BIOGRAPHICAL SKETCH

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NAME: Black, Stephen M.

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

POSITION TITLE: Director, Center for Lung Vascular Pathobiology, Professor of Medicine & Physiology with Tenure, Chief, Division of Translational & Regenerative Medicine, Vice Chair for basic Research

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 Edinburgh, Scotland, U.K.	B.Sc.	07/1986	Molecular Biology
University of Edinburgh, Scotland, U.K.	Ph.D.	07/1990	Molecular Pharmacology
University of Edinburgh, Scotland, U.K.	Postdoctoral	12/1990	Biochemistry
Univ. of California, San Francisco, CA	Postdoctoral	02/1993	Endocrinology

A. Personal Statement

I will serve as the PI for this R01. I believe I am well qualified to do so for many reasons. I have significant expertise in organizing, leading, and participating in large, complex, multi-investigator teams including P01 and LeDuq Foundation awards. Further, my experience as a pulmonary vascular biologist studying mitochondrial function fits well with the overall focus of the application. My laboratory is an integrated cardiovascular laboratory studying vascular function with a focus on understanding how reactive oxygen- (ROS) and reactive nitrogen- (RNS) species generation induces post-translational modifications (PTMs) that alters endothelial mitochondrial bioenergetics and causes pulmonary vascular disease. In addition, we have been pioneering the use of mass spectrometry (MS) to identify the specific sites of these PTMs and to determine how these alter protein function. Our expertise also allows us to use of state-of-the-art cellular techniques to elucidate how ROS and RNS signaling is regulated in endothelial cells in both physiologic and pathologic situations. Further, we also have the expertise to carry these studies into clinically relevant animal models both to confirm our cell culture studies and, through directed interventions, to modulate these signaling pathways to determine effects on mitochondrial- and endothelial-function and pulmonary vascular remodeling in the intact animal. My laboratory is unique in its ability to cover such as breadth of investigations and has the broad experience required to ensure all the studies proposed in this PPG application are completed. We have developed and published the necessary protocols for all of these techniques involved as indicated in the relevant publications shown below. It is also worth noting that I have been collaborating with the co-I, Dr. Fineman for over two decades. Dr. Fineman and I have been collaborators on multiple NIH funded awards indicative of our high standing in the field of vascular biology and our ability to effectively collaborate with each other. Together, we have published 67 peer-reviewed manuscripts. Thus, I have been able to bring together a world-class leadership team that has all the necessary skills to fulfill the goals of this R01 application.

1. Zemskov EA, Lu Q, Ornatowski W, Klinger CN, Desai AA, Maltepe E, Yuan JX, Wang T, Fineman JR, **Black SM**. Biomechanical Forces and Oxidative Stress: Implications for Pulmonary Vascular Disease. Antioxid Redox Signal. 2019 Mar 19. doi: 10.1089/ars.2018.7720. [Epub ahead of print]
2. Rafikov R, Rafikova O, Aggarwal S, Gross C, Desai J, Fulton D, and **Black SM**. Asymmetric dimethylarginine induces endothelial nitric oxide synthase mitochondrial redistribution through the nitration-mediated activation of Akt1. *J. Biol. Chem.* 288:6212-6226, 2013. PMCID: PMC3585057
3. Sun X, Sharma S, Fratz S, Kumar S, Rafikov R, Aggarwal S, Rafikova O, Lu Q, Burns T, Dasarathy S, Wright J, Schreiber C, Radman M, Fineman JR, and **Black SM**. Disruption of endothelial cell mitochondrial bioenergetics in lambs with increased pulmonary blood flow. *Antioxid. Redox Signal*. 18:1739-1752, 2013. PMCID: PMC3619212

4. Fratz S, Fineman JR, Görlach A, Sharma S, Oishi P, Schreiber C, Kietzmann T, Adatia I, Hess J, and **Black SM**. Early determinants of pulmonary vascular remodeling in animal models of complex congenital heart disease. *Circulation*. 123:916-923, 2011. PMCID: PMC3873774

B. Positions and Honors

Positions and Employment

1993-1994 Research Chemist, Department of Pharmaceutical Chemistry, University of California San Francisco, San Francisco, CA
1994-1999 Assistant Professor, Department of Pediatrics, University of California San Francisco, San Francisco, CA
1997-1999 Director, Children's Health Research Center, University of California San Francisco, San Francisco, CA
1999-2003 Associate Professor, Departments of Pediatrics and Molecular Pharmacology, Northwestern Medical School, Chicago, IL
2003-2005 Associate Professor, Department of Molecular Pharmacology, University of Montana, Missoula, MT
2005-2006 Professor, Department of Molecular Pharmacology, University of Montana, Missoula, MT
2003-2006 Director, Vascular Biology, University of Montana, Missoula, MT
2004-2006 Group Leader for Neurodegeneration, Center for Structural and Functional Neuroscience, University of Montana, Missoula, MT
2006-2014 Professor with Tenure, Department of Vascular Biology, Georgia Regents University, August, GA
2008-2014 Basic Science Director, Cardiovascular Discovery Institute, Georgia Regents University, August, GA
2015- Professor, Department of Medicine, The University of Arizona College of Medicine, Tucson, AZ
2015- Director, Center for Lung Vascular Pathobiology, The University of Arizona College of Medicine, Tucson, AZ
2019- Chief, Division of Regenerative and Translational Medicine, The University of Arizona College of Medicine, Tucson, AZ
2019- Vice Chair for Basic Research, Department of Medicine, The University of Arizona College of Medicine, Tucson, AZ

