

BIOGRAPHICAL SKETCH

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NAME Lucas, Alexandra R.	POSITION TITLE Professor of Medicine; Divisions of Cardiology and Rheumatology; Cross appointment Molecular Genetics and Microbiology		
eRA COMMONS USER NAME (credential, e.g., agency login) AEXLUC1			
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>	Dates Attended/ conferred	FIELD OF STUDY
McGill University, Montreal, PQ Canada	B.Sc. Honours	1970-75	Biochemistry
University of Western Ontario, London, Canada	M.Sc.	1976-78	Microbiology & Immunol
University of Alberta, Edmonton, AL, Canada	M.D.	1978-82	Medicine
University of Alberta, Edmonton, AL, Canada	Resident	1982-85	Internal Medicine
University of Alberta, Edmonton, AL, Canada	Fellowship	1985-87	Cardiology
Tufts' University, Boston , MA, USA	PDF	1987-89	Cardiology
Fellow Royal College Physicians and Surgeons	FRCP(C)	1987	Internal Medicine
Fellow American College of Cardiology	FACC	1992	Cardiology

A. Personal Statement

Over 25 years, I have established a broad background in basic research into transplant vasculopathy and atherosclerosis. I have been funded as a PI on grants in Canada (CIHR and CSATVB) and the US (NIH and AHA). A small biotech company was developed around our discoveries and patents from work done on viral immune modulating proteins in collaboration with Dr McFadden. My lab's excellent postdoctoral fellows and graduate students have established transplant models and developed point mutations of the M-T7 protein. We have an established track record in developing viral immunomodulatory proteins, and one such serpin protein has demonstrated efficacy, with reduced markers of myocardial damage after stent implant in patients with acute coronary syndrome. This current work builds naturally on our prior work and has the potential to improve understanding of the role of chemokine:GAG interactions in innate immune responses in transplants as well as potential for development of new immunomodulatory drugs designed to block the chemokine:GAG interactions.

With this research we investigate the role of chemokine:GAG interactions in chronic transplant allograft vasculopathy (AV) development, a leading cause of late transplant loss, as well as the capacity of a remarkable, virus derived anti-inflammatory protein, M-T7, to block chronic transplant rejection. The M-T7 protein uniquely blocks native interactions between arterial glycosaminoglycans (GAGs) and a wide range of C, CC, and CXC chemokines that line up along the GAGs to form a gradient that attracts inflammatory cells to sites of tissue injury or infection. Recent work has demonstrated prolonged reduced transplanted-organ damage, reduced AV, and increased survival in aortic and renal transplant models. We will examine the role of GAGs in AV as well as analyzing the mechanism of action of M-T7 using mouse models with selective genetic deficiency for GAGs and chemokines. Selected M-T7 mutants developed by site directed mutagenesis with demonstrated loss of anti-inflammatory activity will be assessed and compared to M-T7 for capability to interfere with normal GAG:chemokine interactions. My research group has the expertise, leadership, and motivation necessary to successfully carry out the proposed work.

B. Positions and Honors

Positions

1989-1996	Alberta Heritage Foundation Clinical Investigator, Div Cardiology, University of Alberta
1989-1995	Assistant Professor, Department of Medicine, University of Alberta, Edmonton, AB
1989-1996	Clinical Interventional Cardiologist, University Alberta and Hospitals, Edmonton, AB
1996-present	Clinical Interventional Cardiologist, University of Western Ontario, London, ON
1994-1996	Associate Professor, Div Cardiology / Dept of Medicine, University of Alberta
1996-2003	Associate Professor, Div Cardiology / Medicine, University of Western Ontario (UWO)
1996-2007	Cross Appointment, Depts of Microbiology/Immunology & Biophysics, UWO, London

1997-present Chief Clinical Officer, Viron Therapeutics, Inc., London, ON
1997-2000 Site Director, Coronary Care Unit, London Health Sciences Centre – University Campus
1997-2005 Coordinator Resident Teaching Coronary Care Unit, London Health Sciences, UWO
2003-present Professor, Faculty of Medicine & Dentistry, University of Western Ontario, London, ON
2006-present Professor, Div Cardiology and Div Rheumatology, College of Medicine, University of Florida
2006-present Clinical Interventional Cardiologist, University of Florida, Gainesville, FL
2006-present [Director, Vascular Biology Research Section, Cardiovascular Medicine](#) [Professor, Cross Appointment Molecular Genetics and Microbiology, UFI](#), Gainesville, FL
2006-present Ethel Smith Research Professorship, College of Medicine, University of Florida

