BIOGRAPHICAL SKETCH

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NAME: Guillaume François Hugues de Lartigue

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

POSITION TITLE: Assistant Professor

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
Royal Holloway, University of London, UK	BSc (hons)	1999-2002	Medical Biochemistry
University of Liverpool, UK	PhD	2002-2007	Cellular and Molecular Physiology
University of Liverpool, UK	Postdoctoral	2007-2008	Cellular and Molecular Physiology
University of California, Davis	Postdoctoral	2009-2011	Endocrinology

A. Personal Statement

My interests and expertise are in the neurobiology and physiology of gut-brain signaling. The overarching focus of my research revolves around identifying signaling pathways of vagal afferent neurons involved in the control of food intake and determining mechanisms by which these are altered in obesity. The vagus is the main neural route by which the gastrointestinal (GI) system communicates to the central nervous system. Current tools available in the field lack the specificity to target sensory neurons, let alone selectively target vagal afferent neurons that innervate the gut. As part of my K99/R00 “Transition to Independence” grant from the National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health, I have developed novel pharmacological, molecular and genetic tools to target and manipulate the function of these previously intractable subset of neurons. I currently have published 27 papers in the field of metabolism including a recent paper in Cell in which we utilized a combinatorial viral approach to target and modulate the activity of previously intractable subsets of vagal sensory neurons based on their site of innervation.

i. Han W, Tellez LA, Perkins MH, Perez IO, Qu T, Ferreira J, Ferreira TL, Quinn D, Liu ZW, Gao XB, Kaelberer MM, Bohórquez DV, Shammah-Lagnado SJ, **de Lartigue G**, de Araujo IE. 2018. A Neural Circuit for Gut-Induced Reward. Cell. 175(3):665-678.e23.

A continuous thread throughout my career has been studying the mechanisms of CCK induced satiation as can be seen in publication 1a-c and 2a,b,d and 3d in section C below. ApoAIV is a necessary co-factor for CCK signaling and therefore the proposed research is a natural extension of my previous work. My role as a co-investigator in this application will be to train and advise on the use of Targeted Recombination of Active Populations (TRAP) technology to assess the causal role of PVN neurons in mediating ApoAIV-induced sympathetic activity. My lab has been using this approach for the past 2 years (see abstract ii) to dissociate the gut-brain circuits involved in fat and sugar reward. Some of this work is included as preliminary data in this research application. I will travel to Ohio to provide hands on training for using this simple yet powerful tool, and help with troubleshooting and experimental design over the course of the grant to ensure that this aim is achieved successfully.

ii. Fats and sugars recruit distinct peripheral neural circuits to the brain. Mcdougle MJ, de Araujo AM, Singh A, **de Lartigue G**. 2019. 27th annual Society for the Study of Ingestive Behavior meeting. Utrecht, Netherlands

iii. Gut brain signaling mediates fat and sugar reward. Mcdougle MJ, de Araujo AM, Singh A, **de Lartigue G**. 2018. 1st Center for Integrative Cardiovascular and Metabolic Diseases meeting. Gainesville Florida

B. Positions and Honors

Employment

2001	Summer Research Program, Procter & Gamble, UK
2001-2002	Research Project, Veterinary Laboratory Association, UK
2002-2007	Doctoral student, University of Liverpool, UK (Mentor: Prof. Dockray)
2003-2006	Teaching assistant, Department of Physiology, University of Liverpool, UK
2007-2008	Medical Research Council funded Postdoctoral Research Associate, University of Liverpool, UK (Mentor: Prof. Dockray)
2009-2011	NIH Postdoctoral Fellow, University California, Davis, USA (Mentor: Dr. Raybould)
2011-2015	Assistant Project Scientist, University California, Davis
2015-2018	Assistant Fellow, John B. Pierce Laboratory, New Haven
2015-2018	Assistant Professor, Yale, New Haven
2018- present	Assistant Professor, University of Florida, Gainesville

