BIOGRAPHICAL SKETCH

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NAME: Leiter, James C.

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

POSITION TITLE: Professor of Physiology and Neurobiology and 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
Dartmouth College	B.A.	07/1975	Chemistry
Dartmouth Medical School	M.D	07/1979	Medicine

A. Personal Statement

My research focus is Neuroscience, especially oxidant neuronal injury, autonomic neuroscience and neuronal network development and function. My studies extend from clinical studies in human patients to comparative studies of cell physiology in vertebrates and invertebrates and involve methods ranging from voltage clamp studies to clinical trials to mathematical modelling. I have been studying the use of deep brain stimulation for decades. I was particularly interested in using neurotransmitters as the feedback signal for feedback-controlled DBS – a contrarian view since feedback control at the present time is based on electrical activity. Hence, electrodes that provide both multiple chemical signals simultaneously from locations in the brain relevant diagnostically and therapeutically in a variety of neuropsychiatric disorders is extremely interesting and relevant to my previous studies in animals and longstanding research interests, especially in disorders where the primary defect is neurochemical (and not electrical) like Parkinson's Disease.

I have one other highly relevant experience. Starting about 2005, I began consulting for medical device companies. I started as an individual consultant, became Chief Medical Officer at a boutique consulting firm, Maxis, which was subsequently purchased by Avania, a large contract research organization. It turned out that my knowledge of physiology, experimental design, and statistical analysis had great value to these companies. I have presented at the FDA in innumerable presubmissions and shepherded many devices through the 510k, de novo, and PMA processes as these companies, generally start-ups, sought approval for their devices. In this process, I also designed numerous safety, pilot and pivotal trials, often using Bayesian analytical methods. I am familiar with and capable of organizing and executing the development processes for biomedical start-up companies.

<u>Ongoing and recently completed projects that I would like to highlight include:</u>

R01DA047637 Lu (PI) 07/01/2020-05/31/2025
NIH/NIDA
Characterization of Novel Neural Respiratory Circuit to Counter Opioid-Induced Respiratory Depression
These studies will provide an anatomical and electrophysiological characterization of the respiratory circuit within the cervical spine and provide practical information for the treatment of opioid-induced respiratory depression.
Role: Co-Investigator

UH3NS119772 Lu (PI) 08/01/2021-07/31/2026
NIH/NINDS
Stimulation of Novel Spinal Respiratory Circuit to Restore Breathing in Ventilator-Dependent Patients with SCI.
Respiratory failure due to neurological conditions, such as spinal cord injury, is treated with mechanical ventilation, which may result in significant mortality and morbidity. Our previous studies demonstrated that

epidural stimulation can be used to control the excitability of localized neural circuits in the cervical spine such that respiratory function can be modulated and enhanced. The proposed studies will investigate the safety and feasibility of using high-density epidural stimulation to target the cervical respiratory circuit and restore respiratory function in patients with spinal cord injury.
Role: Co-Investigator

R01HD100823 Dymecki (PI) 09/04/2020 – 08/31/2025

NIH/NICHD
Does neurotransmitter plasticity of para-serotonergic neurons augment autoresuscitation following perinatal stress and buffer SIDS risk?
We propose deep functional and molecular characterization of para- serotonergic neurons, motivated by their potential as a therapeutic target for pediatric disorders involving cardiorespiratory dysfunction.
Role: Co-investigator

2042544 Andreescu (PI) 05/01/2021 - 04/30/2024
NSF
Collaborative research: a multiplexed microbiosensing platform for understanding real time neurotransmitter dynamics in the brain
The project will develop biosensing devices that incorporate nanoparticles as oxygen donors and redox active catalysts bound to or embedded in electrode surfaces for in vivo monitoring of neuronal activity. The detection depends on amperometry as enzymes embedded in the electrode surface provide analyte specificity.
Role: Co-investigator

Renal Research Institute Leiter (PI) 01/01/2023–12/31/2023
Validation of a model of dynamic regulation of intravascular volume during hemodialysis
Role: PI
This is a computer modeling project in which we implemented the revised Starling model for use in whole animal studies (humans undergoing dialysis).