Honours

1975 First Class Honours, Biochemistry, McGill University
1977-1978 Medical Research Council of Canada, Studentship, University of Western Ontario
1981-1982 Alberta Heritage Foundation for Medical Research Studentship, University of Alberta
1986-1987 Chief Resident, Cardiology, University of Alberta
1987-1989 AHFMR Clinical Research Fellowship, Tufts' University
1989-1996 AHFMR Clinical Investigator, University of Alberta
1994 American Society for Lasers in Surgery and Medicine, Award for Outstanding Research
2001-2004 Delegate/Councilor Canadian Society of Atherosclerosis, Thrombosis Vascular Biology
2005 Symposia Chair - Canadian Society of Atherosclerosis, Thrombosis Vascular Biology
2005 Prix Galien Award, Viron Therapeutics, (Drs. A. Lucas & G. Mcfadden, Co-Founders)
2005-present 3rd degree black belt, Kenpo Karate; Shotokan karate
2006-present Ethel Smith Vasculitis Research Chair, University of Florida
2007&2008 Department of Medicine Research Awards of Excellence for Lucas lab
~~2007 Canadian Society Atherosclerosis, Thrombosis Vascular Biology - Certificate of Appreciation~~
2007 Canadian Society Atherosclerosis, Thrombosis Vascular Biology - Symposium speaker
2008 American Heart Association, Symposium speaker
2009 Department of Medicine Excellence in Teaching Award
2011 Keystone conference "Bugs to Drugs" Invited Symposium chair and speaker
2012 FEBS course –invited speaker, Spetses, Greece
2011 & 2014 Serpin symposium, Planning committee, Chapel Hill, NC and Leogang Austria, Invited speaker
2014 World Heart congress organizing committee and invited speaker
[2014 Endothelium and Glycocalyx Symposium Invited Speaker, Mt. Desert, Bar Harbour ME](#)

Granting Agencies - Reviewer

Canadian Institutes of Health Research (CIHR) Cardiovascular System B panel (1999-2003), Heart & Stroke Foundation of Ontario (HSFO) (2004), American Heart Association (2008- present)

Granting Agencies – External Reviewer - Medical Research Council, CIHR, Canadian Medical Discoveries Foundation, HSFO, National Cancer Institute, AHFMR, Lung Association

Journals a) Editor-in-Chief – Current Drug Targets: Cardiovascular & Hematological Disorders (CDT:CHD) (2000-2006); J Clinical Experimental Cardiology (2011-present); Book editor Bentham (2007 to present)
b) Editorial board member – International Journal of Cardiovascular Medicine and Science, CDT: Cardiovascular & Hematological Disorders (CDT:CHD), Patents & Drugs, Open Biochemistry Journal
Reviewer – Biochem Biophys Acta, Lasers Surgery and Medicine, Stroke, FASEB, Circulation, Circ Research, Open Biochemistry J, Proteins, Thromb Haemostasis, Cell Mol Biology, Frontiers Science, FEBS Letters

C. Selected peer-reviewed publications (selected from 120 peer-reviewed papers and reviews, 27 past 5 years, 17 patents, over 170 abstracts)

