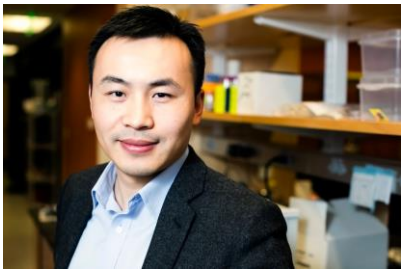
Dong Kong, PhD

Assistant Professor of Neuroscience
Department of Neuroscience
Tufts University School of Medicine
Co-Director of Transgenic Core, Boston Nutrition & Obesity Research Center (BNORC)



The long-term interest of our laboratory is to bridge molecular, cellular, and system approaches to decipher the neuronal modulatory and circuitry mechanisms underlying metabolic and nutritional regulation. By leveraging and combining a cornucopia of cutting-edge technologies, ranging from genetically engineered mouse models, recombinant viral vectors and viral tracing system, optogenetic and pharmacogenetic approaches, patch-clamp electrophysiology, to 2-photon laser scanning microscopy and 2-photon laser uncaging methods (2PLSM/2PLU), we are interrogating the following questions: 1) how neurons in the central nervous system translate their intrinsic firing properties to the controlling of feeding behaviors and metabolic regulations, and what circuits are involved; 2) how metabolic and nutrient signals, including circulating metabolites, hormones, and neuropeptides, act on circuit neurons, shape their firing outputs, and modulate related synaptic neurotransmission; and 3) what kinds of molecules, ion channels, or cellular signaling pathways are rooted to bear these physiological processes and how their dysfunctions contribute to the pathogenesis of disorders in both metabolism and cognition. Understanding these above questions will provide novel insights on the treatment and prevention of various human diseases related to metabolic and mental dysfunction.

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Kong, Dong

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

POSITION TITLE: Assistant Professor of Neuroscience

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
Nanjing University, Nanjing, China	B.Sc.	06/01	Biochemistry
MARC, Nanjing University, Nanjing, China	Ph.D.	06/06	Genetics
Van Andel Research Institute (Exchange PhDstudent), Grand Rapids, MI		11/02	Genetics
Harvard Medical School (Exchange PhD student), Boston, MA		05/04	Mouse genetics
Beth Israel Deaconess Medical Center/Harvard Medical School, Boston, MA	Postdoc	09/06	Hypothalamus
Dept. of Neurobiology/Harvard Medical School, HHMI, Boston, MA	Postdoc	10/11	2-photon, synaptic plasticity

A. Personal Statement

During my PhD program, I was trained in mouse genetics and cellular and molecular biology, and I established and deployed a variety of genetic mouse models, by using both forward and reverse mouse genetic approaches to study gene function. This work inspired my postdoctoral research to use genetically engineered mice, especially those based on Cre-loxP system, to study the link between neurobiological processes and physiological responses. I joined the laboratory of Professor Brad Lowell at Beth Israel Deaconess Medical Center and Harvard Medical School, as postdoctoral fellow and later as Instructor, to acquire and develop new skills necessary to study hypothalamic circuits. Since I joined Dr. Lowell's group, I have embarked on many mouse-engineering projects and the genetic tools that I established allowed us to specifically perturb molecular pathways in specific hypothalamic neurons, and to assess their functions in controlling glucose homeostasis, energy expenditure, and feeding behaviors. Later, one of my findings on glutamatergic transmission in hypothalamic AgRP neurons and their dendritic spines made me realize how little is known about the synaptic plasticity in neural circuits controlling metabolism. To purse this line of research and being supported by an NIH/NIDDK K01 grant, I joined Dr. Bernardo Sabatini's lab at the Department of Neurobiology, Harvard Medical School and HHMI, where I have acquired further trainings in electrophysiology, optogenetics, 2-photon laser scanning microscopy, Ca^{2+} imaging, and 2-photon laser uncaging technology, which are the advanced approaches to study synaptic transmission and neuronal functions. My prior experience in genetic mouse engineering, metabolism, electrophysiology, opto- and pharmaco-genetics, 2-photon laser imaging microscopy, together with my long-term interest in brain-based metabolism regulation, put me in a unique position to address the questions underlying metabolism-related neuromodulaiton, its physiologic functions, and its pathologic roles in human disorders. In 2013, I was offered a competitive package and an internally promoted position at Harvard Medical School to establish my independent research. Instead, I decided to join the faculty of Tufts Medical School, which I believe could offer me a much larger platform to pursue my research. My laboratory at Tufts was opened in 2014. We are now employing multidisciplinary approaches and establishing new technologies to decipher the neural circuits and synaptic plasticity that are subject to metabolic regulation. Regarding the mentoring experience, I have mentored 6 postdoc fellows /visiting scholars, 5 PhD students, and 9 research assistants in the past 5 years.

