
BIOGRAPHICAL SKETCH

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NAME: Thomas Louis Kash

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

POSITION TITLE: John Andrews Distinguished Professor, Vice-Chair

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
SUNY College of Environmental Science	BS	1999	Chemistry
Weill Cornell Graduate School of Medical Sciences	PhD	2004	Neuroscience
Vanderbilt University Medical Center	Post-Doc	2008	Molecular Physiology

A. Personal Statement

I am a Professor in Pharmacology and a member of the Bowles Center for Alcohol Studies and the Neuroscience Curriculum at UNC. I am currently PI or co-PI on multiple research grants, including Project 5 and the NIAAA-funded UNC P60 Alcohol Research Center. I am highly involved in scientific training as the Vice-Chair of Faculty Development in my Department and the Co-PI of the NIGMS funded IMSD program.

My broad scientific goal is to understand how modulation of discrete neuronal circuits can shape behavior and to deconstruct the molecular mechanisms that underlie this modulation. Research in my lab is focused on understanding how stress, pain and alcohol abuse can alter neuronal function in brain regions that regulate emotional behavior. These topics are fascinating from a basic science standpoint, but also absolutely critical from the public health standpoint, as these disorders exert a tremendous economic impact on our society. These investigations are performed using a multidisciplinary approach, ranging from behavioral analysis to detailed mechanistic signaling analysis in individual neurons. My long term goal is to integrate our studies using translational and reverse translational approaches to identify novel treatments and biomarkers for psychiatric disorders.

P60 Component 5: I am highly qualified to continue as Project Lead together with Dr. Montse Navarro on this component. Dr. Navarro and I have productively worked together since 2012 as collaborators, and as co-PIs on this research project in the P60 since 2016, resulting in 7 coauthored papers to date. Our work has identified Kappa Opioid Receptor (KOR) signaling in the insula as a key driver of alcohol consumption that works in a sex specific fashion. Dr. Navarro has extensive expertise in behavioral approaches to study alcohol abuse in animal models, whereas my expertise is focused on modulation of brain circuits. Together we form a powerful team which leverages both of expertise to develop a mechanistic understanding of aspects of alcohol abuse. For this renewal we are focusing on assessing the aversive properties of ethanol, something Dr. Navarro is extremely well qualified to do.

Administrative Core/Overall. I am highly qualified to continue as PI for the P60. Prior to becoming the Program Director of the P60, I was the co-Scientific Director of the P60. It is noteworthy that all of the ARC Directors have worked together for more than 9 years and collaborated on the ARC administration. I have shown leadership as the UNC Department of Pharmacology, serving as Vice-chair for Faculty Development where I am responsible for mentoring junior faculty, all of which who have gone up for tenure have received it. In addition, I am a recognized leader in the field. I have shown scientific leadership on an international scale by organizing scientific conferences (Kappa Opioid Research Conference, Amygdala Gordon Research Conference, Cold Spring Harbor DREADD meeting, and an upcoming Keystone Conference on Addiction). Further, I have chaired or been involved in multiple faculty searches in the Alcohol Center, Department of Pharmacology and the Department of Psychiatry (chair search committee). I have also won multiple research awards, the PECASE (NIAAA), RSA Young Investigator Award, Volterra Conference Young Investigator, and

the Waletzky Award (SfN) establishing his scientific excellence. Taken together, these highlight that I am well qualified for this role. As a long established member of the alcohol field, this alcohol research center represents a powerful collaborative commitment to enhance alcohol research on both a local and national level.

Ongoing and recently completed projects that I would like to highlight include:

R01AA019454-01A1 (PI: Kash) 8/5/10 – 03/31/22
NIH/NIAAA: *The Role of Serotonin in Alcohol-Withdrawal Induced Anxiety*
Role: PI

U01 AA020911 (PI: Kash) 2/10/12 – 1/31/22
NIH/NIAAA: 6/8: INIA STRESS AND CHRONIC ALCOHOL INTERACTIONS: DECONSTRUCTING THE
ROLE OF EXTENDED AMYGDALA CIRCUITS IN STRESS REGULATED ALCOHOL DRINKING
Role: PI

U24 AA025475 (PI: Kash) 2/2/17 – 1/31/22
NIH/NIAAA: INIA STRESS Core 1: Brain Circuit Validation Core
Role: PI

P60AA011605-16 (Crews) 12/01/17 – 11/30/22
NIH/NIAAA: Molecular and Cellular Pathogenesis in Alcoholism
Role: PI of Component 5

R01AA025582 (Multi PI:Kash, Besheer) 9/30/16 - 09/29/22 (NCE for 1 year)
NIH/NIAAA : Unbiased analysis of molecular and circuit targets of low dose alcohol
Role: Co-PI

