BIOGRAPHICAL SKETCH

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NAME: Sandoval, Darleen

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

POSITION TITLE: 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
University of New Mexico	BS	6/1993	Exercise Technology
Central Washington University	MS	6/1996	Exercise Science
Arizona State University	PhD	12/2000	Exercise Science
Vanderbilt University	Post-Doc	2001-2004	Endo. & Metabolism

Personal Statement

I am a Professor of Pediatrics and Medicine, and I will *serve as the Associate Director of the Colorado Nutrition Obesity Research Center (NORC)*. I have a well-funded research program, and I have extensive leadership experience in NIH-funded NORC and DRC P30 programs. At the University of Michigan, I was Director of the Animal Studies Core and was on the T32 Advisory Committee for the DRC, and was Associate Director of the Pilot and Feasibility Program for the NORC. When transitioning my lab to CU-AMC, I joined the internal executive committee's for both the NORC and DRC. Thus, I have been *entrenched in NIH-funded NORC and DRC leadership for the last 8 years*. In addition, I have extensive leadership in DEI efforts. I was co-founder and inaugural co-chair of the Women's Interprofessional Network of ADA and am founder and director of the Women Inspiring and Elevating Leadership in Diabetes advocacy group. Lastly, I have NIH-funding focused on supporting mentoring and recruitment of minoritized fellows to obesity research. Given my wealth of research and leadership experience and with my 4 years serving as on the executive committee for the NORC at CU-AMC, I am *ideally suited to work with Drs. MacLean and Bessesen as Associate Director of the Colorado NORC and help Dr. Melanson oversee the NORC's enrichment program*.

2023 was a break-through year for obesity treatment. In addition to bariatric surgery, we now have multiple drugs to treat obesity that are reaching the efficacy of bariatric surgery with multiple additional promising drugs in the pipeline. Like bariatric surgery, these drugs target the gut-brain axis, and the metabolic success and widespread physiological effects of these treatments underscore the critical role of the gut in regulating homeostasis. For the last 20 years, my work has focused on using my expertise as a translational physiologist to study *the role of the gut-brain axis in regulation of metabolism*. There are two underlying themes to my work. One is focused on *understanding the physiology, pharmacology, and pathophysiology of the gut peptide, glucagon-like-peptide-1 (GLP-1)*. Pharmacologically, we have demonstrated critical brain GLP-1 receptors responsible for driving the weight loss associated with GLP-1 analogues. The other focus of my research is on *understanding the mechanisms and consequences of bariatric surgery*. Using novel genetic models, we have found that although intestinal GLP-1 secretion is increased after bariatric surgery, it is pancreatic preproglucagon (the gene that codes GLP-1 and glucagon) that is necessary, while intestinal GLP-1 is dispensable, for regulating glucose homeostasis in health, obesity, and after bariatric surgery. We have also found greater postprandial neuronal activation stemming from neural rather than circulatory signals after bariatric surgery compared to sham surgery animals. Bariatric surgery and GLP-1-targeted therapeutics are the most effective strategies for weight loss and associated metabolic complications but access for both treatments remains a challenge. Continued investment in understanding their efficacy and side effects is

critical for continued therapeutic development as the US becomes more and more obese. NORC programs are key to supporting the continued interest in this research area.

Ongoing and recently completed projects that I would like to highlight include:

NIH K26DK138368
Sandoval (PI)
09/2023 – 08/2027
Training for minoritized individuals in gut-brain axis research

NIH R01DK121995
Sandoval/Patti (MPI)
06/2019-05/2024 (NCE)
Mechanisms of Post-Bariatric Hypoglycemia

NIH P01DK117821
Seeley (PI), Role: Co-I-Lead Project 3
09/2019 – 06/2024
Gut-brain axis in metabolic disease

NIH U54 AG062319 (Co-I Project 3)
Kohrt (PI), Role (Co-I)
09/23 – 08/28
Colorado Specialized Center of Research Excellence: Bioenergetic and Metabolic Consequences of the Loss of Gonadal Function

