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: **Buxton, Iain L.O.**

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

POSITION TITLE: **Foundation 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 California, San Diego	BA	05/1973	Molecular Biology
North Carolina State University, Raleigh	PhD Student	12/1975	Biochemistry/Enzymology
University of the Pacific, Stockton, CA	PHMD	05/1978	Pharmacology
VA San Diego Healthcare System, CA	Resident/Fellow	02/1981	Clinical Pharmacology
University of California, San Diego	Postdoc	04/1984	Molecular Biology

A. PERSONAL STATEMENT

I have the expertise, leadership, energy, and motivation necessary to successfully lead the proposed project. I have a broad background in pharmacology and medicine, with specific training and expertise in key research areas of medical pharmacology and cell signaling. My first scientific exposure was at the Salk Institute working in Bob Holley's (1968 Nobelist) laboratory on growth control mechanisms. This was a transformative time as I was able to learn as a student from luminaries such as Nirenberg, Dulbecco, Vogt, Crick, Guillemin, and the then young Salk scientists such as Tony Hunter, Hyam Leffert, Wylie Vale, and others that spent time at the Salk in those early days. As a postdoctoral fellow at University of California, San Diego (UCSD), I performed the first experiments that established compartmentation of cyclic nucleotide action at the cellular level in muscle, which has led to the field of cyclic nucleotide compartmentation and my interest in smooth muscle where we have demonstrated a nitric oxide (NO) signaling exception in human myometrium. While a faculty member in Pharmacology at the University of Nevada, Reno (UNR), I have been PI on NIH grants focused on breast cancer and preterm labor studies where we pursued the mechanistic basis of the failure of nitric oxide-mediated cGMP elevation to relax myometrium. Our work has progressed to the point that we are discovering the mechanisms of S-nitrosation of critical proteins in myometrium. I have developed productive interactions and collaborated with MD colleagues in order to develop a translational research program. I have graduated 14 PhD students and an equal number of postdoctoral fellows in my career to this point. I have expertise in PK analysis and provide chapters for Goodman and Gilman's, The Pharmacological Basis of Therapeutics. I accepted the challenge of leading and rebuilding the Department of Pharmacology at UNR, and while this has affected my recent productivity, I have stepped down now that rebuilding is complete and our group is poised with new motivation and NIH funding to explore S-nitrosation signaling.

B. POSITIONS AND HONORS

B.1 Positions and Employment

1973-1974 Graduate Research Assistant, Dr. RA Main, Biochemistry, North Carolina State University, Raleigh
1974-1975 Graduate Research Associate, Dr. R Holley (1968 Nobelist), Cell Biology Lab, Salk Institute, La Jolla, CA
1978-1979 Resident, Clinical Pharmacy, VA San Diego Healthcare System, CA

1979-1981	Clinical Pharmacologist, Head, Investigational Studies Section, VA San Diego Healthcare System, La Jolla, CA
1981-1984	Postdoctoral Fellow, Dr. LL Brunton, University of California, San Diego
1984-1985	Assistant Research Professor, Department of Medicine, University of California, San Diego
1985-1989	Assistant Professor, Department of Pharmacology, University of Nevada, Reno School of Medicine
1989-1995	Associate Professor (with tenure), Pharmacology, University of Nevada, Reno School of Medicine
1993-1998	Associate Dean, Research, University of Nevada, Reno School of Medicine
1995-Present	Professor, Pharmacology, University of Nevada, Reno School of Medicine
1999-Present	Professor, Obstetrics and Gynecology, University of Nevada, Reno School of Medicine
2013-2018	Foundation Professor and Chair, Department of Pharmacology, University of Nevada, Reno School of Medicine

B.2 Honors

1976	Dami Foundation Scholar Award, University of the Pacific, Stockton, CA
1977	Rho Chi Research Award, University of the Pacific, Stockton, CA
1981	Postdoctoral Trainee, National Institutes of Health
1984	New Investigator Award, National Institutes of Health
1996	Heart of Gold Award, American Heart Association
2009	Researcher of the Year, University of Nevada, Reno
2010	W. Richardson Excellence in Teaching Award, University of Nevada, Reno School of Medicine
2011	Gates Foundation Awardee
2011	Vida Trimble Graduate Student Mentor Award
2011	Regents Researcher Award, Nevada System of Higher Education
2013	Foundation Professor, University of Nevada, Reno
2016	Nevada Healthcare Heroes Award