Other Experience and Professional Memberships

2001 Member, Great America 3A Study Group, American Heart Association, Affiliate
2002 Member, Lung, Respiration and Resuscitation Study Group, American Heart Association, National
2002 Member, ZRG1 REN Study section, Center for Scientific Review
2003-2006 Chair, Lung, Respiration/Resuscitation Study Section, American Heart Association
2006-2011 Member, Board of Scientific Counselors NHLBI, NIH
2009-2014 Member, Pregnancy & Neonatology (PN) Study Section, NIH
2010 Co-Chair, NHLBI Translational Program Project Grants in Lung Diseases
2010 Chair, Vascular Biology, Blood Pressure Clinical/Translational Study Group, American Heart Association
2011-2013 Chair, Vascular Bio BP CT Study Section, American Heart Association
2011-2012 Chair, Utilization of Human Lung Tissue Resource for Vascular Research Study Section, NIH
2013- Member, NHLBP Study Section, NIH
2010 Vascular Pharmacology-Special issue Editor
2013 Charter member, NHLBI P01 Parent Committee
2015- Editorial Board, *Pulmonary Circulation*
2020- Editorial Board, *Antioxidants*

Honors

1997 California Affiliate, American Heart Association
1998 Scientist Development Grant, American Heart Association, National Office
1998 Elected member, Society for Pediatric Research
1998 James A. Shannon Director's Award, NIH

2000 March of Dimes Basic Research Award
2000 Grant-In Aid, American Heart Association, Midwest Affiliates
2004 Grant-In-Aid, American Heart Association, Pacific Mountain Affiliates
2007 Distinguished Faculty Award for Basic Science Research, Medical College of Georgia, School of Medicine
2011 Regents' Professor, Georgia Regents University

C. Contributions to Science

1. ***Demonstrated the key role played by oxidative stress in the development of pulmonary vascular disease.*** For nearly two decades my lab has been at the forefront of the investigation of oxidative stress as a causal factor for the development of pulmonary vascular disease. We have made many seminal contributions in this field including being the first to demonstrate that endothelin-1 mediated activation of ETA receptors plays a key role in regulating superoxide generation in smooth muscle cells. We also were the first to show the important role of NADPH oxidase activation in the development of pulmonary hypertension in fetal lambs and that the oxidative stress that underlies the development of pulmonary endothelial dysfunction associated with increased pulmonary blood flow (PBF) involved temporal changes in xanthine oxidase- and NADPH oxidase-activation as well as increases in eNOS uncoupling. Further we have pioneered investigations into the role of increased levels of asymmetric dimethylarginine in producing mitochondrial dysfunction with the subsequent inhibition of hsp90. Further, we were the first to identify that GTP cyclohydrolase, the rate limiting enzyme in BH_4 biosynthesis, is an hsp90 chaperoned protein and that ADMA targets it for proteasomal degradation through CHIP-mediated ubiquitination and that this underlies the progressive increase in eNOS-uncoupling observed during sustained increases in PBF. Thus, our ongoing work continues to make, sustained significant contributions to our understanding of oxidative stress in the development of pulmonary vascular disease. The studies planned in this application will add another important chapter to our important prior work.
   a. Brennan LA, Steinhorn RH, Wedgwood S, Mata-Greenwood E, Roark EA, Russell JA, and **Black SM.** Increased superoxide generation is associated with pulmonary hypertension in fetal lambs: A role for NADPH oxidase. *Circ. Res*. 92:683-691, 2003.
   b. Rafikova O, Rafikov R, Kumar S, Sharma S, Aggarwal S, Schneider F, Jonigk D, **Black SM**, and Tofovic SP. Bosentan inhibits oxidative and nitrosative stress and rescues occlusive pulmonary hypertension. *Free Radic. Biol. Med*. 56:28-43, 2013. PMCID: PMC3749888
   c. Sun X, Fratz S, Sharma S, Hou Y, Rafikov R, Kumar S, Rehmani I, Tian J, Smith A, Schreiber C, Reiser J, Naumann S, Haag S, Hess J, Catravas JD, Patterson C, Fineman JR, and **Black SM**. CHIP dependent GTP cyclohydrolase I degradation in lambs with increased pulmonary blood flow. *Am. J. Respir. Cell Mol. Biol.* 45:163-171, 2011. PMCID: PMC3145069
   d. Fratz S, Fineman JR, Görlach A, Sharma S, Oishi P, Schreiber C, Kietzmann T, Adatia I, Hess J, and **Black SM**. Early determinants of pulmonary vascular remodeling in animal models of complex congenital heart disease. *Circulation*. 123:916-923, 2011. PMCID: PMC3873774

