BIOGRAPHICAL SKETCH

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NAME: Raab-Graham, Kimberly

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

POSITION TITLE: Associate Professor of Physiology and Pharmacology

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
California State University, Long Beach	B.A.	06/1992	Biology, Cell Biology emphasis, Minor in Chemistry
University of California, Santa Barbara	Ph.D.	12/1998	Cell Molecular Developmental Biology
Cold Spring Harbor		07/1998	Neurobiology Course
University of California, San Francisco	Postdoctoral	08/2007	Neuroscience/Physiology

A. Personal Statement

My group focuses on how synapses remodel their protein composition through local protein synthesis with changes in NMDAR/mTORC1 activity. We seek to understand the ways in which dynamic changes in ion channel and receptor density may influence synaptic integration and the threshold for neuronal firing. Our studies are grounded in mTORC1's established roles in mediating long lasting changes in synaptic efficacy and its aberrant activity in neurological disorders. Many of these disorders, which include addiction, Alzheimer's disease, epilepsy, autism spectrum disorders, and major depressive disorder may be considered channelopathies—diseases with dysregulated ion channel function. My background has provided me with specific training in areas that are fundamental to my work. During my PhD training with Dr. Carol Vandenberg at the University of California, Santa Barbara, I developed biochemical approaches toward studying the structure and function of ion channels. During my postdoctoral training in Dr. Lily Jan's Lab at UCSF, I developed sophisticated techniques to study local translation in dendrites. As a Principal Investigator, my lab has taken a multidisciplinary approach by utilizing molecular tools, live calcium imaging, and behavior to establish key and novel roles for RNA binding factors in the dendritic expression and function of ion channels.

As the PI of university-, NSF-, DOD-, and a NIH-funded pilot grant, I gained the necessary experience in the administration of projects (e.g., keeping timelines, budgets, etc.).

B. Positions and Honors

Positions and Employment

2016 – Present Associate Professor, Department of Physiology and Pharmacology, Wake Forest School of Medicine
2007 - 2016 Assistant Professor, Department of Neuroscience, University of Texas at Austin
2012 - 2014 Co-Director, Institute for Neuroscience Boot Camp, University of Texas at Austin
2007 - 2016 Fellow, Center for Learning and Memory
2007 - 2016 Member, Institute for Neuroscience

2007 - 2016	Member, Institute for Cell and Molecular Biology
2013 - 2016	Member, Waggoner Center for Alcohol and Addiction Research

Other Experience and Professional Memberships

2005-Present	Member, Society for Neuroscience
2007	External Reviewer, NSF MCB
2011	Panel member, NSF IOS review panel
2012, 2016	Reviewer for Alzheimer's Association
2012	External Reviewer, NSF MCB
2012-Present	Member, American Society for Biochemistry and Molecular Biology
2012	Panel member, The National Academies Keck Future Initiative
2013-2015	Guest Associate Editor, *Frontiers in Molecular Neuroscience*
2015-Present	Associate Editor, *Frontiers in Molecular Neuroscience*
2014-Present	Member, Molecular and Cellular Cognition Society
2015	Panel member, CDMRP- TSC review panel
2015	Reviewer for Tuberous Sclerosis Alliance

Selected Invited Talks

2008	Speaker, Society for Neuroscience, Minisymposium, mRNA Transport and Local Protein Synthesis in Development, Plasticity, and Regeneration. Washington, D.C., November
2009	Translation at the Synapse, HHMI, Janelia Farm, Ashburn, VA, November
2010	International Neuroscience Winter Conference, Minisymposium, Solden, Austria, April
2010	Gordon Research Conference, Cell Biology of the Neuron, June
2010	Society for Neuroscience, Short Course II: Posttranscriptional Regulation in Nervous System Development and Plasticity, San Diego, CA, November
2011	EMBO Conference Series, Intracellular RNA Localization & Localized Translation, Tuscany, Italy, August
2015	Session Chair and speaker, RNA Metabolism in Neurological Disease, Society for Neuroscience Satellite meeting, Chicago, IL, October
2016	Gordon Conference – Alcohol and the Nervous System, February

Honors

1994 -1997	American Heart Association Pre-doctoral Fellowship. California Affiliate
1997	Ellen Schamberg Burley Graduate Scholarship, University of California, Santa Barbara
1997	Excellence in Neuroscience Research Award, University of California, Santa Barbara
1999 - 2001	Howard Hughes Medical Institute Postdoctoral Fellow
2001 - 2004	Individual National Research Service Award National Institute of Health Postdoctoral Fellowship, NIMH
2007 - Present	Center for Learning and Memory Fellow, University of Texas at Austin
2008	Summer Research Award, University of Texas at Austin
2015	University of Texas at Austin College of Natural Sciences Teaching Excellence Award

