Dr. Xinfu Guan is a principal investigator in *Nutrition* at the USDA Children's Nutrition Research Center and an assistant professor (tenure-track) of *Nutrition & Metabolism* at Baylor College of Medicine. Dr. Guan's work has been focused on elucidating molecular mechanisms of nutrient-responsive gut hormones, namely glucagon-like peptides (GLP-1/2) and receptors in the control of energy balance and glucose homeostasis specifically in obesity, diabetes and metabolic syndrome. The Guan laboratory (funded by the USDA and NIH) has generated key transgenic mouse lines, employed multiple stable isotopic tracers to quantify tissue-specific insulin sensitivity and postprandial glucose kinetics, and developed MS-based metabolomics to quantify intracellular metabolic fluxes *in vivo*. His work has identified the metabolic function of the brain GLP-2R in food intake and glucose production; and the vasoactive role of the gut GLP-2R in intestinal circulation. Dr. Guan has been selected for the Reeds Outstanding Young Investigator Award by the *American Society for Nutrition (2006)*; the Outstanding Young Investigator Award by the *National Natural Science Foundation of China (2007)*; the New Investigator Award in the Neural Control and Autonomic Regulation by the *American Physiological Society (2012)*; and the Mahesh Award of Excellence in Endocrinology (Postdoc Mentor) by the *American Physiological Society (2016)*.

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: Xinfu Guan

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

POSITION TITLE: Assistant Professor of Pediatrics-Nutrition and Medicine- Diabetes, Endocrinology & Metabolism, Baylor College of Medicine

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
Michigan State University, East Lansing, MI	Ph.D.	2001	Physiology
Baylor College of Medicine, Houston, TX	Postdoc	2004	GI-Nutrition & Endocrinology

A. PERSONAL STATEMENT.

Dr. Guan's work centers on elucidating the physiological roles of glucagon-like peptides (**GLP**) and receptors in the control of energy balance and glucose homeostasis. In particular, he has focused on GLP-2 and GLP-2R that influence energy intake and glucose homeostasis. His specific expertise in molecular endocrinology and metabolic regulation has expanded over the last 10 years, including generating a variety of transgenic mouse lines ($Glp2r^{flox/flox}$ and glucagon-Cre), developing stable isotopic tracer methodology to quantify postprandial glucose kinetics, and dissecting how the gut-brain signals regulate energy balance and glucose homeostasis after gastric bypass. His new evidence indicates that GLP dual activation is an additional molecular target necessary for rapidly improving postprandial glycemic control and insulin sensitivity after gastric bypass, the focus of this RO1 project. As such, he is well positioned to address the specific aims of this R01.

B. POSITIONS AND HONORS.

Professional Positions:

1996-2001 Research Assistant, Department of Animal Science, Michigan State University, East Lansing, MI
2001-2004 Postdoctoral Fellow, USDA/ARS Children's Nutrition Research Center, Department of Pediatrics, Baylor College of Medicine, Houston, TX
2004-2006 Instructor, Department of Pediatrics, Baylor College of Medicine, Houston, TX
2007-present Nutrition Scientist (Principal Investigator), USDA/ARS Children's Nutrition Research Center, Houston, TX
2007-present Assistant Professor (tenure-track faculty), Department of Pediatrics, Baylor College of Medicine, Houston, TX
2007-Present Assistant Professor, Division of Diabetes, Endocrinology & Metabolism, Department of Medicine, Baylor College of Medicine, Houston, TX
2007-Present Visiting Professor of Nutrition, China Ministry of Agriculture Food Industry Center, China Agricultural University, Beijing, China

Selected Awards and Other Professional Activities:

1998 Nutrition Research Achievement Award, BASF Corp.
1998 Annual Biomedicine Research Award (the 1st Place), Michigan State University
2006 The Peter Reeds Outstanding Young Investigator Award, *the American Society for Nutrition*
2006 Honorary Professorship of Nutrition, China Agricultural University, Beijing
2006 NIH NIDDK KO1 Award