B.3 Other Professional Service

2003-2012	Editor, Proceedings of the Western Pharmacology Society
2005	Author, Goodman and Gilman's The Pharmacological Basis of Therapeutics, 11th Edition
2011	Author, Goodman and Gilman's The Pharmacological Basis of Therapeutics, 12th Edition
2017	Author, Goodman and Gilman's The Pharmacological Basis of Therapeutics, 13th Edition
1981-Present	Member, American Society for Pharmacology and Experimental Therapeutics
1990-Present	Member, American Society for Biochemistry and Molecular Biology
2014-Present	Member, American Association for Cancer Research
2012-Present	Member, Human Proteome Organization
2000-Present	Member, Society for Reproductive Investigation
2000-Present	Member, Society for the Study of Reproduction
2018-Present	President Elect, American Heart Association, Northern Nevada

C. CONTRIBUTIONS TO SCIENCE

C.1 Cyclic Nucleotide Compartmentation

I directly addressed the problem of agonist-specific effects of drugs that employed a common second messenger. Steven Mayer and his group at UCSD had gathered evidence in the whole heart preparation that suggested that cAMP was compartmented in the myocardium. This was a highly criticized notion at the time and despite their efforts (Mayer, Hayes, and Brunton), their views were not accepted as plausible. When I joined Brunton in the Department of Medicine in 1981, I was intrigued by this idea. Larry advised me, however, not to work on compartmentation since it could not be demonstrated at the cellular level. This he said was because single cell preparations of the cardiac ventricle suitable for biochemical experiments were not achievable; he had tried. With significant experience in cell biology from my time at the Salk, I decided I could do it. I achieved near 100% yields of Ca2+ tolerant myocytes from rabbit heart and established unequivocally that cAMP was compartmented in the myocyte.

By providing evidence in cardiac muscle, this work established an entire field of interest in non-membrane delimited signaling. While we know much about the probable mechanistic basis of compartmentation in a number of systems today such as scaffolding proteins, caveolae and enzyme gradients, at the time we helped develop data that changed the science of signaling. I served as a PI in all of these studies.

a. **Buxton ILO** and Brunton LL. (1983). “Compartments of cyclic AMP and protein kinase in mammalian cardiomyocytes.” *J Biol Chem*, 258(17):10233-9. PMID: 6309796.
b. **Buxton ILO** and Brunton LL. (1985). “β-adrenergic receptor subtypes and cellular compartmentation of cyclic AMP-dependent protein kinase in cardiomyocytes.” *Biochem Int*, 11(2):137-44. PMID: 2996547.
c. **Buxton ILO** and Brunton LL. (1986). “α-adrenergic receptors on rat ventricular myocytes: characteristics and linkage to cAMP metabolism.” *Am J Physiol*, 251(2 Pt 2):H307-13. PMID: 3017129.
d. **Buxton ILO**, Milton DL, Barnett S, and Tichenor SD. (2010). “Agonist-specific compartmentation of cGMP action in guinea pig myometrium.” *J Pharmacol Exp Ther*, 335(1):256-63. PMID: 20811500.

C.2 The Cyclic GMP Signaling Exception in Myometrium

Nevada was well known in the 1980s, as it is now for smooth muscle research. When at UCSD, I met a number of pharmacologists interested in the actions of cGMP. It had once been proposed that cGMP was a counter to cAMP in the control of cellular metabolism (Yin/Yang). Jack Diamond at UBC had established that while cGMP was involved in smooth muscle relaxation, it was not enough. I became interested in the myometrium. The problem of preterm delivery of a fetus might be averted if we understood how the muscle is maintained in a relaxed state during gestation. We examined the action of NO in myometrium and discovered that the Nobel dogma aside, NO didn’t relax the myometrium in a cGMP-dependent manner. This signaling exception is now recognized as one of the few examples in smooth muscle relaxation where NO likely signals principally through protein nitrosation and not cGMP elevation. This work, together with our recent discovery of splice variants of the stretch-activated channel TREK-1 (a nitrosation target) may lead to the development of new therapeutics for the treatment of spontaneous preterm labor (a problem without reliable treatment).

a. Bradley KK, **Buxton ILO**, Barber JE, McGaw T, and Bradley ME. (1998). “Nitric oxide relaxes human myometrium by a cGMP-independent mechanism.” Am J Physiol Cell, 275(6 Pt 1):C1668-73. PMID: 9843729.
b. **Buxton ILO**. (2004). “Regulation of uterine function: A biochemical conundrum in the regulation of smooth muscle relaxation.” *Mol Pharmacol*, 65(5):1051-9. PMID: 15102932.
c. **Buxton ILO**, Singer CA, and Tichenor JN. (2010). “Regulation of stretch-activated two-pore potassium channels in human myometrium in pregnancy and labor.” *PLoS One*, 5(8):pii:e12372. PMID: 20811500; PMCID: PMC2928262.
d. Barnett, SD, Smith, CR, Ulrich, CC, Baker, JE and **Buxton, ILO**. (2018) S-Nitrosoglutathione reductase underlies the dysfunctional relaxation to nitric oxide in preterm labor. *Nature-Scientific Reports*, vol. 8, Article number: 5614, doi:10.1038/s41598-018-23371-w

