

BIOGRAPHICAL SKETCH

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|---|--|---------|-----------------------------|
| NAME Joseph Charles LaManna | POSITION TITLE Professor | | |
| eRA COMMONS USER NAME (credential, e.g., agency login) LAMANNA | | | |
| EDUCATION/TRAINING <i>(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)</i> | | | |
| INSTITUTION AND LOCATION | DEGREE <i>(if applicable)</i> | YEAR(s) | FIELD OF STUDY |
| Georgetown University, Washington DC | BS | 1971 | Biology |
| Duke University, Durham, NC | PhD | 1975 | Physiology/ Pharmacology |

A. Personal Statement:

The current research in my laboratory has two main components. One area is the study of the physiological adaptations to mild hypoxia. This project focuses on the HIF-1 and non-HIF-1 (Cox-2/PGE2/Ang-2) contributions to angiogenesis and the process of "angioplasticity". The proposed program project grant application is more interrelated to this project because we are using our knowledge and previous data from these angioplasticity studies to design the "readouts" for the protocols which involve the effect of early post natal hypoxia +/- hypercapnia on angioplasticity. The other main research component in the laboratory is the study of brain metabolism of ketones as an alternate fuel to glucose, and in its role as a preconditioning or potential treatment strategy in neurodegenerative situations.

B. Positions and Honors:

Research and Professional Experience

1971 - 1975 NIMH Pre-doctoral Fellowship
 1975 Visiting Investigator, Dept. Neurosurg., Loma Linda Med. Univ., Loma Linda, CA
 1975 - 1977 Research Associate, Dept. Physiol/Pharmacol., Duke Univ. Med. Ctr., Durham, NC
 1980 Visiting Investigator, 2nd Dept. Physiol., Semmelweiss Med. Sch., Budapest, Hungary
 1977 - 1981 Assistant Professor, Associate Professor (1981) Depts. Neurol. and Physiol/Biophys., U. Miami Med. Sch., Miami, FL
 1993 - 2008 Chairman, Dept. Anatomy, (Acting Chair 1993-2004), Case Western Reserve University Medical School, Cleveland, OH
 1981 - pres. Professor, (Associate Professor 1981-1990) Depts. Physiology/Biophysics, Neurology and Neuroscience, Case Western Reserve University Medical School, Cleveland, OH
 2012 – pres. Endowed Chair, Jeannette M. and Joseph S. Silber Professor for the Study of Brain Sciences

Honors and Awards

1975 - 1977 NIH (NINCDS) NRSA Post-doctoral Fellowship
 1977 NIH (NHLBI) Young Investigator Award
 1978 - 1981 NIH (NINCDS) Research Career Development Award
 1986 - 1989 American Heart Association, Brain, Lung and Development Research Study Committee
 1987 - 1990 Veterans Administration Merit Review Board for Neurobiology
 1993 - 1996 NIH Neurology B-1 Study Section
 1998 - 1999 American Heart Association, Cleveland Metro Division, Board of Trustees
 2001 - 03, 06- Journal of Applied Physiology, Editorial Board
 2001 - 2004 Member, American Heart Association (National) Brain 1 Peer Review Committee
 2002 - 2005 Member, Society for Neuroscience Program Committee
 2002 - pres. Brain Research, Editorial Board
 2004 - pres. Journal of Cerebral Blood Flow & Metabolism, Editorial Board
 2007 - 2011 Board of Directors, Winter Conference on Brain Research
 2007 – pres. Board of Dir. (2007-2011), Secretary (2011-pres) Int. Soc. for Cereb. Blood Flow & Metabol.

2007 - 2009 Scientific Program Comm. Chairman, Int. Society for Cerebral Blood Flow & Metabolism
2009 President, International Society on Oxygen Transport to Tissue
2010-2012 President-elect (2010), President (2011), Past President (2012), FASEB
2011 – 2014 Member, NIH BINP Study Section

C. Selected Publications: (from over 160 publications)

LaManna JC, MA Haxhiu, KL Kutina-Nelson, S Pundik, B Erokwu, ER Yeh, WD Lust and NS Cherniack: Decreased energy metabolism in brainstem during central respiratory depression in response to hypoxia. *J Appl Physiol* 81(4):1772-1777 (1996). PMID 8904598

Dore-Duffy, P., Balabanov, R., Beaumont, T., Hritz, M.A., Harik, S.I. and LaManna, J.C., Endothelial activation following prolonged hypobaric hypoxia, *Microvasc.Res.*, 57:75-85 (1999). PMID 10049655