Awards and Honors

2002-2007	Wellcome Trust Prize PhD Studentship
Jan 2006	Best Poster Award, Wellcome Trust Conference, London, UK
Nov 2007	Keystone Symposia Scholarship, Keystone
Jan 2008	Bayliss and Starling Society John Calam fellowship
Sept 2008	2008 Burgen Scholar, Academia Europaea
May 2010	Presidential symposium DDW2010
May 2012	Travel award to attend XIIth Little Brain Big Brain meeting
Sept 2012	Best Oral Presentation Award – XIIth Little Brain Big Brain meeting
May 2013	Travel award to attend *17th Neuro-gastroenterology & Motility Scientific Mee*
Oct 2013	Best Oral Presentation Award - *17th Neuro-gastroenterology & Motility Scientific Meeting*
Sept 2014	Travel award to attend XIIIth Little Brain Big Brain meeting
May 2015	Best Abstract – 17th Society for the Study of Ingestive Behavior Meeting
May 2016	Elected to the board of Society for the Study of Ingestive Behavior
Sept 2017	Invited to the board of Peptide
Sept 2018	Invited to advisory board of Appetite
March 2019	NIH ad-hoc study section member DDK-C subcommittee
Oct 2019	NIH ad-hoc study section member DDK-C subcommittee

1) C. Contributions to Science

Vagal afferent neurons exhibit plasticity in response to nutritional status

My doctoral research in the Dockray laboratory demonstrated that vagal afferent neurons, known to signal gastrointestinal information about a meal to the brain, drastically alter expression depending on nutritional status. Specifically I found that under fed conditions, peptide YY receptors and the neuropeptide cocaine- and amphetamine-regulated transcript (CART), both associated with inhibiting food intake were abundantly expressed in vagal afferent neurons (VAN); while after fasting, expression of these proteins were downregulated, and the neuropeptide melanin concentrating hormone (MCH) associated with stimulating food intake was upregulated. In a series of publications, I went on to demonstrate the mechanisms involved in regulating this neurochemical switch at the cellular and molecular level. More recently, I conceived, designed, and supervised work demonstrating that the receptor for the gastrointestinal hormone glucagon-like peptide 1, is localized on the plasma membrane post-prandially, but is internalized with fasting. *Together, these data provide direct evidence that vagal afferent neurons are the first site of integration of meal related signals, and are more than a simple relay system from the gut to the brain.*

a) **de Lartigue G**, Dimaline R, Varro A, Dockray GJ. *Cocaine- and amphetamine-regulated transcript: stimulation of expression in rat vagal afferent neurons by cholecystokinin and suppression by ghrelin*. J Neurosci. 2007 Mar 14;27(11):2876-82. PMID: 17360909.
b) Burdyga G, **de Lartigue G**, Raybould HE, Morris R, Dimaline R, Varro A, Thompson DG, Dockray GJ. *Cholecystokinin regulates expression of Y2 receptors in vagal afferent neurons serving the stomach*. J Neurosci. 2008 Nov 5;28(45):11583-92. PMID:18987194.
c) **de Lartigue G**, Lur G, Dimaline R, Varro A, Raybould H, Dockray GJ. *EGR1 Is a target for cooperative interactions between cholecystokinin and leptin, and inhibition by ghrelin, in vagal afferent neurons*. Endocrinology. 2010 Aug;151(8):3589-99. PMID:20534729.
d) Ronveaux CC, **de Lartigue G**, Raybould HE. *Ability of GLP-1 to decrease food intake is dependent on nutritional status*. Physiol Behav. 2014 Aug;135:222-9. PMID: 24955496.

2) Development of leptin resistance in vagal afferent neuron drives hyperphagia and weight gain

