BIOGRAPHICAL SKETCH

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NAME: Thomas Louis Kash

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

POSITION TITLE: Associate professor, 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

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 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. This integrative approach has been exciting and has allowed me to move my science beyond correlation to explore causative relationships. I have multiple active projects and grants related to discovering different aspects of stress and alcohol induced behavioral pathologies. Over the past 8 years, I have trained 9 postdocs (4 current) and 5 graduate students (2 current) that have gone on to outstanding positions in science, both in academia and elsewhere. I am confident that my lab will provides a rich training environment for individuals to grow and prosper as a scientist. To date, I have trained a number of post-doctoral fellows in my lab, with my first, Kristen Pleil, successful obtaining both a K99 and an independent tenure track faculty position at Cornell University. My second post-doc, Catherine Marcinkiewcz, has recently accepted a tenure track position at University of Iowa. Beyond this success in academia, several other fellow have gone on to other outstanding positions in science, notably Jon Sugam was a Postdoc in my lab for 2 years before moving on to become a scientist at Merck; and Jess McKlveen was a Postdoc in my lab for 2 years before recently moving on to become a science officer for DoD sponsored research programs. In addition, my graduate students have all gone on to excellent positions. All told, I take mentoring very seriously, and am highly motivated to help all of my trainees reach their maximum potential. Working towards this, my trainees are engaged in science at multiple levels. In the lab, they all have undergraduates that work with them, providing an opportunity to develop managerial skills that they will bring to their own lab. On campus, they are engaged in the many career offerings provided by UNC, and also routinely meet with guest speakers to discuss trends in neuroscience and what it takes to succeed in science. In the greater scientific world, all of my trainees routinely attend multiple meetings each year, including larger meetings such as RSA and SfN, but also smaller meetings, such as Gordon Research Conferences and Winter Brain. At all of these meetings, I strongly encourage my trainees to gives both talks and posters, as it provides them a chance to promote themselves in the greater alcohol research community.

B. Positions and Honors

Positions

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

Honors

2011	White House Presidential Early Career Award for Scientists and Engineers
2013	Research Society for Alcoholism Young Investigator Award
2014	ACNP Associate Member
2014	NARSAD Independent Investigator Award

Other Experience and Professional Memberships

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

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 with manuscripts being prepared for resubmission at high impact journals. 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, Marcinkiewcz 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. Urban DJ, Zhu H, Marcinkiewcz CA, Michaelides M, Oshibuchi H, Rhea D, Aryal DK, Farrell MS, Lowery-Gionta E, Olsen RH, Wetsel WC, **Kash TL**, Hurd YL, Tecott LH, Roth BL (2015) Elucidation of The Behavioral Program and Neuronal Network Encoded by Dorsal Raphe Serotonergic Neurons. Neuropsychopharmacology.

    c. Marcinkiewcz CA, Dorrier CE, Lopez AJ, **Kash TL** (2015) Ethanol induced adaptations in 5-HT2c receptor signaling in the bed nucleus of the stria terminalis: implications for anxiety during ethanol withdrawal. Neuropharmacology 89:157-167.

    d. Lowery-Gionta EG, Marcinkiewcz 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.

    a. Marcinkiewcz 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. Jennings JH, Sparta DR, Stamatakis AM, Ung RL, Pleil KE, **Kash TL** and Stuber GD. Distinct extended amygdala circuits for divergent motivational states. Nature. 2013;496(7444):224-228.

    c. 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.

    d. 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 benzodiapines 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