Kuo, N.-T., Benhayon, D., Przybylski, R.J., Martin, R.J. and LaManna, J.C., Prolonged hypoxia increases vascular endothelial growth factor mRNA and protein in adult mouse brain, *J.Appl.Physiol.*, 86:260-264 (1999). PMID 9887138

Hoxworth, J.M., Xu, K., Zhou, Y., Lust, W.D. and LaManna, J.C., Cerebral metabolic profile, selective neuronal loss, and survival of acute and chronic hyperglycemic rats following cardiac arrest and resuscitation, *Brain Res.* 821:467-479 (1999). PMID 40064834 PMCID 10064834

Kreisman, N.R. and JC LaManna: Rapid and slow swelling during hypoxia in the CA1 region of rat hippocampal slices. *J Neurophysiol.* 82:320-329 (1999). PMID 10400961

Pichiule, P., J.C. Chavez, K. Xu, and J.C. LaManna: Vascular endothelial growth factor upregulation in transient global ischemia induced by cardiac arrest and resuscitation in rat brain. *Mol Br Res* 74: 83-90 (1999). PMID 10640678

Agani, F.H., P. Pichiule, J.C. Chavez, and J.C. LaManna: The role of mitochondria in the regulation of hypoxia-inducible factor-1 expression during hypoxia. *J. Biol. Chem.* 275:35863-35867 (2000). PMID 10961998

Chavez JC, F Agani, P Pichiule, and JC LaManna: Expression of hypoxia inducible factor 1 alpha in the brain of rats during chronic hypoxia. *J. Appl. Physiol.* 89:1937-1942 (2000). PMID 11053346

Agani FH, JC Chavez, P Pichiule, M Puchowicz and JC LaManna: The role of nitric oxide in the regulation of HIF-1 α expression during hypoxia. *Am. J. Physiol.:Cell Physiology* 283:C178-C186 (2002). PMID 12055086

Pichiule P and JC LaManna: Angiopoietin-2 and rat brain capillary remodeling during adaptation and deadaptation to prolonged mild hypoxia. *J. Appl. Physiol.* 93:1131-1139 (2002). PMID 12183511

Agani F, Pichiule P, Chavez JC, LaManna J. Inhibitors of mitochondrial complex I attenuate the accumulation of hypoxia-inducible factor-1 during hypoxia in Hep3B cells. *Comp Biochem and Physiol Part A* 132, 107-109 (2002). PMID 12062197

Chavez JC and JC LaManna: Activation of hypoxia inducible factor-1 in the rat cerebral cortex after transient global ischemia: potential role of insulin like growth factor-1. *J. Neurosci.* 22(20):8922-8931 (2002). PMID 12388599

Pichiule P, JC Chavez, and JC LaManna: Hypoxic regulation of angiopoietin-2 expression in endothelial cells. *J.Biol.Chem.* 279 (13):12171-12180 (2004). PMID 14702352

Puchowicz MA, K Xu, D Magness, C Miller, WD Lust, TS Kern, and JC LaManna: Comparison of glucose influx and blood flow in retina and brain of diabetic rats. *J.Cereb.Blood Flow Metab.* 24:449-457 (2004). PMID 15087714

LaManna JC, JC Chavez, and P Pichiule: Structural and functional adaptation to hypoxia in the rat brain. *J.Exp.Biol.* 207:3163-3169 (2004). PMID 15299038

Drew KL, MB Harris, JC LaManna, MA Smith, XW Zhu, and YL Ma: Hypoxia tolerance in Mammalian heterotherms. *J.Exp.Biol.* 207:3155-3162 (2004). PMID 15299037

Xu K, MA Puchowicz, and JC LaManna: Renormalization of regional brain blood flow during prolonged mild hypoxic exposure in rats. *Brain Res.* 1027:188-191 (2004). PMID 15494170

Ward NL and JC LaManna: The neurovascular unit and its growth factors: coordinated response in the vascular and nervous systems. *Neurol.Res.* 26:870-883 (2004). PMCID 15727271

Aminova LR, JC Chavez, J Lee, H Rye, A Kung, JC LaManna, and RR Ratan: Pro-survival and pro-death effects of HIF-1 α stabilization in a murine hippocampal cell line. *J. Biol. Chem.* 280:3996-4003 (2005). PMCID 15557337

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Ma YL, Zhu X, Rivera PM, Toien O, Barnes BM, LaManna JC, Smith MA, Drew KL., Absence of cellular stress in brain after hypoxia induced by arousal from hibernation in Arctic ground squirrels. *Am J Physiol Regul Integr Comp Physiol.* 289(5):R1297-306 (2005). PMID 15976308