Most relevant to the current application

1. Liu LY, Lalani A, Dai E, Seet B, Macauley C, Singh R, Fan L, McFadden G, **Lucas A**. The viral anti-inflammatory chemokine-binding protein M-T7 reduces intimal hyperplasia after vascular injury. *J Clin Invest*. 2000;105:1613-21. PMID: PMC300852
2. Zalai CV, Kolodziejczyk MD, Pilarski L, ~~Christov A, Nation PN, Lundstrom-Hobman M, Tymchak W, Dzavik V, Humen D, Kostuk W, Jablonsky G, Pflugfelder P, Brown J et al.~~, **Lucas A**. Increased circulating monocyte activation in patients with unstable coronary syndromes *J Am Coll Cardiol*. 2001;38:1340-7. PMID: 11691505
3. Bédard EL, Kim P, Jiang J, ~~Parry N, Liu L, Wang H, Garcia B, Li X, McFadden G et al.~~, **Lucas A**, Zhong R. Chemokine-binding viral protein M-T7 prevents chronic rejection in rat renal allografts. *Transplantation*. 2003;76:249-52.
4. Liu LY, Dai E, Miller L, Seet B, Lalani A, Macauley C, Li X, Virgin HW, Bunce C, Turner P, Moyer R, McFadden G, **Lucas AR**. Viral chemokine-binding proteins inhibit inflammatory responses and aortic allograft transplant vasculopathy in rat models. *Transplantation*. 2004;77:1652-60.
5. **Lucas AR**, McFadden G. Secreted immunomodulatory viral proteins as novel biotherapeutics. *Immunology*. 2004;173:4765-74. PMID: 15470015
6. Dai E, Viswanathan K, Sun YM, ~~Li X, Liu L, Togonu-Bickersteth B, Richardson J, Macaulay C, Nash P, Turner P, Nazarian S, Moyer R, McFadden G et al.~~, **Lucas AR**. Identification of myxomaviral serpin reactive site loop sequences that regulate innate immune responses. *J Biol Chem*. 2006;281:8041-50. PMID: 16407226
7. **Lucas AR**, Mclvor D, McFadden, G. Virus-encoded chemokine modulators as novel anti-inflammatory reagents. In: Moser B, Letts GL, Neote K (editors). *Chemokine Biology—Basic Research and Clinical Application*. Basel, Switzerland: Birkhauser Publishing; 2006. Vol. 1: pp 165-82.
8. Bédard EL, Jiang J, Arp J, Qian H, Wang H, Guan H, Liu L, Parry N, Kim P, Garcia B, Li X, Macauley C, McFadden G, **Lucas AR**, Zhong R. Prevention of chronic renal allograft rejection by SERP-1 protein. *Transplantation*. 2006;81:908-14.
9. Munuswamy-Ramanujam G, Khan G, **Lucas AR**. -Viral anti-inflammatory reagents: ~~the~~ potential for treatment of arthritic and vasculitic disorders. *Endocr Metab Immune Disord Drug Targets*. 2006;6:331-43.
10. Bartee MY, Dai E, Liu L, Munuswamy-Ramanujam G, Macaulay C, Mclvor D, McFadden G, **Lucas AR**. 10 M-T7: measuring chemokine-modulating activity. *Methods Enzymol*. 2009;460: 209-28.
11. Viswanathan K, Richardson J, Togonu-Bickersteth B, Dai E, Liu L, Vatsya P, Sun Y, Yu J, Munuswamy-Ramunajam G, Baker H, **Lucas AR**. Myxoma viral serpin, Serp-1, inhibits human monocyte adhesion through regulation of actin-binding protein filamin B. *J Leukoc Biol*. 2009;85:418-26. PMID: 19052145
12. Munuswamy-Ramanujam G, Dai E, Liu LY, Shnabel M, Sun YM, Bartee M, Lomas D, **Lucas A**. Neuroserpin, a thrombolytic serine protease inhibitor (serpin), blocks transplant vasculopathy with associated modification of T-helper cell subsets. *Thromb Haemost*. 2010;103(3):545-55.
13. Dai E, Liu LY, Wang H, Mclvor D, Sun YM, Macaulay C, King E, Munuswamy-Ramanujam G, Bartee M, Williams J, Davids J, Charo I, McFadden G, Esko JD, **Lucas AR**. Inhibition of chemokine-glycosaminoglycan interactions in donor tissue reduces mouse allograft vasculopathy and transplant rejection. *PLoS One*. 2010;5:e10510. PMID: PMC2865544
14. Tardif JC, L'Allier P, Grégoire J, Ibrahim R, McFadden G, Kostuk W, Knudtson M, Labinaz M, Waksman R, Pepine CJ, Macaulay C, Guertin M-C, **Lucas A**. A randomized controlled, phase 2 trial of the viral serpin Serp-1 in patients with acute coronary syndromes undergoing percutaneous coronary intervention. *Circ Cardiovasc Interv*. 2010;3:543-8. PMID: 21062996
15. Chen H, Zheng D, Abbott J, et al., **Lucas A**. Myxomavirus-derived serpin prolongs survival and reduces inflammation and hemorrhage in an unrelated lethal mouse viral infection. *Antimicrob Agents Chemother*. 2013;57:4114-27. PMID: PMC3754305
16. Bartee MY, Chen H, Dai E, Liu LY, Davids JA, **Lucas AR**. Defining the anti-inflammatory activity of a potent myxomaviral chemokine modulating protein, M-T7, through site directed mutagenesis. *Cytokine*. 2014;65:79-87. **(Appendix 1)**
17. Davids JA, Dai E, Chen H, ~~et al.~~, ~~Bartee MY, Liu L, Fortunel A, Moyer R, McFadden G,~~ **Lucas AR**. Viral anti-inflammatory proteins target diverging immune pathways with converging effects on arterial dilatation, plaque, and apoptosis. *Eur J Inflamm*. 2014;12:131-46 ~~(in press)~~. **(Appendix 3)**

Additional recent publications of importance to the field (in chronological order)