1. **Kong D,** Tong QC, Ye C, Koda S, Fuller PM, Krashes M, Vong L, Ray R, Olson D, Lowell BB. GABAergic RIP-Cre Neurons in the Arcuate Nucleus Selectively Regulate Energy Expenditure**.** ***Cell*****.** 2012, 151(3): 645-657. PMCID: PMC3500616
2. Liu T, **Kong D***, Shah BP, Ye C, Koda S, Saunders A, Ding JB, Yang Z, Sabatini BL, Lowell BB. Fasting Activation of AgRP Neurons Requires NMDA Receptors and Involves Spinogenesis and Increased Excitatory Tone. ***Neuron***. 2012, 73(3): 511-22. (* **Co-first author)** PMCID: PMC3278709
3. **Kong D**, Vong L, Parton LE, Ye C, Tong QC, Hu X, Choi B, Brüning JC, Lowell BB. Glucose Stimulation of Hypothalamic MCH Neurons Involves K_{ATP} Channels, is Modulated by UCP2, and Regulates Peripheral Glucose Homeostasis. ***Cell Metabolism***. 2010, 12(5): 545-52. PMCID: PMC2998191
4. Huang H, **Kong D**, Byun KH, Ye C, Koda S, Lee DH, Oh BC, Lee S, Lee B, Zabolotny JM, Kim MS, Bjorbaek C, Lowell BB, Kim YB. Rho-kinase Regulates Energy Balance by Targeting Hypothalamic Leptin Receptor Signaling. ***Nature Neuroscience*****.** 2012. 15(10): 1391-8. PMCID: PMC3458121
5. Kraus D, Yang Q, **Kong D**, Banks AS, Zhang L, Rodgers JT, Pirinen E, Pulinilkunnil TC, Gong F, Wang Y, Cen Y, Sauve AA, Asara JM, Peroni OD, Monia BP, Bhanot S, Alhonen L, Puigserver P, Kahn BB. Nicotinamide N-Methyltransferase (NNMT) Knockdown Protects Against Diet-induced Obesity. ***Nature.*** 2014. 508(7495):258-62. PMCID: PMC4107212
6. Pekkurnaz G, Trinidad JC, Wang X, **Kong D**, Schwarz TL. Glucose Regulates Mitochondrial Motility via Milton Modification by O-GlcNAc Transferase. ***Cell.*** 2014. 158(1): 54-68. PMCID: PMC4224014

B. Positions and Honors

Positions and Employment

09/2006-01/2011	Postdoctoral Research Fellow, Department of Medicine, Division of Endocrinology, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA
01/2011-12/2013	Instructor in Medicine, Department of Neurobiology, Harvard Medical School; Department of Medicine, Division of Endocrinology, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA
09/2010-present	Co-Director, Transgenic and Gene Knockout Core Boston Nutrition Obesity Research Center (BNORC)
01/2014-present	Assistant Professor of Neuroscience, Department of Neuroscience, Tufts University School of Medicine, Boston, MA

Other Experience and Professional Memberships

2008-	American Diabetes Association
2010-	American Society for Neuroscience
2010-	Boston Nutrition Obesity Research Center (BNORC)
2010-	Boston Area Diabetes Endocrinology Research Center (BADERC)
2012-	American Heart Association
2012-	The Obesity Society
2010-	BNORC Pilot & Feasibility Grant Review Committee
2016-	Chinese American Diabetes Association
2016-	North America Chinese Society for Nutrition