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C. Contribution to Science

1. My early work involved cloning and biochemically characterizing potassium channels. These studies were fundamental in establishing my solid background in ion channel structure and function.

    a. **Raab-Graham, K. F**., Radeke, C. M., and Vandenberg, C. A. (1994) Molecular cloning and expression of a human heart inward rectifier potassium channel. *NeuroReport* 5, 2501 – 2505.
    A figure and discussion of our studies was reproduced in the Chapter entitled *Channels, Ischemia and Stunning: Cellular Electrophysiology and Intercellular Communication* by Marc Ovadia and Peter Brink in the book *Myocardial Viability: A Clinical and Scientific Treatise*

(2000), edited by Vasken Dilsizian.

b. **Raab-Graham, K. F**. and Vandenberg, C.A. (1998) Tetrameric subunit structure of the Native Brain Inwardly Rectifying Potassium Channel Kir 2.2. *Journal of Biological Chemistry* 273, 19699 – 19707.
c. **Raab-Graham, K. F.**, Cirilo, L. J., Boettcher, A. A., Radeke, C. M. and Vandenberg, C. A. (1999) Membrane Topology of the Amino-terminal Region of the Sulfonylurea Receptor. *Journal of Biological Chemistry* 1274, 29122 - 29129.

2. As a postdoc I developed new local translation reporter to characterize post-transcription regulation of ion channel mRNAs, a tool that has been adopted by other labs to study local protein synthesis in dendrites. The motivation for these studies stem from the hypothesis that synaptic activity leading to changes in protein synthesis specifically in the dendrites could control the site-specific expression of ion channels. We focused on the mammalian target of rapamycin complex 1 (mTORC1), an important kinase that regulates dendritic protein synthesis. mTORC1 is required for synaptic plasticity, memory consolidation, and reconsolidation. We found that the mTORC1 inhibitor rapamycin increased the expression of a voltage-gated potassium channel Kv1.1 through local protein synthesis in dendrites. These findings were unexpected since up to this point mTORC1 was best characterized for its role in promoting protein synthesis. Thus, NMDA-mediated suppression of a voltage-gated potassium channel may provide an important positive feedback mechanism at active synapses by enhancing voltage-gated sodium or calcium channel activity during an excitatory postsynaptic potential (EPSP). This work has been cited over 150 times.

   a. **Raab-Graham, K.F**.[a], Haddick, P. C. G.[a], Jan, Y. N., Jan, L. Y. (2006) Activity- and mTOR-dependent suppression of Kv1.1 channel mRNA translation in dendrites. *Science*, 314,144-148.
      Highlighted in Editors' Choice (Sci. STKE 356:348, 2006)
      Highlighted in Previews (Neuron 52:399-401, 2006).
      Highlighted in "Highlights from the Literature" (Physiology 21:3-6, 2007)

3. My initial work showing that mTORC1 can regulate local translation in dendrites has led to a systematic exploration of the RNA-binding factors that regulate dendritic protein synthesis in my own lab, revealing remarkable complexity in their dynamic interactions. We have shown mRNA specificity, such that mTORC1 activation can increase protein synthesis of some, yet repress translation of others. We have identified key and novel roles for both miRNAs and RNA binding proteins in this regulation. Our work has provided new insight into the spatial specificity for regulation of translation, suggesting mechanisms for molecular tagging of dendritic compartments. We have applied these findings to analysis of dynamic changes in ion channel expression, function, and behavior in several animal models of diseases, including epilepsy and autism spectrum disorders.

   a. Sosanya, N. M., Huang, P. C., Cacheaux, L.C., Chen, C.J., Nguyen, K., Perrone-Bizzozero, N.I., and **Raab-Graham, K.F**. (2013) Degradation of High Affinity HuD Targets Releases Dendritic Kv1.1 mRNA Repression by the mammalian Target of Rapamycin (mTORC1), *Journal of Cell Biology,* 202, 53-69.