Xu K, MA Puchowicz, WD Lust, and JC LaManna: Adenosine treatment delays postischemic hippocampal CA1 loss after cardiac arrest and resuscitation in rats. *Br Res* 1071:208-217 (2006). PMID 16412392

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Kanaan A, R Farahani, RM Douglas, JC LaManna, and GG Haddad: Effect of chronic continuous or intermittent hypoxia and reoxygenation on cerebral capillary density and myelination. *Am J Physiol Regul.Integr.Comp Physiol* 290:R1105-R1114 (2006). PMID 16322350

Ward NL, Moore E, Noon K, Spassil N, Keenan E, Ivanko TL, LaManna JC. Cerebral angiogenic factors, angiogenesis, and physiological response to chronic hypoxia differ among four commonly used mouse strains. *J Appl Physiol.* 102(5):1927-35 (2007). PMID 17234796

Occhipinti R, Puchowicz, MA, LaManna JC, Somersalo E, and Calvetti D: Statistical analysis of metabolic pathways of brain metabolism at steady state. *Ann Biomed Eng* 35(6):886-902 (2007). PMID 17385046

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Ndubuizu O and LaManna JC: Brain tissue oxygen concentration measurements. *Antioxidants & Redox Signaling* 9 (8), 1207-1219 (2007). PMID 17536959

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LaManna JC: Hypoxia in the central nervous system. *Essays in Biochemistry* 43:139-152 (2007). PMID 17705798

Bishop GM, MA Smith, JC LaManna, AC Wilson, G Perry, and CS Atwood: Iron homeostasis is maintained in the brain, but not the liver, following mild hypoxia. *Redox.Rep.* 12:257-266 (2007). PMID 17961297

LaManna JC: In situ measurements of brain tissue hemoglobin saturation and blood volume by reflectance spectrophotometry in the visible spectrum. *J Biomed.Opt.* 12:062103(2007). PMID 18163806

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Puchowicz MA, J Zechel, J Valerio, D Emancipator, K Xu, S Pundik, JC LaManna and WD Lust: Neuroprotection in Diet Induced Ketotic Rat Brain Following Focal Ischemia. *J Cereb Blood Flow Metab* 28:1907-1916 (2008). PMID: PMC3621146

Xu, K and JC LaManna: The loss of hypoxic ventilatory responses following resuscitation after cardiac arrest in rats is associated with failure of long-term survival. *Br Res* 1258, 59-64 (2009). PMID: PMC2649988

Ndubuizu OI, JC Chavez, and JC LaManna: Increased Prolyl 4-Hydroxylase (PHD) Expression and Differential Regulation of Hypoxia Inducible Factors (HIFs) in the Aged Rat Brain. *AJP Reg* 297(1): R158-165 (2009). PMID:PMC 2711700

Kawanami D, Mahabeleshwar GH, Lin Z, Atkins GB, Hamik A, Haldar SM, Maemura K, LaManna JC, Jain MK. Kruppel-like factor 2 inhibits hypoxia-inducible factor 1{alpha} expression and function in the endothelium. *J Biol Chem.* 2009 Jul 31;284(31):20522-30. Epub 2009 Jun 1. PMID: PMC2742816.

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Li Longxuan, J Welser, B Erokwu, P Dore-Duffy, GJ del Zoppo, JC LaManna, and R Milner: In the hypoxic central nervous system, endothelial cell proliferation is followed by astrocyte activation, proliferation, and increased expression of the alpha6beta4 integrin and dystroglycan. *GLIA* 2010 Aug. 58(10):1157-67. PMID: PMC2914614

Donovan L, Welford SM, Haaga J, LaManna J, Strohl KP. Hypoxia implications for pharmaceutical developments. *Sleep Breath.* 4(4):291-8 (2010)

Liu Y, Xu K, Chen LM, Sun X, Parker MD, Kelly ML, LaManna JC, and Boron WF (2010), Distribution of NBCn2 (SLC4A10) splices variants in mouse brain. *Neuroscience* 2010 Sep 1;169(3):951-64. Epub 2010 Jun 10. PMID: PMC2914179

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Ndubuizu OI, Tsipis CP, Li A, LaManna JC. Hypoxia-inducible factor-1 (HIF-1)-independent microvascular angiogenesis in the aged rat brain. *Brain Res.* 2010 Dec 17;1366:101-9. PMID: PMC3378376.