B. Positions, Scientific Appointments, and Honors

Professional Positions

Aug 2024-present	Associate Director, Nutrition Obesity Research Center, University of Colorado Anschutz Medical Campus
Feb 2024-present	Co-Director, Department of Pediatrics Junior Faculty Award Program, University of Colorado Anschutz Medical Campus
Aug 2024-present	Director of Faculty Wellbeing for Research Intensive Faculty, Department of Pediatrics, University of Colorado Anschutz Medical Campus
Sept 2020-present	Professor with Tenure, Department of Pediatrics, Section of Nutrition, Department of Internal Medicine, Division of Endocrinology, University of Colorado Anschutz Medical Campus.
2017-Aug 2020	Director, Animal Studies Core, Michigan Diabetes Research Center. University of Michigan
Sept 2017-Aug 2020	Associate Professor with Tenure, Department of Surgery, Department of Internal Medicine, & Department of Nutritional Sciences, University of Michigan
Sept 2014 – Sept 2017	Assistant Professor, Department of Surgery, University of Michigan
2010 – Aug 2014	Assistant Professor, Internal Medicine, Division of Endocrinology, University of Cincinnati
2005 – 2009	Research Assistant Professor, Obesity Research Group, Department of Psychiatry, University of Cincinnati
2001 – 2004	NRSA Postdoctoral Fellow, Division of Diabetes, Endocrinology, and Metabolism; Department of Medicine, Vanderbilt University. Supervisor: Stephen N. Davis, M.D.
1996 – 2001	Research Assistant Exercise Science Department (now Department of Kinesiology) Arizona State University. Supervisor: Kathleen S. Matt, Ph.D.
1994 – 1996	Graduate Assistant Exercise Science Department, Central Washington University Supervisor: Leo D'Acquisto, Ph.D.

1994, & 1995	Respiratory Research Institute, Supervisor: Robert C. Roach, Ph.D.
Jun – Aug 1993,	Summer Research Internship for NIH Training Grant (HL07758), The Lovelace

Scientific Appointments

2023-2024	Chair of the Neuroscience Section, The Obesity Society
2023-2024	Chair of the Neuroscience Track, Obesity Week Annual Meeting, The Obesity Society
2022-2023	Chair Elect of the Neuroscience Section, The Obesity Society
2021-present	Founder and Director of Women Inspiring and Leading Diabetes (WIELD), an independent advocacy group
2021– 2024	Endocrine Society Representative on the FASEB Scientific Research Conference review committee
2019-2023	Associate Editor, *JCI Insight*
2017-2020	Co-founder and Inaugural Co-Chair, Women's Interdisciplinary Network, ADA
2016-2019	Editorial Board, *Diabetes*
2018-2019	Endocrine Society, Annual Meeting Steering Committee (Team Lead)
2017-2019	Endocrine Society, Annual Meeting Steering Committee (member)
2016 – 2017	Editorial Board, *Endocrinology*
2015 – 2018	ADA Scientific Sessions Planning Committee: Chair, In vivo, Animals.
2013 – 2017	Regular Committee Member: Integrative Physiology of Obesity and Diabetes Study Section, Center for Scientific Review, National Institutes of Health
2012 – Present	Consulting Editor, *Molecular Metabolism*
2012	Ad Hoc Committee Member: Integrative Physiology of Obesity and Diabetes Study Section, Center for Scientific Review, National Institutes of Health
2009 – 2012	ADA National Research Grant Funding Program Review Committee
2003	Organizing Committee: Diabetes and Exercise Day Symposium

Honors

2015	Selected participant: Early Career Women Faculty Professional Development Seminar, Englewood, CO, USA
2013	Nominee: Helmholtz Young Investigator Diabetes Award, 1st Annual Helmholtz-Nature Medicine Diabetes Conference, Munich, Germany
2000	American Physiological Society Minority Travel Award to Integrative Biology of Exercise Conference
2002 & 2004	American Diabetes Association Travel Award
1999	ACSM/NASA Space Physiology Student Research Award
1989 – 1993	New Mexico Scholars Program Scholarship
1989 – 1993	University of New Mexico Presidential Scholar

C. Contributions to Science

1. Target Organ Responses to Bariatric Surgery
   We have invested considerable efforts in understanding the overall weight-loss-independent metabolic effects of bariatric surgery. We have found that postprandial lipid handling, specifically by the intestine, is improved after VSG. We have also found that FGF15, and specially intestinal FGF15, is necessary for reducing hepatic inflammation after VSG. Our recent work has found that the intestine responds to bariatric surgery by shifting stem cell differentiation towards enteroendocrine cells. Using scRNAseq, we find that specific intestinal cell populations have differential changes in metabolic pathways.