2. **Identified the key role played by mitochondrial injury in the development of pulmonary endothelial dysfunction.** In a series of studies published over the last decade we have shown that the disruption of fatty acid oxidation plays a key role in the development of pulmonary vascular disease. We have shown that this is due to the disruption of carnitine homeostasis secondary to decreases in carnitine acetyltransferase nitration secondary to the translocation of uncoupled eNOS. Further, we demonstrated that preserving carnitine homeostasis is able to maintain both mitochondrial and endothelial function. These seminal studies have highlighted the important role of eNOS redistribution in regulating mitochondrial function and demonstrate the therapeutic potential of preserving mitochondrial function in pulmonary diseases.
   a. Sharma S, Sud N, Wiseman DA, Carter AL, Kumar S, Hou Y, Rau T, Wilham J, Harmon C, Oishi P, Fineman JR, and **Black SM**. Altered carnitine homeostasis is associated with decreased mitochondrial function and altered nitric oxide signaling in lambs with pulmonary hypertension. *Am. J. Physiol. Lung Cell. Mol. Physiol.* 294:L46-L56, 2008. PMCID: PMC3970936
   b. Sharma S, Sun X, Kumar S, Rafikov R, Aramburo A, Kalkan G, Tian J, Rehmani I, Kallarackal S, Fineman JR, and **Black SM**. Preserving mitochondrial function prevents the proteasomal degradation of GTP cyclohydrolase I. *Free Radic. Biol. Med.* 53:216-229, 2012. PMCID: PMC3527085

c. Sun X, Sharma S, Fratz S, Kumar S, Rafikov R, Aggarwal S, Rafikova O, Lu Q, Burns T, Dasarathy S, Wright J, Schreiber C, Radman M, Fineman JR, and **Black SM**. Disruption of endothelial cell mitochondrial bioenergetics in lambs with increased pulmonary blood flow. *Antioxid. Redox Signal*. 18:1739-1752, 2013. PMCID: PMC3619212
d. Sharma S, Aramburo A, Rafikov R, Sun X, Kumar S, Oishi PE, Datar SA, Raff G, Xoinis, K Kalkan K, Fratz S, Fineman JR, and **Black SM**. L-Carnitine preserves endothelial function in a lamb model of increased pulmonary blood flow. *Pediatr. Res*. 74:39-47, 2013. PMCID: PMC3709010

3. **Identified the key role played by the activation of the ubiquitin-proteasome pathway (UPP) in the development of pulmonary vascular disease.** In a series of studies published over the last several years we have shown that the activation of the UPP plays and important role in the loss of NO signaling associated with increased PBF. We have shown that this is a loss of mitochondrial function and the activation of the E3 ubiquitin ligase in an hsp70-dependent manner and maybe linked to the loss of PPARγ signaling. These seminal studies have highlighted the important role of mitochondrial health in regulating the UPP and demonstrate the therapeutic potential of preserving mitochondrial function in the treatment of children born with congenital heart defects that result in increased PBF.
   a. Tian J, Smith A, Nechtman J, Podolsky R, Aggarwal S, Snead C, Kumar S, Elgaish M, Oishi PE, Goerlach A, Fratz S, Hess J, Catravas JD, Verin AD, Fineman JR, She JX, **Black SM**. (2009) Effect of PPARγ Inhibition on Pulmonary Endothelial Cell Gene Expression: Gene Profiling in Pulmonary Hypertension. Physiol Genomics. 40:48-60. PMC2807211
   b. Sun X, Fratz S, Sharma S, Hou Y, Rafikov R, Kumar S, Rehmani I, Tian J, Smith A, Schreiber C, Reiser J, Naumann S, Haag S, Hess J, Catravas JD, Patterson C, Fineman JR, Black SM. CHIP Dependent GTP Cyclohydrolase I Degradation in Lambs with Increased Pulmonary Blood Flow. Am J Respir Cell Mol Biol. 2011 45:163-71. PMC3145069
   c. Sharma S, Sun X, Kumar S, Rafikov R, Aramburo A, Kalkan G, Tian J, Rehmani I, Kallarackal S, Fineman JR, **Black SM**. Preserving mitochondrial function prevents the proteasomal degradation of GTP cyclohydrolase I. Free Radic Biol Med. 2012 53:216-229. PMC3527085
   d. Sun X, Kellner M, Desai AA, Wang T, Lu Q, Kangath A, Qu N, Klinger C, Fratz S, Yuan JX, Jacobson JR, Garcia JG, Rafikov R, Fineman JR, **Black SM**. Asymmetric Dimethylarginine Stimulates Akt1 Phosphorylation via Hsp70-facilitated CTMP Degradation in Pulmonary Arterial Endothelial Cells.Am J Respir Cell Mol Biol. 2016 55(2):275-87. PMC4979361

