 Nov 18;9(11)e113421. **PMID: 25405505**

i) VETRENO, RP., **CREWS, FT**. *Binge ethanol exposure during adolescence leads to persistent loss of neurogenesis in the dorsal and ventral hippocampus that is associated with impaired adult cognitive functioning.* Frontiers, revision submitted January 2015.

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 Lauriate 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.

1. **CREWS, F.T.** and SMITH, C.B.: Presynaptic *alpha*-receptor subsensitivity after long-term antidepressant treatment. Science 202:322-324, 1978. **PMID: 211589**
2. **CREWS, F.T.,** MORITA, Y., McGIVNEY, A., HIRATA, F., SIRAGANIAN, R.P., and AXELROD, J.: IgE-mediated histamine release in rat basophilic leukemia cells: receptor activation, phospholipid methylation, Ca^{2+} flux, and release of arachidonic acid. Arch. Biochem. Biophys. 212:561-571, 1981. **PMID: 6173018**
3. GONZALES, R.A. and **CREWS, F.T.**: Characterization of the Cholinergic Stimulation of Phosphoinositide Hydrolysis in Rat Brain Slices. *J. Neurosci.* 4:3120-3127, 1984. **PMID: 6094748**
4. GONZALES, R.A. and **CREWS, F.T.**: Guanine Nucleotides Stimulate Production of Inositol Trisphosphate in Rat Cortical Membranes. *Biochem. J.* 232:799-804, 1985. **PMID: 3004420**

5. GONZALES, R.A. and **CREWS, F.T.**: Differential Regulation of Phosphoinositide Phosphodiesterase Activity in Brain Membranes by Guanine Nucleotides and Calcium. *J. Neurochem.* 50:1522-1528, 1988. **PMID: 2834515**
6. CHANDLER, L.J. and **CREWS, F.T.**: Calcium-Versus G Protein-Mediated Phosphoinositide Hydrolysis in Rat Cerebral Cortical Synaptoneurosomes. *J. Neurochem.* 55:1022-1030, 1990. **PMID: 2166771**

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

D. Research Support

Current Research Support

U01 (AA020023), Crews (PI), 9/1/10 - 8/31/15, NIH/NIAAA, UNC-CH NADIA Underage Drinking and Adult Brain Morphology in Rats: The NADIA coordinates a diverse group of basic neuroscientists in a multidisciplinary research project testing the overall hypothesizes that adolescent intermittent ethanol (AIE) treatment will alter adult brain structure and function. Additional hypotheses are that higher alcohol doses, younger individuals and longer periods of abuse will cause more pathology. Role: PI

U24 (AA020024), Crews (PI), 9/1/10 - 8/31/15, NIH/NIAAA,. UNC-CH NADIA Administrative Core: The Administrative core coordinates the NADIA consortium efforts, the Scientific core provides brain morphology, e.g. rat MRI and histology, and the Crews research component investigates models of adolescent binge drinking on adult behavior, brain regional MRI volumes, and brain histology. Role: PI

U24 (AA020022), Crews (PI), 9/1/10 - 8/31/15, NIH/NIAAA, UNC-CH NADIA Scientific Core: The NADIA coordinates a diverse group of basic neuroscientists in a multidisciplinary research project testing the overall hypothesizes that adolescent intermittent ethanol (AIE) treatment will alter adult brain structure and function. Additional hypotheses are that higher alcohol doses, younger individuals and longer periods of abuse will cause more pathology. Role: PI

U54 (AA019767-01), Crews (PI), 8/1/10 - 7/31/15, NIAAA, Mechanisms of Alcoholic Pathology: A Collaborative Partnership Between NCCU & UNC: Chronic ethanol treatment has been shown to inhibit adult brain hippocampal and forebrain neurogenesis and to decrease brain CB1R and CB2 cannabinoid receptor (CB2R). In brain CB1R are primarily neuronal, whereas CB2 cannabinoid receptor (CB2R) are primarily present on glia, particularly proliferation, differentiation and neurogenesis. Chronic ethanol also increases brain microglial markers and proinflammatory cytokine expression. Interestingly, endotoxin (LPS), causes brain microglial activation, increased CB2R, increased proinflammatory cytokine expression and loss of neurogenesis. Role: PI

T32-AA07573-01, Crews (PI), 4/1/97 - 3/31/17, NIAAA, Molecular and Cellular Alcohol Research Training: The training grant promotes the development of promising PhD postdoctoral fellows as independent investigators and future faculty members who will investigate the pathogenesis of alcoholism and alcohol abuse using modern molecular medicine techniques. * Institutional National Research Service Award. Role: PI and Key Administrator

P50-AA11605-17, Crews (PI), 12/1/97 - 11/30/17, NIAAA, Molecular and Cellular Pathogenesis in Alcohol: This P60 is focused on the unifying hypothesis that common cellular and molecular events caused by ethanol lead to alterations in cellular signaling that trigger tissue specific pathologies. Role: PI

Completed Research Support:
R01 (AA006069, Years 19-23), Crews (PI), completed 7/31/10, NIH/NIAAA. Ethanol Effects on Neurotransmission: This grant evolved to a focus on neurodegeneration and neurogenesis over the 23 years of funding. A rat binge drinking model was discovered to induce cortico-limbic neurodegeneration. Hypotheses investigating excitotoxicity as a mechanism of alcohol induced neurodegeneration were not supported by the data. Anti-oxidant protection, innate immune gene induction by ethanol, and ethanol inhibition of neurogenesis were discoveries supported by this completed proposal. The current proposal builds upon these discoveries. Role: PI

R01 (AA014983, Years 5-10), Hodge (PI), 8/05/05 - 6/30/2010, NIH/NIAAA. Molecular Mechanisms of Ethanol Reinforcement: The primary goal of this application was to characterize the involvement of metabotropic glutamate receptors in alcohol's reinforcing effects. Role: Co-PI, was involved in molecular signaling processes associated with the behaviors studied.