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2025-present	Vitanova Biomeical, Inc. Chief Medical Officer
2024-present	MitoSine Technologies, Inc. Co-Founder and Chief Medical Officer
2024-present	NebulaNeuro, Inc. Co-owner and Research Scientist/Regulatory Advisor
2020-present	Research Scientist, White River Junction VA Medical Center
2017-2023	Visiting Professor of Neurosurgery, UCLA Medical School
2017-2020	Professor of Molecular and Systems Biology and Medicine, Geisel School of Medicine
2011-present	President and Chief Scientific Officer, Peroxyium, Inc.
2010-2024	Maxis Medical, Inc. Chief Medical Officer and Strategic Consultant for medical devices
1998-2016	Professor of Physiology and Medicine, Dartmouth Medical School
1993-2001	Chief, Pulmonary Section, Department of Medicine, Dartmouth Medical School
1992-1998	Associate Professor of Physiology and Medicine, Dartmouth Medical School
1987-1992	Assistant Professor of Physiology and Medicine, Dartmouth Medical School
1985-1987	Fellowship in Pulmonary Medicine, MHMH, Hanover, New Hampshire
1982-1985	Postdoctoral Fellow in Physiology, Dartmouth Medical School
1982	Board Certified in Internal Medicine
1980-1982	Residency, Strong Memorial Hospital, University of Rochester
1979-1980	Internship, Strong Memorial Hospital, University of Rochester
1977-1978	Parker B. Francis Foundation Pre-doctoral Fellow, Physiology, DMS.

Other Experience and Professional Memberships

2008-2015	Chairman, DSMB for ROX Medical, Inc.
2006-2007	New England Review Consortium for the American Heart Association
1996-2000	Scientific Advisory Council of the Francis Families Foundation.
1996-1999	ALA American Thoracic Society Fellowship Review Committee

1995-1996	Chairman, Committee F, American Heart Association Affiliate Grant Review
1993-1999	Member of the editorial board of the Journal of Applied Physiology
1991-1994	New England Review Consortium for the American Heart Association

Honors

November 9, 2006 Inaugural Church Lecture in Neuroscience. Glial-neuronal interactions and the role of research in undergraduate education. St. Lawrence University, Canton, NY.

C. Contributions to Science

1. One of my early interests was Obstructive Sleep Apnea (OSA). I made a modest contribution to understanding the role of airway shape in the pathogenesis of OSA, and the adverse effects of GABAergic agents (including alcohol) on upper airway patency in patients with OSA. I was also among the early investigators to model the three-way interaction among airway resistance, upper airway muscle activity and airflow.
    a. **Leiter JC**, Knuth SL, Krol RC, Bartlett D Jr. The effect of diazepam on genioglossal muscle activity in normal human subjects. Am Rev Respir Dis. 1985 Aug;132(2):216-9.
    b. **Leiter JC**, Knuth SL, Bartlett D Jr. Dependence of pharyngeal resistance on genioglossal EMG activity, nasal resistance, and airflow. J Appl Physiol (1985). 1992 Aug;73(2):584-90.
    c. **Leiter JC**. Analysis of pharyngeal resistance and genioglossal EMG activity using a model of orifice flow. J Appl Physiol (1985). 1992 Aug;73(2):576-83.
    d. **Leiter JC**. Upper airway shape. Is it important in the pathogenesis of obstructive sleep apnea? Am J Respir Crit Care Med. 1996 Mar;153(3):894-8.