      Highlighted in *Journal of Cell Biology,* Kepert, I. and Kiebler, M.A. (2013) monitTORing neuronal excitability at the synapse, *Journal of Cell Biology*, 202, 7-9.

   b. Sosanya, N.M., Brager, D., Wolfe, S., Niere, F., and **Raab-Graham, K.F**. (epub: *2014*) Rapamycin reveals an mTOR-independent Repression of Kv1.1Expression during Epileptogenesis, *Neurobiology of Disease*, 73, 96-105.
   c. Sosanya, N.M., Cacheaux, L.P., Workman, E.R., Niere, F., Perrone-Bizzozero, N.I., and **Raab-Graham, K.F.** (2015) Mammalian Target of Rapamycin (mTOR) Tagging Promotes Dendritic Branch Variability through the Capture of Ca2+/calmodulin-dependent protein kinase II α (CaMKIIα) mRNAs by the RNA-binding Protein HuD. *Journal of Biological Chemistry*, 290, 16357-71.
   d. Niere, F.[a], Namjoshi, S.[a], Song, E., Dilly, G.A., Schoenhard, G., Zemelman, B.V., , Mechref, Y., and **Raab-Graham, K.F.** (*2015*) Analysis of proteins that rapidly change upon mTORC1 repression identifies Park7 as a novel protein aberrantly expressed in Tuberous Sclerosis Complex . (*Molecular*

and Cellular Proteomics
;http://www.mcponline.org/content/early/2015/09/29/mcp.M115.055079.full.pdf+html

4. More recently, our studies on NMDAR/mTORC1 regulated protein synthesis has provided insight into therapies to treat major depressive disorder (MDD). MDD is a chronic disease with low remission rates (~33%). Several well-characterized NMDAR antagonists (i.e. Ro-25-6981and ketamine) act as rapid onset antidepressants; however, the mechanism by which this occurs is just beginning to emerge. We made the novel discovery that NMDAR antagonists promote a rapid remodeling of the γ-aminobutyric acid receptor ($GABA_BR$) signaling pathway. We provide evidence that postsynaptic $GABA_BR$ signaling shifts from opening potassium channels (G-protein regulated inwardly rectifying potassium channels or GIRK) to facilitate an increase in dendritic calcium when NMDARs are blocked. The increase in calcium, in turn, activates mTORC1 signaling, specifically in the primary dendrites and leads to protein synthesis of plasticity related proteins (i.e. BDNF and GluA1). Importantly, *in vivo* we demonstrate that $GABA_BR$ activation is required to stimulate mTORC1 kinase activity and protein synthesis. Moreover, antagonism of $GABA_BRs$ block the antidepressant behavioral effect with rapid antidepressants. Our work is the first to show a functional relationship among $GABA_BR$, mTORC1, and Ca^{2+} in regulating anti-depressive behavior.

   a. Workman, E.R., Niere, F., and **Raab-Graham, K.F**. (2013) mTORC1 Dependent Protein Synthesis Underlying Rapid Antidepressant Effect Requires Functional Shift in $GABA_BR$ Signaling, *Neuropharmacology*, 73, 192-203.
   b. Workman, E.R., Haddick, P.C.G., Bush, K, Dilly, G.A., Niere, F., Zemelman, B.V. and **Raab-Graham, K.F**. (*2015*) Rapid Antidepressants Stimulate the Decoupling of $GABA_B$ Receptors from GIRK/Kir3 Channels through increased Protein Stability of 14-3-3η, *Molecular Psychiatry*. 20(3), 298-310.

Invited Cover

   c. Raab-Graham, K.F., Workman, E.R., Namajoshi, S., and Niere, F. (2016) Pushing the threshold: how pharmacology induces homeostasis through protein synthesis to remedy depression. Brain Res. 2016 Apr 26. pii: S0006-8993(16)30215-3. doi: 10.1016/j.brainres.2016.04.020. [Epub ahead of print]

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/18_udJSDlJhQY/bibliography/48346481/public/?sort=date&direction=ascending.

D. Research Support

Ongoing Research Support

IOS – 1355158 National Science Foundation Raab-Graham (PI) 08/01/14-07/31/17
Defining a Role for $GABA_B$ Receptor Signaling in Activation of TORC1 Kinase During Homeostatic Plasticity
Role: PI

DOD-TS130081 Department of Defense Raab-Graham (PI) 04/15/14-04/14/17
Molecular Studies Investigating the Link between Dendritic mRNA Translation and Repression Leading to Epilepsy in TSC
Role: PI

Completed Research Support

Integrated Neuroscience Initiative on Alcoholism (INIA) Raab-Graham (PI) 09/1/13-08/31/15
NIAAA Pilot Grant
Molecular Studies Investigating the Link between Ethanol Blockade of NMDARs and $GABA_BR$ mediated Activation of mTOR Kinase
Role: PI

IOS-1026527 National Science Foundation Raab-Graham (PI) 08/15/10-8/14/14
Posttranscriptional Regulation, a Novel Mechanism for Ion Channel Regulation and Dendritic Excitability
Identify the molecular mechanism for mTOR suppression of Kv1.1

Role: PI