BIOGRAPHICAL SKETCH

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NAME: Rita Marie Cowell, Ph.D.

POSITION TITLE: Associate Professor of Psychiatry & Behavioral Neurobiology

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

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
University of Illinois, Urbana-Champaign, IL	B.S.	05/1997	Biology
University of Michigan, Ann Arbor, MI	Ph.D.	12/2002	Neuroscience
University of Michigan, Ann Arbor, MI	Postdoctoral	08/2006	Neurobiology

A. Personal Statement

Over the past eight years, the Cowell lab has focused on determining the roles for the transcriptional coactivator PGC-1α (peroxisome proliferator activated receptor γ coactivator 1α) in the nervous system. PGC-1α, coined the "master regulator of metabolism" in peripheral tissues, can drive cell-specific transcriptional programs, depending on the complement of transcription factors and coregulators present. A large amount of evidence has emerged demonstrating that PGC-1α expression is reduced in the brain in different neurodegenerative disorders, making it critical to definitively determine its functions in neurons to elucidate its role in the etiology of these diseases. Specifically, the lab is investigating the involvement of PGC-1α and its interacting factors in interneuron and medium spiny neuron dysfunction in animal models of Huntington Disease, Parkinson's Disease, and schizophrenia.

B. Positions and Honors

Positions and Employment

2006-2008 Assistant Professor, research track. Psychiatry and Behavioral Neurobiology, University of Alabama, Birmingham, Alabama.
2008-present Assistant Professor, tenure track. Psychiatry and Behavioral Neurobiology, University of Alabama, Birmingham, Alabama. Secondary appointments in Cell Biology, Psychology, and Neurobiology. Research scientist, Civitan International Research Center and Center for Glial Biology in Medicine.
2014-present Associate Professor, tenure track. Psychiatry and Behavioral Neurobiology, University of Alabama, Birmingham, Alabama.

Other Experience and Professional Memberships

1997-present Society for Neuroscience
2003-2012 Endocrine Society
2003-present American Association for the Advancement of Science
2013-present American College of Neuropsychopharmacology (Associate Member)

Honors and Awards

1994 Howard Hughes Fellowship for Undergraduate Research
1997 Univ. Illinois Med. Scholars Prog. Undergrad. Research Recognition Competition Award
2001 Pfizer Grad. Student Research Award, Dept. Pediatrics, University of Michigan
2002 Outstanding Student Publication Award, Neuroscience Program, University of Michigan
2002 Overall Excellence in Research and Service Award, Prog. Biomedical Sciences, Univ. Mich.
2003 Peripheral Nerve Society Travel Award, biannual meeting, Banff, Alberta

2004 Fine Science Tools Postdoctoral Travel Award for the 34th Annual SFN meeting, Univ. Mich.
2004 Endocrinology Canada Trainee Travel Award for Endocrinology Summit 2004
2005 Travel award, Faculty Horizons Workshop, Univ. Maryland, Baltimore County. NSF ADVANCE
2005 Committee on Women in Neuroscience National Travel Award to attend the 35th SFN meeting
2008 Early Career Travel Award, American College of Neuropsychopharmacology, Scottsdale, AZ
2010 Chairman's Special Commendation for Research Excellence, Dept. Psychiatry, UAB
2011 McNulty Civitan Scientist Award, Civitan International Foundation

C. Contribution to Science

1. When I began my PhD work in 1997, the idea that inflammation could influence the progression of brain injury was a relatively new one. My thesis work provided some of the first evidence for the production of inflammatory mediators such as chemokines and complement components by microglia in response to brain injury in vivo. I went on to demonstrate that the receptors for some of these inflammatory mediators are expressed on neurons themselves and that reducing the availability of systemic complement components can protect the brain from ischemia-induced neuronal injury. During this time, confocal microscopy technology was becoming mainstream, and I developed and honed my skills as a microscopist and neuroanatomist. These are skills that I have used throughout my career, skills that I pass on to all of my trainees, as the majority of my studies to date have involved defining unique characteristics of sparsely distributed brain cell populations.

a. **Cowell RM**, Xu H, Galasso JM, Silverstein FS. (2002) Hypoxic-ischemic injury induces macrophage inflammatory protein-1α expression in immature rat brain. ***Stroke.*** 33:795-801. PMID: 11872906.
b. **Cowell RM**, Silverstein FS. (2003) Developmental changes in the expression of chemokine receptor CCR1 in the rat cerebellum. ***J. Comp. Neurol.*** 457:7-23. PMID: 12541321.
c. **Cowell RM**, Plane JM, Silverstein FS. (2003) Complement activation contributes to hypoxic-ischemic brain injury in neonatal rats. ***J. Neurosci.*** 23:9459-68. PMID: 14561876.
d. **Cowell RM**, Xu H, Parent JM, Silverstein FS. (2006) Microglial expression of chemokine receptor CCR5 during rat forebrain development and after perinatal hypoxia-ischemia. ***J. Neuroimmunol.*** 173:155-65. PMID: 16516309.