Benderro GF, Lamanna JC. Hypoxia-induced angiogenesis is delayed in aging mouse brain. *Brain Res.* 2011 1389:50-60. PMID: PMC3082052

Xu K, Sun X, Erokwu BO, Cernak I, Lamanna JC. A heat-shock protein co-inducer treatment improves behavioral performance in rats exposed to hypoxia. *Adv Exp Med Biol.* 2011;701:313-8. PubMed PMID: 21445803.

Crumrine RC, Marder VJ, Taylor GM, LaManna JC, Tsipis CP, Scuderi P, Petteway SR Jr, Arora V. Intra-arterial administration of recombinant tissue-type plasminogen activator (rt-PA) causes more intracranial bleeding than does intravenous rt-PA in a transient rat middle cerebral artery occlusion model. *Exp Transl Stroke Med.* 2011 Sep 20;3(1):10. PMID: PMC3184064.

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Zhang Y, Kuang Y, Xu K, Harris D, Lee Z, LaManna JC, Puchowicz MA: Ketosis Proportionately Spares Glucose Utilization in Brain, *J Cereb Blood Flow Metab*, June 2013

D. Research Projects Ongoing, Pending or Completed During the Last 3 Years:

Active:

“Brain vascular and metabolic adaptations to hypoxia”, Principal Investigator: Joseph C. LaManna; USPHS NIH; Type: R01 NS 38632, Period: 8-15-10–6-30-15

We propose to examine the structural aspects of the rat brain adaptation to prolonged continuous and intermittent hypoxia.

“Angiogenic Response to Hypoxia and Ketosis in Rat Brain”, PI: JC LaManna; Agency: USPHS NIH; Type: 1R01 HL092933-01A1; Project Period: 4-1-09 – 3-31-2014 (no cost extension)

We propose to investigate whether ketosis induces angiogenesis in aged brain and to investigate if ketosis induces HIF-1 α in aged rat brain and improves adaptation to mild hypoxia.

“Role of the PVN in Chronic Intermittent Hypoxia-Induced Cardiorespiratory Changes”, PI: P Kc; Co-Mentors: JC LaManna and RJ Martin, USPHS NIH 1K99/R00 HL087620; Period: 1/1/08 -2/28/14

“Refinement of lead compounds to modulate water permeability through AQP4”, PI: WF Boron (Aeromics); Type: Phase II SBIR; Consultant: JC LaManna; Period: 1/1/10 – 12/31/16

We have a subcontract to test the efficacy of identified compounds against cerebral edema.

“Athersys, Inc. Service Agreement”, PI: JC LaManna; Period: 9/19/11 – 9/1/13

We have a subcontract to test the efficacy of identified compounds against cerebral edema.

“Endowed Chair, The Jeannette M. and Joseph S. Silber Professorship for the Study of Brain Sciences”, PI: JC LaManna (Private Fund); Period: 12/11/12 – 11/30/17

This endowed chair/professorship was established to improve the outcome of stroke patients.

Training Grant Participation for both pre and postdoctoral fellows (no salary):

“Training in Neurodegenerative Diseases”, PIs: JC LaManna/Xiongwei Zhu, T32 NS077888, 7-1-13 – 6-30-18

“Medical Scientist Training Program”, C Harding, T32 GM007250; 7-1-95--6-30-14

“Sleep Medicine Neurobiology and Epidemiology”, KP Strohl, T32 HL07913-10; 09/30/05--06/30/15

“Interdisciplinary Biomed Imaging Training Program”, T32 EB007509-04; 09/01/07--08/31/13; D Wilson/J Duerk

Pending:

“Neuroprotective Properties of Ketosis in Aging Brain”, PIs: MA Puchowicz/JC LaManna, R01 HL092933, (revision to be submitted)

Completed:

“Collaborative MS Research Center Award”, PI: PD Duffy, Outside Collaborator: JC LaManna, National Multiple Sclerosis Society, Period: 4-1-07 – 3-31-13

ARRA Administrative Supplement to 5R01 NS038632, “Brain vascular and metabolic adaptations to hypoxia”, Principal Investigator: Joseph C. LaManna; USPHS NIH; Type: 3R01 NS28632-10S1; Project Period: 9/30/09 – 8/31/11

“Energy Balance During Ketosis in Rat Brain”, PI: JC LaManna; Agency: USPHS NIH NHLBI; Type: R21 NS062048; Project Period: 5-1-09 – 4-30-11

The goal of this project is to investigate the effects of ketosis on brain metabolism of glucose (CMRglu) using image (PET) analysis in ketotic rat and to determine if there is improved outcome following cardiac arrest and resuscitation.