1. Nahid MA, Rivera M, **Lucas A**, Chan EK, Kesavalu L. Polymicrobial infection with periodontal pathogens specifically enhances microRNA miR-146a in ApoE^{-/-} mice during experimental periodontal disease. *Infect Immun*. 2011;79:1597-605. PMID: PMC3067556.
2. Rivera M, Lee J, Aneja M, et al., **Lucas AR**, Kesavalu LN. Polymicrobial infection with major periodontal pathogens induced periodontal disease and aortic atherosclerosis in hyperlipidemic ApoE^{null} mice. *PLoS ONE*. 2013;8(2):e57178. PMID: PMC3581444.
3. **Lucas AR**, Verma RK, Dai E, Liu L, Chen H, Kesavalu S, Rivera M, Velsko I, Ambadapadi S, Chukkapalli S, Kesavalu L. Myxomavirus **A**anti-inflammatory **C**hemokine binding **P**rotein **R**educes the **I**ncreased **P**laque **G**rowth **I**nduced by **C**hronic *Porphyromonas gingivalis* **O**ral **I**nfection after **B**alloon **A**ngioplasty **-a**Aortic **I**njury in **M**ice. *PLoS One*. 2014 (Revisions requested). (**Appendix 2**)

Patents (17 total) - 1. Lucas AR. "Serpine Peptides, Compositions and Therapeutic Uses Thereof". 2008, 2. Lucas AR, Moyer R, Biessen E. "Novel cross class serpins with anti-apoptotic activity block human cell apoptosis, inflammation and atherosclerosis". 2006 3) Lucas AR, Zhong R, McFadden G. "Compositions and Methods for Preventing and Treating Transplant Rejection", European Patent No. 1 223 971, 2005.

D. Research Support

Active Research Support

F008570 Lucas (PI) 2006 – present
Ethel Smith Endowed Vasculitis Research Chair
The central aim for this research chair is to provide support for research into chronic vasculitic disorders.

1 RO1 DE020820-01A1 Kesavalu (PI) 03/01/2011 – 02/28/2016
NIH/NIDCR
Periodontal Pathogens and Cardiovascular Disease
The objective of this investigation is to determine the potential role of major periodontal pathogen(s) *P gingivalis*, *T denticola*, *T forsythia*, and *F nucleatum* in atherosclerosis.
Role: co-I

1 R01 AI100987-01A1 McFadden, Rahman (co-PIs) 03/01/2013- 02/28/2018
Manipulation of Inflammasomes and NF-κB signaling in human myeloid cells by Myxoma
The objective of this proposal is to investigate suppression of inflammasome activation in disease models, macular degeneration and transplant.
Role: co-I

Add in Progulske-Fox grant R56 HL122140-01A1 Progulske-Fox (PI) 07/01/2014-06/30/2019
P. Gingivalis Mediated Disruption of Autophagy in Endothelial Dysfunction
To investigate how a bacterium from the mouth that is proposed to also be involved in atherosclerosis causes or makes atherosclerosis worse. We also propose to test potential drugs that may prevent the bacterium from participating in the disease process.
Role: co-I

00095057 Lucas (PI) 07/01/2013-06/30/2015
UF Department of Medicine
Serpine Regulation of Inflammation
To assess serpin inhibition of human and mouse pancreatic tumors in syngeneic mouse models,
with
and without co-administration of gemcitabine.

00115070 Lucas (PI) 07/01/2014-06/30/2016
UF Department of Medicine
Inhibition of Allograft Vasculopathy (AV) through Blockade of Chemokine:GAG Interaction

To investigate the role of chemokines and GAG activation in AV and the potential for preventative treatment. in mouse solid organ (renal) allograft transplants.

Completed Research Support

1RC1HL100202-01 Lucas (PI) 10/01/2009 – 9/30/2012

NIH - ARRA grant

Serpin Modulation of Inflammatory Vasculitis: Potential for Immunomodulatory Therapy

~~The objective is to examine the effects of serpin modulation of inflammatory vasculitis in animal models.~~

~~0855421 E & 0855421 E Lucas (PI) 07/01/2008 – 06/30/2010 & 2012-2014~~

~~0855421 E Lucas (PI) 07/01/2012 – 06/30/2014~~

~~American Heart Association~~

~~*Inhibition of Transplant Vasculopathy by Chemokine Modulation*~~

~~The objective of this proposal was to examine the role of chemokine: GAG interactions in AV and rejection.~~

MOP-57682 & MOP-77578 -Lucas (PI) 1) 2002 – 2005

Canadian Institute of Health Research (CIHR) Two grants 2) 2005 - 2010

1) Serpin regulation of vascular responses to injury. ~~To examine serpin regulation of vascular inflammation.~~

2) Inhibition of Transplant Vasculopathy by Chemokine Modulation.

CSATVB grants (multiple) Lucas (PI) 1990-2006 by Chemokine

~~Modulation. Terminated 2007 due to relocation to UF~~

~~#T 5772 Lucas (PI) 2006 – 2009~~

~~Heart & Stroke Foundation of Ontario (HSFO)~~

~~Serpin regulation of innate immune response and vascular repair. Examination of serpin regulation of vascular inflammation and atherosclerotic plaque in mouse knockout models. Terminated 2007 due to relocation to UF~~