Having demonstrated the cellular and molecular mechanisms by which leptin potentiates CCK-induced satiation in the Dockray lab, I reported during my postdoctoral work in the Raybould lab that vagal afferent neurons of diet-induced obese rats become unresponsive to exogenous leptin. I went on to demonstrate that leptin resistance in vagal afferent neurons coincides with the onset of hyperphagia. Subsequently, I developed a novel conditional knockout mouse lacking leptin receptors selectively in VAN, to mimic VAN leptin resistance in diet-induced obesity. On a chow diet, these conditional knockout mice became hyperphagic, and gained significantly more body weight and adiposity than their wildtype counterparts. *These data provide the first concrete evidence that chronic disruption of gut-brain signaling is sufficient for the development of obesity.*

a) **de Lartigue G**, Lur G, Dimaline R, Varro A, Raybould H, Dockray GJ. *EGR1 Is a target for cooperative interactions between cholecystokinin and leptin, and inhibition by ghrelin, in vagal afferent neurons.* Endocrinology. 2010 Aug;151(8):3589-99. PMID: 20534729.
b) **de Lartigue G**, Barbier de la Serre C, Espero E, Lee J, Raybould HE. *Diet-induced obesity leads to the development of leptin resistance in vagal afferent neurons.* Am J Physiol Endocrinol Metab. 2011 Jul;301(1):E187-95. PMID: 21521717
c) **de Lartigue G**, Barbier de la Serre C, Espero E, Lee J, Raybould HE. *Leptin resistance in vagal afferent neurons inhibits cholecystokinin signaling and satiation in diet induced obese rats.* PLoS One. 2012;7(3):e32967. PMID: 22412960
d) **de Lartigue G**, Ronveaux CC, Raybould HE. *Deletion of leptin signaling in vagal afferent neurons results in hyperphagia and obesity*. Mol Metab. 2014 Jun 27;3(6):595-607. PMID: 25161883.

3) Loss of plasticity in vagal afferent neurons is a crucial mechanism leading to the onset of obesity

I found that the normal switch in the neurochemical phenotype of vagal afferent neurons that occurs in lean rats, is lost following chronic ingestion of a high fat diet for 6 weeks. I demonstrated that in diet-induced obesity expression of proteins associated with satiation remains low in vagal afferent neurons irrespective of the feeding state of the animal; instead, these neurons constitutively express orexigenic receptors and neuropeptides. Specifically, I showed that this loss in plasticity results in blunted postprandial CART expression in vagal afferent neurons and prevents satiation by endogenous CART release from vagal afferent neurons into the nucleus of the solitary tract. I proposed a mechanism by which neuropeptides modulate feeding behavior, and subsequently confirmed that reducing expression of the neuropeptide CART in vagal afferent neurons in vivo results in significant body weight gain and hyperphagia in chow fed rats. *Thus, the loss of vagal afferent plasticity prevents appropriate gut-brain satiation and this is a key event in the development of obesity*.

a) **de Lartigue G**, Barbier de la Serre C, Espero E, Lee J, Raybould HE. *Leptin resistance in vagal afferent neurons inhibits cholecystokinin signaling and satiation in diet induced obese rats.* PLoS One. 2012;7(3):e32967. PMID: 22412960
b) **de Lartigue G**, Ronveaux CC, Raybould HE. *Deletion of leptin signaling in vagal afferent neurons results in hyperphagia and obesity.* Mol Metab. 2014 27;3(6):595-607. PMID: 25161883.
c) **de Lartigue G**. *Putative roles of neuropeptides in vagal afferent signaling*. Physiol Behav. 2014 Sep;136:155-69. PMID: 24650553
d) Lee, S. J., Krieger, J. P., Vergara, M., Quinn, D., McDougle, M., de Araujo, A., Darling, R., Zollinger, B., Anderson, S., Pan, A., Simonnet, E. J., Pignalosa, A., Arnold, M., Singh, A., Langhans, W.,

Raybould, H. E., & **de Lartigue, G**. *Blunted Vagal Cocaine- and Amphetamine-Regulated Transcript Promotes Hyperphagia and Weight Gain*. *Cell Reports*. 2020. *30*(6):2028- 2039. PMID: 32049029

4) Gut microbiota activates gut-brain signaling to regulate host food intake and body weight