2007 Outstanding Young Investigator Award, the National Natural Science Foundation of China
2008 Bristol-Myers Squibb/Mead Johnson Nutrition Award
2010 NIH NIDDK RO3 Award
2011 The Mead Johnson Research Award in Endocrinology and Metabolism Section (Postdoc Mentor), *the American Physiological Society*
2012 The New Investigator Award in the Neural Control and Autonomic Regulation Section, *the American Physiological Society*
2012 The ENDO 2012 Research Summaries Book, *the Endocrine Society*
2012 The Research Recognition Award in Endocrinology and Metabolism Section (Postdoc Mentor), *the American Physiological Society*
2013 The Takeda Travel Award in the Gastrointestinal and Liver (GI&L) Physiology Section (Postdoc Mentor), *the American Physiological Society*
2014 The Research Recognition Award in the Gastrointestinal and Liver (GI&L) Physiology Section (Postdoc Mentor), *the American Physiological Society*
2016 The Virendra B. Mahesh Award of Excellence in Endocrinology in Endocrinology and Metabolism Section (Postdoc Mentor), *the American Physiological Society*

Editorial Board: Austin J Endocrinol Diabetes; Austin J Pediatrics; Diabetes Res; Int J Diabetes Clin Res; J Endoc Disord; J Endocrinol Diabetes Obes; J Endocrinol MetS; J Nutr Disord Ther; J Obes Weight Loss Ther; Obesity

Reviewer: Am J Physiol Endocrinol Metab; J Nutr; Br J Nutr; Eur J Nutr; J Cell Physiol; JCI; Am J Physiol-Cell Physiol; J Nutr Biochem; Endocrinol; Int J Nanomedicine; Int J Obesity; Gastro; Mol Neurob; Molecules; Neurogastroenterol Motil; Neuropeptides; Regul Pept

Reviewer: American Diabetes Association Research Grants

Member: American Gastroenterological Association; American Society for Nutrition; American Physiological Society; the Endocrine Society; Society for Experimental Biology and Medicine; Sigma Xi

C. CONTRIBUTIONS TO SCIENCE

The Guan lab has contributed significantly to our understanding of the physiological role of nutrient-responsive glucagon-like peptide-2 (GLP-2) and receptors in the regulation of energy balance and glucose homeostasis. GLP-2 is co-secreted with GLP-1 from enteroendocrine L cells in the gut and preproglucagon neurons in the brain, and has receptors in the gut and brain. Dr. Guan's work has sought to identify how GLP-2 as a gut-brain peptide conveys nutritional information from the gut to the brain, and to dissect the physiological roles of endocrine vs neural GLP-2 via this gut-brain axis. Dr. Seeley's lab recently identified the bile acid nuclear receptor FXRα as a key molecular target mediating gastric bypass-induced metabolic benefits. The ability of the bile acid membrane receptor TGR5 (in enteroendocrine L cells) to enhance GLP secretion suggests a further functional link to a bile acid-GLP axis in metabolic homeostasis after gastric bypass. This link suggests that GLP dual activation may be an additional molecular target necessary for rapidly improving postprandial glycemic control and insulin sensitivity after gastric bypass, the focus of this RO1 project.