Awards and Honors

2014	Charles H Hood Foundation Child Health Research Award
2013	American Heart Association Scientist Development Award
2013	Harvard Chinese Life Science Annual Distinguished Research Award
2012	Keystone Symposia Scholarship Synapse and Circuit, Steamboat, CO
2012	Boston Nutrition and Obesity Research Center (BNORC) Pilot/Feasibility Grant
2011	Boston Area Diabetes Endocrinology Research Center (BADERC)

	Pilot/Feasibility Grant
2009	Keystone Symposia Scholarship
	Neuronal Control of Appetite, Metabolism and Weight, Keystone
2008-2011	American Diabetes Association Mentor-Based Postdoctoral Fellowship
2006-2007	Sainland Innovative Postdoctoral Fellowship

C. Contribution to Science

1. As a postdoctoral fellow in the lab of Dr. Brad Lowell (Prof. of Medicine, Beth Israel Deaconess Medical Center and Harvard Medical School), I have employed genetically engineered mice to study hypothalamic circuits. During this period of time, I have built up the expertise and applied novel genetic tools to specifically perturb neurobiological pathways that operate in defined sets of hypothalamic neurons, and to investigate their physiological functions in controlling metabolism. For example, I specifically manipulated proteins involved in glucose-sensing pathways in neurons expressing melanin concentration hormone and revealed a novel brain-based mechanism for these neurons to detect glucose change and maintain whole body glucose homeostasis (Kong et al, 2010). In another study, I investigated a unique population of hypothalamic neurons controlling body weight, by modifying mice such that they have a specific defect in releasing the inhibitory neurotransmitter, GABA. Mice with this defect developed marked obesity, which was caused entirely by dysfunctional thermogenesis in brown fat. To expand the use of Cre-loxP mice and to further explore the circuitry behind this thermogenic regulation, I built an AAV stereotaxic injection system in the Lowell lab. This system, especially in combination with the various genetic mice that I have generated, has turned to be extremely powerful and greatly extended our flexibilities to manipulate gene expression in neurons. For example, by using AAV virus carrying the excitatory DREADD, I mapped the subpopulation of neurons controlling thermogenesis to a restricted area in the hypothalamus. I also initiated the optogenetic studies in the Lowell lab. With the state-of-art ChR2-assisted circuit mapping method (CRACM), combined with retrograde tracing, I uncovered a "wiring-diagram" engaged by these neurons to control brown fat activity. These versatile mouse and viral genetic tools, in conjugation with pharmacogenic and optogenetic methods, greatly assisted us in deconvoluting a complex neurocircuit controlling thermogenesis and preventing obesity (Kong et al. 2012). The latter study has also established the premises for the current proposal.

    a. **Kong D**, Vong L, Parton LE, Ye C, Tong QC, Hu X, Choi B, Brüning JC, Lowell BB. Glucose Stimulation of Hypothalamic MCH Neurons Involves K_{ATP} Channels, is Modulated by UCP2, and Regulates Peripheral Glucose Homeostasis. ***Cell Metabolism***. 2010, 12(5): 545-52. PMCID: PMC2998191

    b. **Kong D,** Tong QC, Ye C, Koda S, Fuller PM, Krashes M, Vong L, Ray R, Olson D, Lowell BB. GABAergic RIP-Cre Neurons in the Arcuate Nucleus Selectively Regulate Energy Expenditure. ***Cell***. 2012, 151(3): 645-657. PMCID: PMC3500616
        - *Comment in Cell Metabolism: 16(5):557-8, 2012*
        - *Highlighted by Faculty 1000*

2. The neurons expressing agouti-related peptide (AgRP neurons) in the arcuate hypothalamus are critical drivers of feeding. Their regulation by fast neurotransmitters from other neurons in the brain, however, has been largely overlooked. In a prior study, we have demonstrated that glutamatergic synaptic transmission mediated by NMDARs plays a pivotal role in AgRP neurons and their related feeding behavior (Liu*, Kong* et al, 2012). In particular, I made the observation that AgRP neurons possess dendritic spines, which are 1μm^3 protrusions where the majority of glutamatergic synapses reside and within which glutamate NMDARs operate to control synaptic plasticity. In addition, I found that dendritic spines on AgRP neurons are very dynamic. 24-hour fasting induces remarkable spinogenesis, which is paralleled by, and likely contributes to, enhanced glutamatergic inputs and increased feeding. These observations reveal that, like neurons in the cortex and hippocampus, neurons controlling feeding behaviors are also controlled by synaptic plasticity. This innovative discovery had also inspired my research direction toward the understanding of synaptic mechanisms underlying metabolic regulation. Based on this finding, I have been awarded an NIH/NIDDK K01 grant, which supported me to receive my second training with Dr. Bernardo Sabatini (Prof. of Neurobiology, HHMI and Harvard Medical School), who has been a leading expert in understanding