As part of a collaborative project with the Mills lab, I demonstrated that *Bifidobacteria infantis* could directly communicate with enteroendocrine cells of the gut via secretion of a soluble factor. B. infantis activate different signaling mechanisms in enteroendocrine cells and have varying beneficial effects on gut permeability depending on the availability of nutrients. The Mills lab had previously demonstrated that in response to milk oligosaccharides B. infantis activate a cassette of genes. I demonstrated that B.infantis reduced internalization of tight-junction proteins in a gut epithelial cell line, and increase the release of gastrointestinal satiation hormone cholecystokinin from an enteroendocrine cell line when the bacteria were grown on milk oligosaccharides compared to when grown on lactose. I went on to show in vivo that B.infantis grown on milk oligosaccharides produced greater level of satiation in rats compared to B.infantis on non-milk oligosaccharides by activating an endocrine-vagal pathway. Finally, I demonstrated that chronic low-doses of lipopolysaccharide, the by-product of gram-negative bacteria that are preferentially found in the gut following western diet ingestion, increases weight gain and food intake by promoting leptin resistance in vagal afferent neurons. *Together these data demonstrate mechanisms by which gut-microbiota interact with the host to directly control food intake and body weight.*

a) **de Lartigue G**, de La Serre CB, Raybould HE. *Vagal afferent neurons in high fat diet-induced obesity; intestinal microflora, gut inflammation and cholecystokinin.* Physiol Behav. 2011 Nov 30;105(1):100-5. PMID: 21376066.
b) de La Serre CB, **de Lartigue G**, Raybould HE. *Chronic exposure to low dose bacterial lipopolysaccharide inhibits leptin signaling in vagal afferent neurons.* Physiol Behav. 2015 Feb;139:188-94. PMID: 25446227
c) Chichlowski M, **de Lartigue G**, German JB, Raybould HE, Mills DA. *Bifidobacteria isolated from infants and cultured on human milk oligosaccharides affect intestinal epithelial function.* J Pediatr Gastroenterol Nutr. 2012 Sep;55(3):321-7. PMID: 22383026.
d) **de Lartigue G**, Boudry G, Hamilton MK, Barile, D, Mills DA and Raybould HE. Activation of gut endocrine cells and the gut-brain pathway by substrate-specific soluble factors released from *Bifidobacteria longum ssp. Infantis.* Am J Physiol Endocrinol Metab. Under review

Complete List of Published Work in MyBibliography:
https://www.ncbi.nlm.nih.gov/myncbi/1FwaRpwPtf4Qn/bibliography/public/

D. Additional Information: Research Support and/or Scholastic Performance

Ongoing research support

R01 DK116004 de Lartigue, Guillaume (PI) 02/05/18 – 01/31/23

Evaluating the therapeutic potential of vagal CART circuitry for treating metabolic syndrome

The aim of this grant is to determine whether restoring CART expression in vagal afferent neurons can cause voluntary reduction in food intake, reduce body weight and sustain weight loss in diet-induced obesity. My role on this application is PI.

NHMRC Oldfield (PI) 09/01/18-08/30/23

The vagus brain and gut-brain interactions: the underpinnings of successful weight loss surgery through recruitment of brown adipose tissue.

The aim of this grant is to determine the role of the sensory vagal fibers that innervate the gut in modulating the beneficial effects of vertical sleeve gastrectomy, one the most effective treatments of obesity. My role on this application is as a consultant

R35 HL150750 Krause (PI) 02/01/20 - 31/1/27

Interogating stress-relieving neural circuits to alleviate cardiovascular disease

This grant consolidates 3 funded R01 grant by Dr. Krause. The proposed work generally encompasses the role of oxytocin in energy homeostasis. My role on this application is a co-investigator.

Completed research support

R21 DK110511 de la Serre (PI) 08/01/16 – 2/1/20

Microbiome-Vagal-Brain signaling: impact on the reward system and food intake

The overall goal of this exploratory grant was to determine the role of gut-microbiota in reward behavior. As part of this project my lab developed novel tools to ablate gut-brain signaling, and map central projections from nodose ganglia into the brain of rats. My role on this application was co-investigator.

R00 DK094871 de Lartigue (PI) 05/01/15 – 04/30/18

The role of vagal afferent neurons in regulating feeding behavior

The aim of this grant was to apply the techniques developed in the K99 phase to determine whether targeting vagal afferent signaling could be used as an effective treatment for obesity. My role on this application was PI.