C.3 Mechanism of Action of Nitric Oxide in Uterine Smooth Muscle

The actions of NO in uterine smooth muscle are unique. We reasoned that at least with respect to the relaxant effects of NO, it was likely these would be mediated by S-nitrosation. We sought to determine the proteins that were S-nitrosated by relaxing concentrations of NO when applied as GSNO, the likely endogenous for of NO in tissues. Because our lab has access to preterm laboring myometrium, we were able to determine that there is a distinct difference in the proteins that are nitrosated by GSNO in myometrium and, furthermore, that in preterm laboring myometrium, the rerlaxation to NO is blunted. This research has led to the proposal presented here to examine the specific S-nitrosation regulation of relaxation of human myometrium and the introduction of the guinea pig as a preterm labor model.

a. Ulrich C, Quillici D, Schegg K, Woolsey R, Nordmeier A, and **Buxton ILO**. (2012). “The uterine smooth muscle S-nitrosoproteome in pregnancy.” *Mol Pharm*, 81:143-153.
b. Ulrich C, Quilici DR, Schlauch KA, and **Buxton ILO**. (2013). “The human uterine smooth muscle Snitrosoproteome fingerprint in pregnancy, labor and preterm labor.” *Am J Physiol Cell Physiol*, 305(8): C803-16. PMID: 23948706; PMCID: PMC3798678.
c. Ulrich CC, Quilici DR, Schlauch KA, and **Buxton ILO**. (2015). “Proteomic Network Analysis of Human Uterine Smooth Muscle in Pregnancy, Labor, and Preterm Labor.” *Integr Mol Med*, 2(4):261-269. PMID: 26413312; PMCID: PMC4582795.
d. Ulrich CC, Quilici DR, Schlauch KA, Burkin HR, and **Buxton ILO**. (2015). “LC/MS/MS data analysis of the human uterine smooth muscle S-nitrosoproteome fingerprint in pregnancy, labor, and preterm labor.” Data Brief, 4:591-4. PMID: 26322325; PMCID: PMC4543089.

C.4 The Nucleotide Axis Hypothesis

After moving to Nevada in 1985, I became interested in the extracellular actions of ATP. It seemed heretical to me that the energy currency of the cell would be released to the outside and act on extracellularly directed receptors. I knew by this time of course that just because it seemed implausible did not mean it was not so. I developed an endothelial cell and isolated blood vessel model from heart and established that indeed endothelial cells released ATP and that it was further metabolized and re-phosphorylated in a fashion that supported increased blood flow regionally in the heart and served venous dilation as well. My lab devised the Nucleotide Axis Hypothesis to explain our findings that have helped explain the moment-to-moment regulation of blood flow in the heart where nerves do not control flow.

a. Yang S, Cheek DJ, Westfall DP, and **Buxton ILO**. (1994). "Purinergic axis in cardiac blood vessels: Agonist mediated release of ATP from cardiac endothelial cells." *Circ Res*, 74(3):401-7. PMID: 8118 948.
b. Oxhorn BC, Cheek DJ, and **Buxton ILO**. (2000). "On the role of nucleotides and nucleosides in the regulation of blood flow." *AACN Clin Issues*, 11(2):241-51. PMID: 11235433.
c. **Buxton ILO**, Kaiser RA, Oxhorn BC, and Cheek DJ. (2001). "Evidence supporting the Nucleotide Axis Hypothesis: ATP Release and metabolism by coronary endothelium." *Am J Physiol Heart Circ Physiol*, 281(4):H1657-66. PMID: 11557556.
d. Kaiser RA, Andrews G, Oxhorn BC, and **Buxton ILO**. (2002). "Functional compartmentation of endothelial P2Y receptor signaling." *Circ Res*, 91(4):292-9. PMID: 12193461.