1 The function of GLP-2R in the brain

Through the gut-brain axis, GLP-2 may play a key role in the control of energy intake and glucose homeostasis. The role of GLP-2 has been focused in the gut including promoting intestinal crypt cell proliferation, glucose transport and blood flow. However, the functional relevance of GLP-2 in the brain (extra-gut) to energy intake and peripheral metabolism was less defined. The Guan lab was the first to generate *Glp2r*-floxed mouse line (PMID: 22829581) that has provided a powerful genetic tool to dissect tissue-specific Glp2r action, and discovered that GLP-2R activation in hypothalamic POMC neurons inhibits food intake, slows down gastric emptying, and suppresses hepatic glucose production (PMCID:3469617; PMID:3752162). Moreover, the Guan lab has identified a key signaling pathway for the GLP-2 receptor in the CNS, i.e., GLP-2R interacts with the PI3K regulatory subunit p85α and enhances hepatic insulin sensitivity (PMID: 23823479). The Guan lab was also the first to demonstrate GLP-2 directly excites POMC neurons, regulating the hypothalamic melancortin system (PMID: 23823479). His work was highlighted in the ENDO 2012 Research Summaries Book by *the Endocrine Society*; featured in *Cell Metab* (2013); and selected as the cover stories by *Am J Physiol* (2010; 2012).

a) Shi X, Zhou F, Li X, Chang B, Li D, Wang Y, Tong Q, Xu Y, Fukuda M, Zhao JJ, Li D, Burrin DG, Chan L, **Guan X**. Central GLP-2 enhances hepatic insulin sensitivity via activating PI3K signaling in POMC neurons. Cell Metab. 2013 Jul 2;18(1):86-98. PMCID:3752162. ***Featured in this issue.***

b) **Guan X**, Shi X, Li X, Chang B, Wang Y, Li D, Chan L. GLP-2 receptor in POMC neurons suppresses feeding behavior and gastric motility. Am J Physiol Endocrinol Metab. 2012 Oct 1;303(7):E853-64. PMCID:3469617. ***Highlighted in this issue.***

c) Wang Y, **Guan X**. GLP-2 potentiates L-type Ca^{2+} channel activity associated with stimulated glucose uptake in hippocampal neurons. Am J Physiol Endocrinol Metab. 2010 Feb;298(2):E156-66. PMCID:2822481. ***Selected as the covered in this issue.***

d) Shi X, Li X, Wang Y, Zhang K, Zhou F, Chan L, Li D, **Guan X**. Glucagon-like peptide-2-stimulated protein synthesis through the PI 3-kinase-dependent Akt-mTOR signaling pathway. Am J Physiol Endocrinol Metab. 2011 Mar;300(3):E554-63. PMCID:3279303.

2 The physiological role of GLP-2 in the gut

The Guan lab has also contributed significantly to the functional characterization of GLP-2 in the gut. In addition to the brain, GLP-2R is localized to distinct types of cells in the gut including enteroendocrine cells and enteric neurons, and required for GLP-2 function in the gut (PMID: 16401478). Dr. Guan was the first to identify the vasoactive effect of GLP-2 (PMID: 12851879). This discovery has provided a proof of the concept that GLP-2 is tested clinically to promote intestinal circulation including "GLP-2-mediated increased SMA blood flow in patients with short bowel syndrome" (ClinicalTrials.gov Identifier: NCT00673751) and "The importance of GLP-2 in mesenteric blood flow in humans" (ClinicalTrials.gov Identifier: NCT00273000). Dr. Guan's work and others show that GLP-2 promotes rapid appearance rate of ingested glucose after meal (PMID: 12851879), creating a portal-systemic gradient of glucose required for GLP-1 incretin action via the enteroinsular axis. This evidence has led to our current hypothesis that GLP synergistically improve postprandial glycemic control and insulin sensitivity after gastric bypass.

a) **Guan X**, Karpen HE, Stephens J, Bukowski JT, Niu S, Zhang G, Stoll B, Finegold MJ, Holst JJ, Hadsell D, Nichols BL, Burrin DG. GLP-2 receptor localizes to enteric neurons and endocrine cells expressing vasoactive peptides and mediates increased blood flow. Gastroenterology. 2006 Jan;130(1):150-64. PMID: 16401478.

b) **Guan X**, Stoll B, Lu X, Tappenden KA, Holst JJ, Hartmann B, Burrin DG. GLP-2-mediated up-regulation of intestinal blood flow and glucose uptake is nitric oxide-dependent in TPN-fed piglets. Gastroenterology. 2003 Jul;125(1):136-47. PMID: 12851879.