   - Stefater MA, **Sandoval DA**, Chambers AP, Wilson-Pérez HE, Hofmann SM, Jandacek R, Tso P, Woods SC, Seeley RJ. Sleeve Gastrectomy in Rats Improves Postprandial Lipid Clearance by Reducing Intestinal Triglyceride Secretion. Gastroenterology. 141(3):939-949.e1-4, 2011. PMC3163733
   - Myronovych A, Bhattacharjee J, Salazar-Gonzalez RM, Tan B, Mowery S, Ferguson D, Ryan KK, Zhang W, Zhao X, Oehrle M, Setchell KD, Seeley RJ, Sandoval DA, Kohli R. Assessment of the role of FGF15 in mediating the metabolic outcomes of murine Vertical Sleeve Gastrectomy (VSG). Am J Physiol Gastrointest Liver Physiol. 2020 Sep 23; PubMed Central PMCID: PMC7792670.

- Kim KS, Peck BC, Hung YH, Koch-Laskowski K, Wood L, Dedhia PH, Spence JR, Seeley RJ, Sethupathy P, **Sandoval DA.** Vertical sleeve gastrectomy induces enteroendocrine cell differentiation of intestinal stem cells through bile acid signaling. JCI Insight. 2022 Jun 8;7(11):e154302. doi: 10.1172/jci.insight.154302. PMID: 35503251
- Koch-Laskowski K, Kim KS, Bethea M, Fuller KNZ, **Sandoval DA**, Sethupathy P. Intestinal epithelial adaptations to vertical sleeve gastrectomy defined at single-cell resolution. Genomics. 2024 Mar;116(2):110805. doi: 10.1016/j.ygeno.2024.110805. Epub 2024 Feb 1. PMID: 38309446

2. Neurophysiology of GLP-1

Over the last 10y, a large part of my research efforts have focused on understanding the role of the gut hormone, glucagon-like peptide-1 (GLP-1) on glucose homeostasis and how dysregulation of GLP-1 is involved with the onset of type 2 diabetes mellitus. My early work found that GLP-1 receptors, specifically in the arcuate nucleus of the hypothalamus were sufficient to regulate hepatic glucose production but not food intake. This work further clarified that the various populations of GLP-1 receptors within the CNS have divergent functions. We further found that CNS GLP-1 signaling was dependent, not just on nutrient availability, but also nutrient type. Together with collaborators, Randy Seeley and David D'Alessio, we invested in the generation of multiple mouse models targeted to the GLP-1 system including the ability to perform targeted tissue-specific gain- or loss-of-function of the GLP-1 receptor and the gene preproglucagon which makes GLP-1. Our work recently demonstrated that intestinal GLP-1 is dispensable while pancreatic GLP-1 is necessary for regulation of glucose homoeostasis. We hypothesize that pancreatic GLP-1 acts in a paracrine fashion to regulate insulin secretion.

- **Sandoval, DA**, D'Alessio, D, Woods, SC, Seeley, RJ Arcuate GLP-1 receptors regulate glucose homeostasis but not food intake. *Diabetes*. 2008 Aug;57(8):2046-54. PMC2494674
- Sisley, S, Gutierrez-Aguilar, R, Scott, M, D'Alessio, DA, **Sandoval, DA**, Seeley, RJ. CNS GLP-1R mediate anorectic, not glucose-lowering, effects of liraglutide. J. Clin. Invest. 2014, 2;124(6):2456-63. PMC4038572
- Chambers, A.P., Sorrell, J., Haller, A., Roelofs, K., Hutch, C.R., Kim, K.S., Gutierrez-Aguilar, R., Li, B., Drucker, D.J., D'Alessio, D.A., Seeley, R.J., **Sandoval, D.A.** The role of pancreatic preproglucagon in glucose homeostasis in mice. Cell Metab. 2017 Apr 4; 25(4):927-934.
- Kim KS, Hutch CR, Wood L, Magrisso IJ, Seeley RJ, Sandoval DA: Glycemic effect of pancreatic preproglucagon in mouse sleeve gastrectomy. JCI Insight 4(20): 2019.