2. Reduction in expression of the transcriptional regulator peroxisome proliferator-activated receptor γ coactivator-1α (PGC-1α) has been documented in a number of neurological disorders, yet its role in the pathophysiology of these disorders is not known. The initial assumption was that PGC-1α was a ubiquitous regulator of transcriptional programs for mitochondrial function and biogenesis; however, my lab's work has demonstrated that PGC-1α is a key regulator of parvalbumin (PV)-positive interneuron function by driving the expression of PV, metabolic genes required for maintenance of firing rate, and synaptic molecules that regulate synchronous neurotransmitter release. This work has redefined the field's view of PGC-1α's roles in the central nervous system, shaping how neuroscientists view the cell-specific control of gene expression and the functional consequences of PGC-1α deficiency in neurological disorders.

a. **Cowell RM**, Blake KR, Russell JW. (2007) Localization of the transcriptional coactivator PGC-1α to GABAergic neurons during maturation of the rat brain. ***J. Comp. Neurol.*** 502:1-18. **Cover image.** PMID: 17335037.
b. Lucas EK, Markwardt S, Gupta S, Meador-Woodruff JH, Lin JD, Overstreet-Wadiche L, **Cowell RM**. (2010) Parvalbumin deficiency and GABAergic dysfunction in mice lacking PGC-1α. ***J. Neurosci.*** 30:7227-35. PMID: 20505089. PMCID: 2888101.
c. Dougherty SE,* Bartley AF,* Lucas EK, Hablitz JJ, Dobrunz LE,' **Cowell RM**.' (2014) Mice lacking the transcriptional coactivator PGC-1α exhibit alterations in inhibitory synaptic transmission in the motor cortex. ***Neuroscience*** 271:137-48. PMID: 24769433. PMCID: 40688733. *Contributed equally. 'Co-corresponding authors.
d. Lucas EK, Dougherty SE, McMeekin LJ, Reid CS, Dobrunz LE, West AB, Hablitz JJ, **Cowell RM**. (2014) PGC-1α provides a transcriptional framework for synchronous neurotransmitter release from parvalbumin-positive interneurons. ***J. Neurosci.*** 34(43):14375-87. PMID: 25339750. PMCID: 4205559.

3. Based on the observation of PGC-1α expression in parvalbumin-positive interneurons (PV-INs) and the reduction in PGC-1α expression in Huntington Disease, we postulated that PV-INs would be vulnerable to dysfunction in HD. While some descriptive evidence supported this hypothesis, our work was the first to show

that expression of mutant huntingtin within PV-positive neurons could cause a hyperactive locomotor response (similar to patients with HD) and a loss of inhibitory tone in the motor cortex. This is surprising considering the long-standing hypothesis for selective vulnerability of medium spiny neurons of the striatum, yet these data complement emerging findings of cortical pathology in this disorder. In addition, our work with different models of HD indicates that the soluble form of mutant huntingtin (as opposed to the aggregated form) is associated with neuronal dysfunction, providing support for the hypothesis that inclusion formation may act to attenuate the toxic effects of mutant huntingtin.

a. Dougherty SE, Reeves JL, Lucas EK, Gamble KL, Lesort M, **Cowell RM**. (2012) Disruption of Purkinje cell function prior to huntingtin accumulation and cell loss in an animal model of Huntington Disease. ***Exp. Neurol.*** 236:171-8. PMID: 22579526. PMCID: 3367067.
b. Dougherty SE, Reeves JL, Lesort M, Detloff PJ, **Cowell RM**. (2013) Purkinje cell dysfunction and loss in a knock-in model of Huntington Disease. ***Exp. Neurol.*** 240:96-102. PMID: 22579526. PMCID: 3552014.
c. Dougherty SE, Hollimon J, McMeekin LJ, Bohannon AS, West AB, Lesort M, Hablitz JJ, **Cowell RM**. (2014) Hyperactivity and cortical disinhibition in mice with restriction of mutant huntingtin expression to parvalbumin-positive cells. ***Neurobiol. Disease*** 62:160-71. PMID: 24121117. PMCID: 3877729.