C.5 Extracellular Actions of Nucleoside Diphosphate Kinase in Cancer Metastasis

We made a rather curious discovery when we used cancer cells as a control in our endothelial cell experiments. A kinase, Nm23 appeared outside cells and stimulated angiogenesis. We have now refined our understanding of this phenomenon and show that Nm23 when acting outside the cell released in exosomes in not a tumor suppressor but rather serves to enhance tumor development.

a. Rumjahn SM, Javed MA, Wong N, Law WE, and **Buxton ILO**. (2007). "Purinergic regulation of angiogenesis by human breast carcinoma-secreted NDPK." *Br J Cancer*, 97(10):1372-80. PMID: 17940 513; PMCID: PMC2360243.
b. Rumjahn SM, Yokdang N, Baldwin KA, Thai J, and **Buxton ILO**. (2009). "Purinergic regulation of vascular endothelial growth factor signaling in angiogenesis." *Br J Cancer*, 100(9):1465-70. PMID: 19367276; PMCID: PMC2694426.
c. Yokdang N, Tellez J, Tian H, Norvell J, Barsky SH, Valencik M, and **Buxton ILO**. (2011). "A Role for nucleotides in support of breast cancer angiogenesis: Heterologous receptor signaling." *Br J Cancer*, 104(10):1628-40. PMID: 21505453; PMCID: PMC3101911.
d. Yokdang N, Nordmeier S, Speirs K, Burkin HR, and **Buxton ILO**. (2015). "Blockade of Nucleoside Diphosphate Kinase or its Endothelial Target Slows Breast Cancer Growth and Metastasis." *Integr Cancer Sci Ther*, 2(4):192-200. PMCID: PMC4580248.

D. ADDITIONAL INFORMATION

D.1 Current Research Support

ACTIVE

NIH R01 HD091114-01A1 (PI Buxton) 09/2018-08/2022
National Institute of Child health and Human Development. Regulation of CAP Protein S-Nitrosation in Preterm Labor.
This project proposes to determine the functional significance of S-nitrosation of myometrial contraction-associated proteins myosin light chain kinase, myosin light chain 9 and profilin-1 known to be differentially S-nitrosated in women in different states of pregnancy and to be examined in a guinea pig model of preterm labor.

NIH R01 AR064338-05 (PI: Burkin, D; Buxton Co-I) 4/2014-3/2019
Laminin Protein Therapy for Congenital Muscular Dystrophy
This project will determine if laminin-111 prevents further muscle damage after disease onset, preserves muscle function and improves survival in the dyW-/- mouse model of MDC1A. The second aim will determine if transgenic expression of human laminin-111, recombinant human laminin-111 or recombinant human laminin-211 improves preclinical outcomes in the dyW-/- mouse model of MDC1A. Finally we will determine scalability of laminin-111 protein therapy and define the pharmacokinetic and pharmacodynamic profiles in mouse and dog models.

COMPLETED

UNSOM Women's Health Research Grant. Buxton (PI) 07/01/15-10/30/17
Exosomal NM23 in Breast Cancer Metastasis. This research funds studies of the role of exosomes in the delivery of NDPK to the metastatic niché in mice. We developed evidence that NM23 is secreted in exosomes that prep the metastatic niche. This data supports the progression of metastasis as an early event in the development of breast cancer. This effect of NM23 to stimulate angiogenesis is inhibitable and doing so prevents metastases in the mouse model.

UNSOM Women's Health Research Program. Buxton (PI) 07/01/15-06/30/20
Super-Resolution Microscopy: Leica DMi8 with SR GSD 3D System. This is a Women's Health Initiative grant from the state of Nevada to build research infrastructure.

NIH 1U54GM 104944-01; CTR Pilot. Buxton (PI) 01/01/14-12/31/14
Post-Translational S-nitrosation of Therapeutic Targets in Pregnancy and Labor. This pilot grant was foundational to the current request. We developed proteomic methodology required for absolute quantification of post-translational S-nitrosation of proteins.

NIH 8P20GM103554-02. Von Bartheld (PI), Buxton, Mentor 04/01/12-03/31/17
Cell Biology of Signaling Across Membranes. This was a CoBRE grant focused on developing expertise in neuroscience related signaling. Dr. Buxton served as a mentor for Ruben Dagda who received NIH R01 funding in 2018.

Bill and Melinda Gates Foundation Grand Challenges; Buxton (PI) 05/01/11-10/31/12
Phase I: Effective Treatment to Prevent Preterm Delivery. This project was focused on developing an effective treatment for preterm labor that allows a fetus to remain in the mother's womb until term.

NIH RO1 HD053028-07. Buxton (PI) 03/05/07-02/28/13
Regulation of Myometrial Relaxation: Agonist-specific cGMP Action. This research developed the cGMP signaling exception to the action of nitric oxide in uterine smooth muscle.

March of Dimes Prematurity Initiative. Buxton (PI) 03/01/10-02/28/13
Stretch-Activated Two-Pore Potassium Channel Variants in Preterm Labor. This project characterized the mechano-sensitive 4-transmembrane domain, 2-pore potassium channel TREK-I in human myometrium as a way to predict the occurrence of spontaneous preterm labor.