3. The regulation and role of GLP-1 in Bariatric Surgery

My early work in bariatric surgery found equivalent improvements in hepatic insulin sensitivity and equivalent increases in postprandial GLP-1 between two different bariatric surgeries, the roux-en-Y gastric bypass (RYGB), and the vertical sleeve gastrectomy (VSG). In addition, I have established that VSG causes rapid gastric emptying and the chronic intestinal adaptations that are a key to the increase in GLP-1 with surgery. Our current work finds that these intestinal adaptations include a shift towards enteroendocrine differentiation of intestinal stem cells. We also find that this occurs via bile acid signaling.

- Chambers AP, Jessen L, Ryan KK, Sisley S, Wilson-Pérez HE, Stefater MA, Gaitonde SG, Sorrell JE, Toure M, Berger J, D'Alessio DA, Woods SC, Seeley RJ, **Sandoval DA**. Weight-Independent Changes in Blood Glucose Homeostasis After Gastric Bypass or Vertical Sleeve Gastrectomy in Rats. Gastroenterology. 141(3):950-8, 2011. PMC3163733
- Chambers, AP, Smith, EP, Begg, DP, Grayson, BE, Sisley, S, Greer, T, Sorrell, J, Lemmen, L, LaSance, K, Woods, SC, Seeley, RJ, D'Alessio, DA, **Sandoval, DA**. Regulation of Gastric Emptying Rate and its Role in Nutrient-Induced GLP-1 Secretion in Rats after Vertical Sleeve Gastrectomy. Am J Physiol Endocrinol Metab. 306(4):E424-32, 2014, Epub 2013 Dec 24. PMC3923088
- Kim KS, Hutch CR, Wood L, Magrisso IJ, Seeley RJ, Sandoval DA: Glycemic effect of pancreatic preproglucagon in mouse sleeve gastrectomy. JCI Insight 4(20): 2019.
- Kim, K-S, Peck, BC, Hung, Y-H, Koch-Laskowski, K, Wood, L., Dedhia, PH, Spence, JR, Seeley, RJ, Sethupathy, P, Sandoval, DA. Vertical sleeve gastrectomy induces enteroendocrine cell differentiation of intestinal stem cells through bile acid signaling. JCI Insight. 2022 Jun 8;7(11):e154302. doi: 10.1172/jci.insight.154302. PMID: 35503251

4. Biological sex differences in metabolism

Since my graduate work I have been interested in the sexual dimorphisms in metabolic response to stress. During my postdoctoral fellowship at Vanderbilt University, my research demonstrated that estradiol causes women and male rats to have a blunted stress hormone response to hypoglycemia. In rats, I further delineated that this was through central mechanisms. I then went on to determine that while females were less responsive to a low glucose challenge, they have greater feeding and metabolic responses to low levels of fatty acids. Our latest work focuses on the impact of biological sex on metabolic responses to bariatric surgery. We find that the surgery-induced changes in hepatic gene expression and triglyceride levels are blunted in female vs. male rats and mice. This latter work is translationally important as 80% of bariatric surgery patients are women but the vast majority of preclinical work is in males.

- **Sandoval, DA**, Ertl, AC, Richardson, MA, Tate, DB, and Davis, SN. Estrogen Blunts Neuroendocrine And Metabolic Responses To Hypoglycemia. Diabetes, 52(7):1749-55, 2003.
- **Sandoval DA**, Ryan, KK, de Kloet, AD, Woods, SC, Seeley, RJ. Female Rats Are Relatively More Sensitive To Reduced Lipid versus Reduced Carbohydrate Availability. Nutrition and Diabetes. 2, e27 2012.
- Grayson BE, Gutierrez-Aguilar R, Sorrell JE, Matter EK, Adams MR, Howles P, Karns R, Seeley RJ, **Sandoval DA**: Bariatric surgery emphasizes biological sex differences in rodent hepatic lipid handling. Biol Sex Differ. 8: 4, 2017. PMID28149499/PMC5273842
- Hutch CR, Stelmak D, Kanke M, Koch-Laskowski K, Cummings B, Griffin C, Leix K, Sethupathy P, Singer K, **Sandoval DA.** Diet-dependent sex differences in the response to vertical sleeve gastrectomy. Am J Physiol Endocrinol Metab. 2021 Jul 1;321(1):E11-E23. doi: 10.1152/ajpendo.00060.2021. Epub 2021 May 17.

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