synaptic functions underlying cognitive and reward-related behaviors. In his lab, I learned to establish and use advanced optical approaches, including 2-photon laser scanning microscopy (2PLSM) and 2-photon laser uncaging method (2PLU) to study neuronal transmission mechanisms. Using these technologies and by combining with my expertise in genetics, I then identified a signaling pathway operating inside of AgRP neurons and governing fasting-induced synaptic plasticity. A manuscript describing the findings is now under review.

a. Liu T, **Kong D***, Shah BP, Ye C, Koda S, Saunders A, Ding JB, Yang Z, Sabatini BL, Lowell BB. Fasting Activation of AgRP Neurons Requires NMDA Receptors and Involves Spinogenesis and Increased Excitatory Tone. ***Neuron***. 2012, 73(3): 511-22. (* **Co-first author)** PMCID: PMC3278709
   - *Comment in Cell Metabolism: 15(3) 275-276, 2012*
   - *Comment in Disease Models & Mechanisms 5(5):574-575, 2012*

b. **Kong D**, Dagon Y, Campbell JN, Guo Y, Yang Z, Kahn BB, Sabatini BL, Lowell BB. A Postsynaptic AMPK→p21-Activated Kinase Pathway Drives Fasting-Induced Synaptic Plasticity in AgRP Neurons. (*Revised at* ***Neuron***) (First and Co-corresponding author)

3. Finally, being a local expert on mouse genetics and Co-director of the Transgenic Core of NIH-funded Boston Nutrition and Obesity Research Center, I have been generating or assisting other investigators on the generation and use of various mouse genetic models and viral vectors. Most of the genetic tools that we generated are now shared from the Jackson Laboratory or Addgene, and have greatly promoted the research in many different areas. Through these genetic tools and other of my expertise, the following publications were made possible.

a. Huang H, **Kong D**, Byun KH, Ye C, Koda S, Lee DH, Oh BC, Lee S, Lee B, Zabolotny JM, Kim MS, Bjorbaek C, Lowell BB, Kim YB. Rho-kinase Regulates Energy Balance by Targeting Hypothalamic Leptin Receptor Signaling. ***Nature Neuroscience*****.** 2012. 15(10): 1391-8. PMCID: PMC3458121
b. Kraus D, Yang Q, **Kong D**, Banks AS, Zhang L, Rodgers JT, Pirinen E, Pulinilkunnil TC, Gong F, Wang Y, Cen Y, Sauve AA, Asara JM, Peroni OD, Monia BP, Bhanot S, Alhonen L, Puigserver P, Kahn BB. Nicotinamide N-Methyltransferase (NNMT) Knockdown Protects Against Diet-induced Obesity. ***Nature.*** 2014. 508(7495):258-62. PMCID: PMC4107212
c. Pekkurnaz G, Trinidad JC, Wang X, **Kong D**, Schwarz TL. Glucose Regulates Mitochondrial Motility via Milton Modification by O-GlcNAc Transferase. ***Cell.*** 2014. 158(1): 54-68. PMCID: PMC4224014
d. Allister EM, Robson-Doucette CA, Prentice KJ, Hardy AB, Sultan S, Gaisano HY, **Kong D**, Gilon P, Herrera PL, Lowell BB, Wheeler MB. UCP2 Regulates the Glucagon Response to Fasting and Starvation. ***Diabetes***. 2013, 62(5): 1623-33. PMCID: PMC3636632
e. Pulinilkunnil T, He H, **Kong D**, Asakura K, Peroni OD, Lee A, Kahn BB. Sympathetic Regulation of AMP-activated Protein Kinase in Brown Adipose Tissue. ***Journal of Biological Chemistry*****.** 2011, 286:8798-8809. PMCID: PMC3059037
f. Hardy AB, Wijesekara N, Genkin I, Prentice K, Bhattacharjee A, **Kong D**, Chimienti F, Wheeler MB. Effects of high-fat diet feeding on Znt8-null mice: differences between beta cell and global knockout of Znt8. ***Am J Physiol Endocrinol Metab***. 2012, 302(9):E1084-96. PMCID: PMC3774340
g. Yan H, **Kong D*,** Ge X, Gao X, Han X. Generation of Conditional Knockout Alleles for PRL-3. ***J Biomed Res***. 2011, 25(6):438-43. (***Co-first author)** PMCID: PMC3596724
h. Angers M, Uldry M, **Kong D**, Gimble JM, Jetten AM. Mfsd2a Encodes A Novel Major Facilitator Superfamily Domain-containing Protein Highly Induced in Brown Adipose Tissue During Fasting and Adaptive Thermogenesis. ***Biochemical Journal*** 2008; 416(3): 347-355. PMCID: PMC2587516
i. Li J, Gu X, Ma Y, Calicchio ML, **Kong D**, Teng YD, Yu L, Crain AM, Vartanian TK, Pasqualini R, Arap W, Liermann TA, Snyder EY, Sidman RL. Nna1 Mediates Purkinje Cell Dendritic Development via Lysyl Oxidase Propeptide and NF-kB Signaling. ***Neuron.*** 2010, 68(1):45-60.