2. Comparative Physiology interested me even as a student, and we used an invertebrate model, the pulmonate snail, to study central chemosensitivity to CO2. Judging by the citations and editorial comment, others found this useful. The general principles electrophysiological and ionic principles that we first described remain true of mammalian central chemosensitivity as well to this day. Here again, we were among the early adopted of mathematical modeling in this field. Joe Erlichman and I were also the first to appreciate that astrocytic function in the brainstem might be a determinant and regulator of central chemosensitivity.
    a. Erlichman JS, **Leiter JC**. CO2 chemoreception in the pulmonate snail, Helix aspersa. Respir Physiol. 1993 Sep;93(3):347-63.
    b. Denton JS, McCann FV, **Leiter JC**. CO2 chemosensitivity in Helix aspersa: Three potassium currents mediate pH-sensitive neuronal activity. Am J Physiol Cell Physiol. 2007 Jan;292(1):C292-304.
    c. Chernov MM, Daubenspeck JA, Denton JS, Pfeiffer JR, Putnam RW, **Leiter JC**. A computational analysis of central CO2 chemosensitivity in Helix aspersa. Am J Physiol Cell Physiol. 2007 Jan;292(1):C278-91.
    d. Erlichman JS, Hewitt A, Damon TL, Hart M, Kurascz J, Li A, **Leiter JC**. Inhibition of monocarboxylate transporter 2 in the retrotrapezoid nucleus in rats – a test of the lactate shuttle hypothesis. J Neurosci. 2008 May 7;28(19):4888-96. PMCID: PMC2645067.

3. We are making a significant contribution to explaining the physiological basis of risk factors for SIDS. These studies focus on the interface of vagally-mediated reflex mechanisms, immunological function and control of neurotransmitters within the dorsal brainstem as these factors affect autonomic function. Most recently, we found that prenatal hypoxia prolonged reflex apneas and reduced the effectiveness of serotonin terminating apneas. We believe that the effects of prenatal hypoxia are mediated by hypoxia-induced neuroinflammation.
    a. **Leiter JC**, Böhm I. Mechanisms of pathogenesis in the Sudden Infant Death Syndrome. Respir Physiol Neurobiol. 2007 Nov 15;159(2):127-38.
    b. Cummings, K.J. and J**.C. Leiter**. Take a Deep Breath and Wake Up: The Protean Role of Serotonin in Preventing Sudden Death in Infancy, Exp. Neurol. 326:113165, 2020. PMCID: PMC6956249.
    c. Donnelly, W.T., R.L. Hayes, K.G. Commons, D. Erickson; C.M. Panzini; L. Xia, Q.J. Han, and **J.C. Leiter**. Prenatal intermittent hypoxia sensitizes the laryngeal chemoreflex, blocks serotoninergic shortening of the reflex, and reduces 5-HT_3 receptor binding in the NTS in anesthetized rat pups. Exp. Neurol. 326:113166, 2020. PMCID: PMC7028519
    d. Cummings KJ, **Leiter JC**, Trachtenberg FL, Okaty BW, Darnall RA, Haas EA, Harper RM, Nattie EE, Krous HF, Mena OJ, Richerson GB, Dymecki SM, Kinney HC, Haynes RL. Altered 5-HT2A/C receptor binding in the medulla oblongata in the sudden infant death syndrome (SIDS): Part II. Age-associated

alterations in serotonin receptor binding profiles within medullary nuclei supporting cardiorespiratory homeostasis. J. Neuropathol. Exp. Neurol. 83(3):144-160, 2024. PMID: 38323418

