BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors in the order listed on Form Page 2. Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

MORROW, A. LESLIE	POSITION TITLE John Andrews Distinguished Professor of Psychiatry and Pharmacology
eRA COMMONS USER NAME (credential, e.g., agency login) Leslie_Morrow	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
University of California, Davis	B.S.	1977	Psychobiology
University of California, San Diego	Ph.D.	1985	Neuroscience
National Institute of Mental Health	Post-Doc	1988	Molecular Neuropharm.

A. Personal Statement

My work is focused on developing an understanding of the role of $GABA_A$ receptors and neuroactive steroids in normal brain function and neuropsychiatric disease, particularly alcohol use disorders. My group has made landmark discoveries on the role of $GABA_A$ receptors and neuroactive steroids in ethanol action, ethanol sensitivity, tolerance and dependence. We contributed evidence for GABAergic neurosteroid regulation of ethanol drinking and self-administration in rats. We have also contributed to understanding the association of neurosteroid deficits with history of major depression, premenstrual dysphoric disorders and schizophrenia. We developed the only GCMS assay that validated simultaneous measurement of all eight GABAergic neurosteroids for use in human and rat plasma. We have established evidence for local production of allopregnanolone across brain using immunohistochemistry and co-localization with specific neuron markers. All of this work provides a strong rationale for neuroactive steroid targeted therapeutics in human disease. Over my career, I have trained 1 Psychiatry fellow, 14 post-docs, 10 graduate students and 18 postbaccalaureate students with successful careers. I am enthusiastic about science, mentoring and opportunities at UNC.

Positions and Employment

1988-1990: Senior Research Associate, Laboratory of Molecular Pharmacology, NIMH, Bethesda, MD
1990-1996: Assistant Professor, Dept. of Psychiatry and Bowles Center for Alcohol Studies, School of Medicine, University of North Carolina at Chapel Hill (UNC-CH), Chapel Hill, NC
1996-2001: Associate Professor, Depts. of Psychiatry & Pharmacology and Center for Alcohol Studies, UNC-CH
1998-pres: Associate Director, Bowles Center for Alcohol Studies, UNC-CH
2001-pres: Professor, Depts. of Psychiatry and Pharmacology and Center for Alcohol Studies, UNC-CH

Editorial and Advisory Appointments

Principal Editor, Psychopharmacology, 2010 – present.
Associate Editor, Pharmacological Reviews, 2010 – present.
Associate Editor, Frontiers in Neuropharmacology 2009 – present.
Review Editor, Alcoholism: Clinical and Experimental Research, 2004 – present.
Biochemistry, Physiology and Medicine Study Section, NIH, NIAAA, September 1997 - August 2001.
Biochemistry, Physiology and Medicine Study Section, NIH, NIAAA, Chairperson, October 2001 – 2003.
Alcohol Biomedical Research Review Committee, ZAA-4 DD, NIAAA, NIH, October 2007 – 2011.

Honors

Bowles Lectureship Award, 2015
Johns Andrews Distinguished Professor, 2010
APA Frontier of Science Lecturer, APA Annual Meeting, Toronto, Canada, May 24, 2006 NIH
R37 Merit Award, 2001- 2011.
University of North Carolina at Chapel Hill Faculty Development Award Jan - Dec 1995.
Pharmaceutical Manufacturers Research Starter Award, Jan 1992 - Dec 1993.
American College of Neuropsychopharmacology Travel Award: Annual Meeting, Dec 10-15, 1989.
National Academy of Sciences, National Research Council Associate Award, June 1988 -July 1990.
Pharmacology Research Associate Fellowship (PRAT Fellow). NIGMS, NIH, June 1986-1988.
NIMH Predoctoral Individual Fellowship MH08898: Oct., 1982 - Oct., 1985.

C. Contributions to Science

Over my career, I have published over 180 scientific articles in the field of neuropsychopharmacology. These accomplishments are broken into several general themes that are relevant to the proposed studies.

Regulation of $GABA_A$ receptor function and expression: Like many receptors, $GABA_A$ receptors are regulated by the neuromodulators that activate or inhibit them. As a post-doc, I studied the effects of benzodiazepines, barbiturates, neuroactive steroids and ethanol on $GABA_A$ receptor function and further demonstrated regulation of these receptors by chronic exposure to both ethanol and pentobarbital. Later, my group focused on ethanol regulation of various $GABA_A$ receptors at the levels of transcription, protein expression, and receptor trafficking. We further established the intracellular signaling mechanisms that underlie ethanol effects on several $GABA_A$ receptor subtypes, including mechanistic roles for PKCγ, PKA and histone acetylation. These studies have therapeutic implications for treatment of ethanol dependence pathology.