c) Burrin DG, Stoll B, **Guan X**, Cui L, Chang X, Holst JJ. Glucagon-like peptide 2 dose-dependently activates intestinal cell survival and proliferation in neonatal piglets. Endocrinology. 2005 Jan;146(1):22-32. Epub 2004 Oct 14. PMID: 15486229.

d) Burrin DG, Stoll B, **Guan X**, Cui L, Chang X, Hadsell D. GLP-2 rapidly activates divergent intracellular signaling pathways involved in intestinal cell survival and proliferation in neonatal piglets. Am J Physiol Endocrinol Metab. 2007 Jan;292(1):E281-91. PMID:16954336.

3 Innovative stable isotopic tracer approaches

Hyperinsulinemic euglycemic clamp (**Insulin clamp**) is a golden method to dissect tissue-specific insulin sensitivity at postabsorptive state, such as endogenous glucose production (**EGP**). One crucial metabolic process namely gluconeogenesis cannot be quantified using this conventional, radioactive isotope-based insulin clamp. Thus, the Guan lab has improved the insulin clamp using dual stable isotopic tracers (^2H_2O and 6, 6- $^2H_2$-d-glucose) to quantify hepatic gluconeogenesis (PMID: 23823479), which has provided a diagnostic tool to evaluate insulin-mediated suppression of gluconeogenesis in patients. It is very challenging to sort out endogenous production of glucose vs exogenous intake of glucose during postprandial non- steady state. It is critical to examine the role of endogenous glucagon-like peptides in postprandial glycemic control when they are secreted in response to meal. In general, the molecular mechanisms underlying postprandial glycemic control have not been explored largely in transgenic rodent models. Dr. Guan has devoted his significant effort to developing the state-of-the art stable isotopic tracer technique (PMID: 12042438; PMID: 12851879; PMCID: 3752162) and LC-MS/MS metabolomics (PMID: 26212543) to quantify metabolic fluxes. To quantify postprandial glucose fluxes, the Guan lab has recently developed a triple stable isotopic tracer approach, i.e., an integration of intravenous infusion of 6, 6- $^2H_2$-d-glucose (for assessing EGP), intragastric delivery of U-^{13}C-d-glucose formulated in liquid elementary diet (for assessing appearance rate of ingested glucose derived from meal), and ip injection of ^2H_2O (for defining fractional gluconeogenesis) in rodent models. This triple stable isotopic tracer approach will provide a powerful tool to dissect distinct glucose fluxes at postprandial non-steady state, and allow scientists to elucidate how postprandial glycemic control is regulated using transgenic rodent models. As shown in the preliminary results, the Guan lab has identified that gastric bypass-mediated

rapidly rising appearance of injected glucose is a physiological trigger to initiate a negative neuroendocrine feedback on postprandial glycemic control.

a) Liu X, Lu Y, **Guan X**, Dong B, Chavan H, Wang J, Zhang Y, Krishnamurthy P, Li F. Metabolomics reveals the formation of aldehydes and iminium in gefitinib metabolism. Biochem Pharmacol. 2015 Sep 1;97(1):111-21. PMID: 26212543.
b) **Guan** X, Bequette BJ, Calder G, Ku PK, Ames KN, Trottier NL. Amino acid availability affects amino acid flux and protein metabolism in the porcine mammary gland. J Nutr. 2002 Jun;132(6):1224-34. PMID: 12042438.
c) Bos C, Stoll B, Fouillet H, Gaudichon C, **Guan X**, Grusak MA, Reeds PJ, Burrin DG, Tomé D. Postprandial intestinal and whole body nitrogen kinetics and distribution in piglets fed a single meal. Am J Physiol Endocrinol Metab. 2005 Feb;288(2):E436-46. PMID:15507535.
d) Bos C, Stoll B, Fouillet H, Gaudichon C, **Guan X**, Grusak MA, Reeds PJ, Tomé D, Burrin DG. Intestinal lysine metabolism is driven by the enteral availability of dietary lysine in piglets fed a bolus meal. Am J Physiol Endocrinol Metab. 2003 Dec;285(6):E1246-57. PMID:12851176.