j. Sha H, Xu J, Tang J, Ding J, Gong J, Ge X, **Kong D**, Gao X. Disruption of A Novel Regulatory Locus Results in Decreased Bdnf Expression, Obesity, and Type 2 Diabetes in Mice. ***Physiological Genomics*** 2007; 31(2): 252-263.
k. Wang PF, **Kong D***, VanBrocklin MW, Peng J, Zhang C, Potter SJ, Gao X, Teh BT, Zhang N, Williams BO, and Holmen SL. Simplified Method for the Construction of Gene Targeting Vectors for Conditional Gene Inactivation in Mice. ***Transgenics*** 2005; 4(3): 215-228. (* Co-first author)

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/1Z_1znzr3iRQs/bibliography/47419481/public/?sort=date&direction=ascending

D. Research Support

Ongoing Research Support

1 K01DK094943-01A1 Kong (PI) 07/15/2013-05/31/2016
Dendritic Spines on AgRP Neurons as Communication Hubs
The goal of this study is to study synaptic plasticity in the hypothalamus.
Role: PI

Charles Hood Foundation Award Kong (PI) 08/01/2014-07/31/2016
Mitochondria, Cognitive Defects, and Child Obesity
The goal of this study is to study the dysfunction of mitochondria in obesity-induced cognition problems.
Role: PI

1 R01DK108797-01 Kong (PI) 04/1/2016-03/31/2021
A Neural Circuit of Energy Expenditure Preventing Obesity
The goal of this study is to study a circuit in the hypothalamus that stimulates energy expenditure and prevents diet-induced obesity.
Role: PI

HMS/BIDMC-FNL Core Fund (Kong-PI) 11/2014-
"Tufts-FNL-Neuron-Nutrition Core"
The goal of this fund is to establish a neuron-nutrition core to provide neuron imaging and sequencing facilities at Tufts.
Role: PI

Completed Research Support

2011-2013 Blood glucose control by hypothalamic glucose-sensing neurons
Boston Area Diabetes Endocrinology Research Center (BADERC) P&F Grant
Role: PI
Goal: To identify the glucose-lowering neural transmitters in the hypothalamus

2012-2014 Ghrelin, dendritic spines and synaptic regulation of AgRP neurons
Boston Obesity and Endocrinology Research Center (BNORC) P&F Grant
Role: PI
Goal: To study the synaptic regulation of AgRP neurons by Ghrelin

2013 Synaptic plasticity of AgRP neurons and related feeding control
American Heart Association Scientist Development Award
Role: PI
Goal: To study the synaptic regulation of AgRP neurons in feeding