Several examples of this work are listed here:

DEVAUD, L.L., SMITH, F.D., GRAYSON, D.R. AND **MORROW, A.L.** Chronic ethanol consumption differentially alters $GABA_A$ receptor subunit mRNAs in rat cerebral cortex: Competitive quantitative RT/PCR analysis. Mol. Pharmacol., 48:861-868 (1995).

KUMAR, S., KRALIC, J. E., O'BUCKLEY, T. K., GROBIN, A.C. AND **MORROW, A.L.** Chronic ethanol consumption enhances internalization of α1 subunit-containing $GABA_A$ receptors in cerebral cortex. J. Neurochem 86: 700-708 (2003). PMID: 12859683

WERNER D.F., KUMAR S., CRISWELL, H.E., SURYANARAYANAN, A., FETZER, A.J., COMERFORD, C.E., AND **MORROW, A.L.** PKCγ is required for ethanol-induced increases in $GABA_A$ receptor α4 subunit expression in cultured cerebral cortical neurons. J. Neurochem. 116: 554-563, (2011). PMCID: PMC3033448
CARLSON S.L., KUMAR S., WERNER D.F., COMERFORD C.E., **MORROW A.L**. Ethanol activation of PKA regulates $GABA_A$ α1 receptor function and trafficking in cultured cerebral cortical neurons. J. Pharmacol. Exp. Ther. 345(2):317-25 (2013). PMCID: PMC3629799

CARLSON S.L., O'BUCKLEY, T. K., THOMAS, R. T., THIELE, T.E., AND **MORROW, A.L.** Altered $GABA_A$ receptor expression and seizure threshold following acute ethanol challenge in mice lacking the RIIβ subunit of PKA. Neurochemical Research 39(6): 1079-1087 (2014). PMCID: PMC3981963

Role of neuroactive steroids in ethanol sensitivity, tolerance and dependence: The mechanisms of ethanol action evaded the field for many years until we discovered that ethanol-induced increases in brain levels of GABAergic neuroactive steroids were required for many ethanol actions and contributed to other actions. The adrenal and brain mechanisms of ethanol effects on neurosteroid production were elucidated and the physiological significance of the effect was established. Chronic ethanol exposure leads to tolerance to increases in the neurosteroid allopregnanolone, but sensitization to its GABAergic effects. Chronic ethanol exposure also leads to deficits in brain levels of allopregnanolone that may worsen symptoms of ethanol dependence including anxiety, seizure susceptibility, and excessive drinking. This work established a rationale for therapeutic elevations of allopregnanolone in alcohol use disorders.

Several examples of this work are listed here:
VANDOREN, M.J., MATTHEWS, D.B., JANIS, G.C., GROBIN, A.C., DEVAUD, L.L., **MORROW, A.L.** Neuroactive steroid 3α-hydroxy-5α-pregnan-20-one modulates electro-physiological and behavioral actions of ethanol. Journal of Neuroscience 20(5):1982-1989 (2000).

BOYD K.N., KUMAR, S., O'BUCKLEY, T.K., **MORROW, A.L.** Chronic ethanol exposure produces tolerance to elevations in neuroactive steroids: mechanisms and reversal by exogenous ACTH. J. Neurochem. 115: 142–152 (2010). PMCID: PMC3037825

COOK J.B., NELLI, S. M., NEIGHBORS, M.R., MORROW, D.H., O'BUCKLEY T.K., MALDONADO-DEVINCCI, A.M., **MORROW A.L**. Ethanol alters local cellular levels of (3α,5α)-3-hydroxypregnan-20-one (3α,5α-THP) independent of the adrenals in subcortical brain regions. Neuropsychopharmacology 39:1878-87 (2014). PMCID: PMC4059907

MALDONADO-DEVINCCI, A.M., COOK, J.B., O'BUCKLEY T.K., MORROW, D.H., MCKINLEY, R.E., LOPEZ, M.F., BECKER, H.C. AND **MORROW, A.L**. Chronic intermittent ethanol exposure and withdrawal alters (3α,5α)-3-hydroxy-pregnan-20-one immunostaining in cortical and limbic brain regions of C57BL/6J mice. Alcoholism Clinical and Experimental Research 38(10):2561-2571 (2014) PMCID: PMC4211975