4 Nutritional control of energy homeostasis

One of the Guan lab's goals is to identify food-based nutritional strategy to improve energy homeostasis to prevent and treat obesity and diabetes. His early work demonstrates that dietary chromium improves glucose tolerance (PMID: 10801929). More recently, the Guan lab found that α-lipoic acid increases energy expenditure in aged mice (PMCID:2882509), and nutrient-sensor SIRT1 regulates intestinal function (PMCID:3341113).

a) Wang Y, Shi X, Qi J, Li X, Uray K, **Guan X**. SIRT1 inhibits the mouse intestinal motility and epithelial proliferation. Am J Physiol Gastrointest Liver Physiol. 2012 Jan 15;302(2):G207-17. PMCID:3341113. **S*elected as the cover of this issue.***
b) Wang Y, Li X, Guo Y, Chan L, **Guan X**. alpha-Lipoic acid increases energy expenditure by enhancing adenosine monophosphate-activated protein kinase-peroxisome proliferator-activated receptor-gamma coactivator-1alpha signaling in the skeletal muscle of aged mice. Metabolism. 2010 Jul;59(7):967-76. PMCID:2882509. (Top citation)
c) **Guan X**, Bequette BJ, Ku PK, Tempelman RJ, Trottier NL. The amino acid need for milk synthesis is defined by the maximal uptake of plasma amino acids by porcine mammary glands. J Nutr. 2004 Sep;134(9):2182-90. PMID:15333702.
d) **Guan** X, Matte JJ, Ku PK, Snow JL, Burton JL, Trottier NL. High chromium yeast supplementation improves glucose tolerance in pigs by decreasing hepatic extraction of insulin. J Nutr. 2000 May;130(5):1274-9. PMID: 10801929.

List of Recently Published Work in Dr. Guan's Bibliography:
http://www-ncbi-nlm-nih-gov.ezproxyhost.library.tmc.edu/pubmed/?term=Xinfu+Guan+or+%22Guan+and+Trottier%22

D. RESEARCH SUPPORT

ACTIVE

1) Granting agency: USDA CRIS 6250-51000-054-00D
Start and end dates: 10/01/2013 – 09/30/2018
Project title: **Metabolic Effects of Ghrelin and Glucagon-like Peptide Hormones**
The goal of this grant is to identify the metabolic impact of gut hormones on energy intake. No overlay.
Role of applicant: PI

2) Granting agency: LUCTA Innovation Research Award
Start and end dates: 07/01/2014-06/30/2017
Project title: **Promotion of Intestinal Adaptation by Novel TGR5 Agonists**
The goal of this grant is to determine if novel TGR5 agonists promote intestinal hypertrophy. No overlay.
Role of applicant: PI

PENDING

3) Granting agency: NIH NIDDK

Project title: **Molecular Mechanisms for Glycemic Improvement after Bariatric Surgery**
The goals of this grant are to **a**) define the function of digenic GLP in postprandial glycemic control after vertical sleeve gastrectomy; **b**) determine if the brainstem DVC is the key site for GLP synergistic action in postprandial glycemic control; and **c**) establish the functional role of GLP-mediated neural circuitry in postprandial glycemic control. No overlay.
Role of applicant: PI

COMPLETED:

Granting agency: NIH DK58338 (DDC 2014 Pilot/Feasibility Award)
Start and end dates: 01/01/2014-01/30/2016
Project title: **GLP-2-Directed Metabolic Reprograming and Cell Proliferation in the Gut**
The goal of this grant is to identify if GLP-2 reprograms glucose metabolism in the gut. No overlay.