4. As part of a collaborative effort with Dr. Andrew West (Associate Professor, Dept. Neurology, University of Alabama at Birmingham), I was assisting with the cell-specific localization of the Parkinson's Disease (PD) susceptibility gene LRRK2 (leucine-rich repeat kinase 2) in the brain. In preliminary immunohistochemical studies, I found that immunoreactivity for LRRK2 was concentrated in microglia in the brain after intrathecal injection of lipopolysaccharide. In combination with the strong in vitro evidence from the West lab showing that LRRK2 mutations exacerbate inflammation, these findings have been extremely influential in shaping the field's view of LRRK2's role in inflammation and the progression of PD. I went on to assist the West lab with localization studies and confocal microscopy and found that the highest concentration of LRRK2 in the normal brain is within medium spiny neurons (MSNs) of the striatum, suggesting that LRRK2's pathogenic site of action may be in MSNs instead of the substantia nigra; these collaborations resulted in four co-authorships.

a. Moehle MS, Webber PJ, Tse T, Sukar N, Standaert DG, DeSilva TM, **Cowell RM**, West AB. (2012) LRRK2 inhibition attenuates microglial inflammatory responses. ***J. Neurosci.*** 32:1602-11. PMID: 22302802. PMCID: 3532034.
b. Davies P, Hinkle KM, Sukar NN, Sepulveda B, Mesias R, Serrano G, Alessi DR, Beach TG, Benson DL, White Iii CL, **Cowell RM**, Das SS, West AB, Melrose HL (2013) Comprehensive Characterization and Optimization of Leucine Rich Repeat Kinase 2 (LRRK2) Monoclonal Antibodies. ***Biochem. J.*** 453(1):101-13. PMID: 23560750. PMCID: 3682752.
c. Fraser KB, Moehle MS, Webber PJ, Daher JPL, Williams JY, Stewart CA, Yacoubian TA, **Cowell RM**, Dokland T, Ye T, Chen D, Siegal GP, Galemmo RA, Tsika E, Moore DJ, Standaert DJ, Kojima K, Mobley JA, West AB (2013) LRRK2 secretion in exosomes is regulated by 14-3-3***. Human Mol. Genetics*** 22:4988-5000. PMID: 23886663. PMCID: 3836478.
d. West AB,* **Cowell RM**,* Daher JPL, Moehle MS, Melrose H, Standaert DG, Volpicelli-Daley LA. (2014) Differential LRRK2 expression in the cortex, striatum, and substantia nigra in transgenic and nontransgenic rodents. ***J. Comp. Neurol.*** 522:2465-80. PMID: 24633735. PMCID: 4076169. *Contributed equally to this manuscript.

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/collections/bibliography/41160475/

D. Research Support

Ongoing Support

5R01 NS070009-05 Cowell (PI) 04/01/2010-03/31/2016
NINDS $192,610
PGC-1α and GABAergic Dysfunction in Huntington Disease

The main goals of this project are to determine the roles of PGC-1α in parvalbumin-positive interneuron function in the striatum and motor cortex in normal mice and in animal models of Huntington Disease.
Role: PI

1R01MH098534-01 Dobrunz (PI) 07/01/2012-06/30/2017
NIMH $250,000
Interneuron Dysfunction Alters the Dynamics of the Inhibition-Excitation Balance

This project investigates dynamic changes in the balance of inhibition and excitation in the hippocampus in an animal model of interneuron transcriptional dysfunction.
Role: Co-investigator (0.6-person months)

Completed Support (within the last three years)

Individual Research Grant Cowell (PI) 06/01/2012-010/01/2014
Tourette Syndrome Association $75,000
The Impact of Neonatal Hypoxia on the Transcriptional Regulation of Basal Ganglia Development

The main goals of this project are to determine how neonatal hypoxia 1) disrupts interneuron and medium spiny neuron-specific gene expression in development and 2) influences developmental establishment of normal motor coordination, vocalization, and grooming.
Role: PI

K01 MH077955-05 Cowell (PI) 08/31/2007-04/30/2012
NIMH $126,701
Transcriptional Regulation of Metabolism in Schizophrenia

The main goals of this project were to identify the roles of the transcriptional coactivator PGC-1α in metabolic gene expression in cell culture and animal models, to investigate how changes in histone acetylation and/or DNA methylation influence PGC-1α expression and activity, and to determine whether PGC-1α and PGC-1α-target gene expression is altered in postmortem tissue from patients with schizophrenia.
Role: PI