R21AA027460 (PI: Kash) 5/10/2019 – 04/31/2021
NIH/NIAAA: Dissecting the role of ethanol-induced plasticity in the PAG to BNST pathway in pain-related
behaviors
Role: PI

B. Positions and Honors

Positions

2019- Professor, Department of Pharmacology
2017- Vice Chair of Faculty Development, Department of Pharmacology
2015 – 2019 Associate Professor, Department of Pharmacology
2009 - 2015 Assistant Professor, Department of Pharmacology
2008 - 2009 Research Instructor, Department of Molecular Physiology and Biophysics, Vanderbilt University
2004 - 2008 Post-doctoral Research Fellow, Mentor: Danny G. Winder, Ph.D.
Department of Molecular Physiology and Biophysics ,Vanderbilt University
2000 - 2004 Ph.D. in Neuroscience, Mentor: Neil L. Harrison, Ph.D.
Weill Graduate College of Biomedical Science, Cornell University

Honors

2019 Jacob Waletzky Award
2019 Amygdala GRC Vice Chair
2018 ACNP Member
2014 NARSAD Independent Investigator Award
2014 ACNP Associate Member
2013 Research Society for Alcoholism Young Investigator Award
2011 White House Presidential Early Career Award for Scientists and Engineers

Other Experience and Professional Memberships

2018 Ad Hoc NIH Peer Review, NAL

2015-	Editorial Board: Molecular Pharmacology, Neuropharmacology, Molecular Neuropsychopharmacology
2014-2017	NIH Peer Review, MNPS Member
2011-13	NIH Peer Review Committee: MNPS Ad hoc
2006-	Member, Research Society for Alcoholism
2001-	Member, Society for Neuroscience

C. Contribution to Science

1. **ALCOHOL/STRESS REGULATION OF 5HT SYSTEMS** As I began my lab, I developed an interest in 5-HT. This stemmed from a number of interesting clinical pharmacology papers from the Kranzler, Krystal and Heilig groups. Moreover, given the rich pharmacology of 5HT, I thought it was something that may develop traction translationally. In the initial stage of this exploration, the lab did more basic work trying to understand how alcohol exposure modulated synaptic function across the brain. We then directly targeted 5HT signaling in the bed nucleus of the stria terminalis (BNST) following chronic intermittent alcohol exposure, looking at both electrophysiological adaptations, markers of activity and relating this to behavior. At the same time, we began looking at alcohol's impact in the dorsal raphe (DR), and found some interesting effects with chronic alcohol altering function, and response to acute alcohol, suggesting that this is a potential site of negative reinforcement. From here, we began to focus on more mechanistic circuit based work, trying to understand Gq signaling in the BNST and 5HT modulation of function. Both of these areas of interest have been quite productive. More importantly, this ground work has set us up for understanding how alcohol can impact these circuits.
 - a. Pleil KE, Lowery-Gionta EG, Crowley NA, Li C, Marcinkiewicz CA, Rose JH, McCall NM, Maldonado-Devincci AM, Morrow AL, Jones SR, **Kash TL** (2015a) Effects of chronic ethanol exposure on neuronal function in the prefrontal cortex and extended amygdala. *Neuropharmacology* 99:735-749.
 - b. Marcinkiewicz CA, Dorrier CE, Lopez AJ, **Kash TL** (2015) Ethanol induced adaptations in 5-HT_{2c} receptor signaling in the bed nucleus of the stria terminalis: implications for anxiety during ethanol withdrawal. *Neuropharmacology* 89:157-167.
 - c. Lowery-Gionta EG, Marcinkiewicz CA, **Kash TL** (2015) Functional alterations in the dorsal raphe nucleus following acute and chronic ethanol exposure. *Neuropsychopharmacology* 40:590-600.
2. **DISSECTING CIRCUITS UNDERLYING PATHOLOGICAL BEHAVIORS.** With the advent of optogenetics and chemogenetics, there are now many tools available to probe the role of circuits and cells in given behaviors and modulation. My focus has primarily been on how the extended amygdala can regulate anxiety like behavior, publishing several high impact papers focusing on the role of neuromodulation in the BNST and how that is related to both alcohol and anxiety.
 - a. Marcinkiewicz CA*, Mazzone CM*, D'Agostino G, Halladay LR, Hardaway JA, DiBerto JF, Navarro M, Burnham N, Cristiano C, Dorrier CE, Tipton GA, Ramakrishnan C, Kozicz T, Deisseroth K, Thiele TE, McElligott ZA, Heisler LK and **Kash TL**. Serotonin Activates an Anxiety and Fear Promoting Circuit in the BNST. *Nature*.
 - b. Vardy E, Robinson JE, Li C, Olsen R, Crowley NA, Pleil KE, Mazzone CA, **Kash TL**, Krashes M, Roth BL. A New DREADD Facilitates the Multiplexed Chemogenetic Interrogation of Behavior. *Neuron*.
 - c. Li C, Sugam JA, Lowery-Gionta EG, McElligott ZA, McCall NM, Lopez AJ, McKlveen JM, Pleil KE, **Kash TL** (2016) Mu Opioid Receptor Modulation of Dopamine Neurons in the Periaqueductal Gray/Dorsal Raphe: A Role in Regulation of Pain. *Neuropsychopharmacology*.
3. **NEUROPEPTIDE MODULATION OF SYNAPTIC FUNCTION AND PLASTICITY.** While a post-doc I also began examining how neuropeptides, in particular CRF and NPY, interact and regulate synaptic function and plasticity. This work was critical as it built on a large body of behavioral data suggesting that these modulators can play critical roles in the regulation of both stress and addiction related behavior. I provided the first evidence of a direct molecular interaction between CRF and NPY, and in addition demonstrated