<u>GABAergic neuroactive steroids are important modulators of ethanol consumption in animal models of alcohol use disorders:</u> Since GABAergic neuroactive steroids mimic many ethanol actions and ameliorate many symptoms of ethanol withdrawal, we explored the effects of these steroids on ethanol reinforcement and consumption. Various neuroactive steroids reduce ethanol intake, particularly in dependent rats, but we also found evidence for reductions in ethanol reinforcement after administration of GABAergic neuroactive steroids and precursors. We further demonstrated that genetic variation in brain levels of the steroids is inversely related to ethanol consumption and place preference. Most recently, we used viral-mediated gene delivery to enhance steroidogenesis in VTA neurons and demonstrated long-term reductions in ethanol reinforcement and intake. These studies further substantiate the therapeutic potential for these steroids in alcohol use disorders.
BESHEER, J., LINDSAY, T.G., O'BUCKLEY, T.K., HODGE, C.W., **MORROW, A.L**. Pregnenolone and ganaxolone reduce operant ethanol self-administration in alcohol-preferring P rats. Alcoholism, Clin. Exp. Research. 34(12): 2044-2052 (2010). PMCID: PMC2988984

PORCU, P., O'BUCKLEY, T.K., SONG, S.C., HARENZA, J.L., LU, L., WANG, X., WILLIAMS, R.W., MILES, M.F., AND **MORROW, A.L**. Genetic analysis of the neurosteroid deoxycorticosterone and its relation to alcohol phenotypes: Identification of QTLs and downstream gene regulation. PLOS One 6:e18405 (2011). PMCID: PMC3072994

PORCU, P., **MORROW, A.L**. Divergent neuroactive steroid responses to stress and ethanol in rat and mouse strains: relevance for human studies. Psychopharmacology (Berl). 231:3257-72 (2014). PMCID: PMC4135033

COOK J.B., WERNER, D.F., MALDONADO-DEVINCCI, A.M., LEONARD, M.N., FISHER, K.R., O'BUCKLEY T.K., PORCU, P. MCCOWN, T.J., BESHEER, J., HODGE, C.W., **MORROW A.L**. Overexpression of the steroidogenic enzyme cytochrome P450 side chain cleavage in the ventral tegmental area increases 3α,5αTHP and reduces long-term operant ethanol self-administration. J. Neuroscience 34: 5824-5834 (2014). PMCID: PMC3996211

<u>Dysregulation of neuroactive steroids in premenstrual dysphoric disorder, depression and schizophrenia</u>: We have been fortunate to collaborate with leaders in studies of the etiology of these diseases and established that neuroactive steroids contribute to their pathophysiology. We have used radioimmunoassays to measure allopregnanolone and developed the only GCMS assay to measure all eight GABAergic neuroactive steroids – specifically in human serum. Our studies show that allopregnanolone is elevated in patients with PMDD and this results in blunted stress responses, including the stress-induced elevation of allopregnanolone. Subjects with a history of depression have reduced levels of all the pregnane neuroactive steroids and blunted responses to progesterone challenge. Pregnenolone supplementation has therapeutic benefits in patients with schizophrenia. Taken together, our work suggests that deficits in neuroactive steroids promote risk and pathophysiology of various neuropsychiatric diseases.

Several examples of this work are listed here:

KLATZKIN, R.R., **MORROW, A.L**., LIGHT, K.C., PEDERSEN, C.A. AND GIRDLER, S.S. Histories of depression, allopregnanolone responses to stress and premenstrual symptoms in women. Biological Psychiatry, 71:2 -11 (2006). PMID: 15951099

MARX, C.E., KEEFE, R.S., KILTS, J.D., BUCHANAN, R.W., HAMER, R.M., BRADFORD, D.W., STRAUSS, J.L., NAYLOR, J.C., PAYNE, V.M., LIEBERMAN, J.A., LEIMONE, L., SAVITZ, A.J., DUNN, L., PORCU, P., **MORROW, A.L.** AND SHAMPINE, L.J. Proof-of-Concept trial with the neurosteroid pregnenolone targeting neurocognitive and negative symptoms in schizophrenia. Neuropsychopharmacology, 34(8):1885-903 (2009). PMID: 19339966 PORCU, P., O'BUCKLEY, T.K., ALWARD, S.E., MARX, C.E., SHAMPINE, L.J., GIRDLER, S.S. AND **MORROW, A.L**. Simultaneous quantification of GABAergic 3α,5α・3α,5β neuroactive derivatives of pregnenolone in human and rat serum. Steroids 74:463-73 (2009). PMCID: PMC2832187

GIRDLER, S.S., LINDGREN, M., PORCU, P., RUBINOW, D.R., JOHNSON, J.L. AND **MORROW, A.L**. A History of depression in women is associated with an altered GABAergic neuroactive steroid profile. Psychoneuroendocrinology 37:543-53 (2012) PMCID: PMC3233657

A more extensive list of my publications can be found here:
http://www.ncbi.nlm.nih.gov/sites/myncbi/a.leslie.morrow.1/bibliography/48146177/public/?sort=date&direction=ascending