4. Dr. Erlichman and I have become interested in cerium oxide – a nanoparticle with unusually durable redox activity. We have been testing these nanoparticles in a variety of disease models of oxidative stress and neurodegeneration. In all of these disease models, the cerium oxide nanoparticles have provided exceptional neuroprotection. In addition to the published work, we have evidence of unusual efficacy in the SOD1 transgenic model of Amyotrophic Lateral Sclerosis.
    a. Heckman KL, DeCoteau W, Estevez A, Reed KJ, Costanzo W, Sanford D, **Leiter JC**, Clauss J, Knapp K, Gomez C, Mullen P, Rathbun E, Prime K, Marini J, Patchefsky J, Patchefsky AS, Hailstone RK, Erlichman JS. Custom cerium oxide nanoparticles protect against a free radical mediated autoimmune degenerative disease in the brain. ACS Nano. 2013 Dec 23;7(12):10582-96.
    b. Estevez AY, Pritchard S, Harper K, Aston JW, Lynch A, Lucky JJ, Ludington JS, Chatani P, Mosenthal WP, **Leiter JC,** Andreescu S, Erlichman JS. Neuroprotective mechanisms of cerium oxide nanoparticles in a mouse hippocampal brain slice model of ischemia. Free Radic Biol Med. 2011 Sep 15;51(6):1155-63.
    c. DeCoteau W, Heckman KL, Estevez AY, Reed KJ, Costanzo W, Sandford D, Studlack P, Clauss J, Nichols E, Lipps J, Parker M, Hays-Erlichman B, **Leiter JC**, Erlichman JS. Cerium oxide nanoparticles with antioxidant properties ameliorate strength and prolong life in mouse model of amyotrophic lateral sclerosis. Nanomedicine. 2016 Nov;12(8):2311-2320.
    d. Erlichman JS, **Leiter JC**. Complexity of the Nano-Bio Interface and the Tortuous Path of Metal Oxides in Biological Systems. Antioxidants (Basel). 2021 Apr 1;10(4):547. PMCID: PMC8066112.

5. In collaboration with Dr. Dan Lu at UCLA investigating neuronal network function and neuromodulation in spinal cord injured patients. As a physician-scientist, it has been tremendous fun to enter into these projects, which have an immediate impact on patients. To the extent we can modulate spinal central pattern generators for dormant, but accessible functions, from breathing to bladder control to motor function, patients with spinal cord injuries benefit immediately. We have papers related to neuromodulation of respiratory function in mice and humans, neuromodulation of bladder function, and neuromodulation in Parkinson's Disease. In all of these publications, we have demonstrated that spinal or brain stimulation, whether electrically or with pulses of magnetic energy, enhanced or made possible previously limited or impossible motor functions driven by spinal pattern generators below the level of the spinal cord injury. In Parkinson's Disease, we have been interested in feedback control of neuromodulation, which we hope will be more broadly applicable to other disorders in which neuromodulation is sued. This is an exciting new area of investigation for me in which I can apply expertise developed over years of previous basic and clinical research in neuroscience.
    a. Niu T, Bennett CJ, Keller TL, Leiter JC, Lu DC. A Proof-of-Concept Study of Transcutaneous Magnetic Spinal Cord Stimulation for Neurogenic Bladder. Sci Rep. 2018 Aug 22;8(1):12549. PMCID: PMC6105631.
    b. Huang R, Worrell J, Garner E, Wang S, Homsey T, Xu B, Galer EL, Zhou Y, Tavakol S, Daneshvar M, Le T, Vinters HV, Salamon N, McArthur DL, Nuwer MR, Wu I, Leiter JC, Lu DC. Epidural electrical stimulation of the cervical spinal cord opposes opioid-induced respiratory depression. J Physiol. 2022 May 31. doi: 10.1113/JP282664.
    c. Galer EL, Huang R, Madhavan M, Wang E, Zhou Y, Leiter JC, Lu DC. Somatostatin-Expressing Neurons in the Dorsal Cervical Spinal Cord in Rats. J. Neurosci. 2023;43(3):419-432. doi: 10.1523/JNEUROSCI.1958-21.2022. Epub 2022 Dec 7. PMID:36639888
    d. Chernov, M.M., C. B. Swan, and J. C. Leiter. In Search of a Feedback Signal for Closed-Loop Deep Brain Stimulation: Stimulation of the Subthalamic Nucleus Reveals Altered Glutamate Dynamics in the Globus Pallidus in Anesthetized, 6-Hydroxydopamine-Treated Rats. Biosensors 2023, *13*(4), 480; doi.org/10.3390/bios13040480

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