that biogenic amines such as dopamine and norepinephrine can engage peptide signaling in this structure, and these systems are altered by cocaine exposure. Subsequent experiments in my own lab have begun to explore cell type genetic modulation of these systems and have contributed widely to understanding how these compounds can exert their effects on behavior.

- a. ***Kash TL**, *Nobis WP, Matthews RT and Winder DG. Dopamine enhances fast excitatory synaptic transmission in the extended amygdala by a CRF-R1-dependent process. *J Neurosci*. 2008;28(51):13856-13865.
- b. Nobis WP*, **Kash TL***, Silberman Y and Winder DG. beta-Adrenergic receptors enhance excitatory transmission in the bed nucleus of the stria terminalis through a corticotrophin-releasing factor receptor-dependent and cocaine-regulated mechanism. *Biol Psychiatry*. 2011;69(11):1083-1090.
- c. **Kash TL** and Winder DG. Neuropeptide Y and corticotropin-releasing factor bi-directionally modulate inhibitory synaptic transmission in the bed nucleus of the stria terminalis. *Neuropharmacology*. 2006;51(5):1013-1022.

4. CIRCUIT ANALYSIS OF BINGE-LIKE ALCOHOL DRINKING. After moving to UNC, I started collaborating with Todd Thiele examining how neuropeptides can influence binge-drinking. Together we have published several high impact papers delineating mechanisms by which and adaptations in neuropeptide systems in the extended amygdala. These work were critical to the field because they demonstrated that high level drinking could engage stress systems such as CRF without the animals being alcohol dependent.

- a. Pleil KE, Lowery-Gionta EG, Rinker JA, McCall NM, Sprow GM, Olson DP, Mazzone CM, Lowell BB, Grant KA, Thiele TE, **Kash TL**. NPY Signaling Inhibits Extended Amygdala CRF Neurons to Suppress Binge Alcohol Drinking. *Nature Neuroscience*
- b. Lowery-Gionta EG, Navarro M, Li C, Pleil KE, Rinker JA, Cox BR, Sprow GM, **Kash TL** and Thiele TE. Corticotropin releasing factor signaling in the central amygdala is recruited during binge-like ethanol consumption in C57BL/6J mice. *J Neurosci*. 2012;32(10):3405-3413.
- c. Sparrow AM, Lowery-Gionta EG, Pleil KE, Li C, Sprow GM, Cox BR, Rinker JA, Jijon AM, Pena J, Navarro M, **Kash TL** and Thiele TE. Central neuropeptide Y modulates binge-like ethanol drinking in C57BL/6J mice via Y1 and Y2 receptors. *Neuropsychopharmacology*. 2012;37(6):1409-1421.

5. ION CHANNEL MOLECULAR ANALYSIS My initial publications were focused at delineating the structural mechanisms involved in the activation of ligand gated ion channels, with a particular focus on GABAA receptors. This was a critically important topic, as these receptors are targets of many drugs, including anesthetics, ethanol and benzodiazepines and are involved in a bevy of brain disorders. At this point in time, the mechanism by which the energy of ligand binding was coupled to channel opening was unknown. Using a combination of site directed mutagenesis, electrophysiology, and molecular modeling, I was the lead on multiple manuscripts describing a molecular interaction within the GABAA receptor that was responsible for the coupling of these processes. These key findings have formed the basis for a greater understanding of ion channel function and the concepts proposed a decade ago have been validated in new crystal structures.

- a. **Kash TL**, Jenkins A, Kelley JC, Trudell JR and Harrison NL. Coupling of agonist binding to channel gating in the GABA(A) receptor. *Nature*. 2003;421(6920):272-275.
- b. **Kash TL**, Dizon MJ, Trudell JR and Harrison NL. Charged residues in the beta2 subunit involved in GABAA receptor activation. *J Biol Chem*. 2004;279(6):4887-4893.

My NCBI Bibliography:

<http://www.ncbi.nlm.nih.gov/myncbi/browse/collection/40778790/?sort=date&direction=ascending>