4. **Pioneered the use of MS to study structure-function changes associated with reactive nitrogen species (RNS)-mediated protein modifications.** For over a decade my lab has been focused on developing new methodologies to investigate how RNS alter structure-function relationships in proteins that are involved in controlling endothelial cell signaling. I was a pioneer researcher that demonstrated that the S-nitrosylation of eNOS resulted in the disruption of the dimeric structure of the protein. Further using MS analyses we published seminal papers identifying the cysteine residues susceptible to both S-nitrosylation and oxidation and the Tyrosine residues susceptible to nitration. More recently we have been pioneering work that melds MS with molecular modeling techniques to gain a more fundamental understanding of how RNS-mediated protein modifications results in changes in structure-function relationships. This has so far resulted in three seminal publications that identify how protein nitration events in Akt1, PKG-1α and RhoA result in changes in enzyme activity. This body of work continues to improve our understanding of the role of protein nitration in the development of various pulmonary diseases including acute lung injury, pulmonary endothelial dysfunction associated with increased pulmonary blood flow, and pulmonary hypertension.
   a. Ravi K, Brennan LA, Levic S, Ross PA, and **Black SM**. S-nitrosylation of endothelial nitric oxide synthase is associated with monomerization and decreased enzyme activity. *Proc. Natl. Acad. Sci. USA*. 101:2619-2624, 2004. PMCID: PMC356999
   b. Rafikov R, Rafikova O, Aggarwal S, Gross C, Desai J, Fulton D, and **Black SM**. Asymmetric dimethylarginine induces endothelial nitric oxide synthase mitochondrial redistribution through the nitration-mediated activation of Akt1. *J. Biol. Chem.* 288:6212-6226, 2013. PMCID: PMC3585057
   c. Rafikov R, Dimitropoulou C, Aggarwal S, Kangath A, Gross C, Pardo D, Sharma S, Jezierska-Drutel A, Patel V, Snead C, Lucas R, Verin A, Fulton D, Catravas JD, and **Black SM**. Lipopolysaccharide induced lung injury involves the nitration-mediated activation of RhoA. *J. Biol. Chem.* 289:4710-4722, 2014. PMCID: PMC3931033

d. Aggarwal S, Gross CM, Rafikov R, Kumar S, Fineman JR, Ludewig B, Jonigk D, and **Black SM**. Nitration of tyrosine 247 inhibits protein kinase G-1α activity by attenuating cyclic guanosine monophosphate binding. *J. Biol. Chem.* 289:7948-7961, 2014. PMCID: PMC3953305

Complete List of Published work in MyBibliography:
http://www.ncbi.nlm.nih.gov/pubmed/?term=Stephen+M+Black
More than 200 peer-reviewed publications and 15 book chapters/invited reviews with a Google Scholar h-index of 65.

D. Additional Information: Research Support and/or Scholastic Performance

Ongoing Research Support (Selected)

R01HL142212 Black/Zemskov (MPI) 07/01/2018-05/31/2022
NIH/NHLBI
PKG Signaling and Sepsis Induced ALI
Objectives: To investigate the role of PKG nitration in the disruption of endothelial barrier function in ALI/ARDS
Role: PI

P01HL134610 Black (PI) 02/05/2018-01/31/2023
NIH/NHLBI
Genetics, epigenetics, and post-translational modifications and the development of ventilator- induced lung injury (VILI)
This PPG is focused on studying the critical role of mechanical ventilation, a life-saving intervention in critically ill patients with respiratory failure, in creating excessive mechanical stress that directly augments lung injury, a syndrome known as ventilator-induced lung injury (VILI).
Role: PI

P01HL146369 Black (PI) 08/010/2020-07/31/2025
NIH/NHLBI
Metabolic Reprogramming and Pulmonary Vascular Disease in Congenital Heart Disease
This PPG is focused on studying the critical role of metabolic reprogramming in the development of pulmonary vascular disease in children born with complex congenital heart defects.
Role: PI

R01HL137282 Black/Mansour/Fineman (MPI) 04/01/2017-02/28/2022 (NCE)
NIH/NHLBI
Perinatal NO Signaling in Congenital Heart Disease
This proposal is designed to increase our understanding of the mechanisms underlying the loss of $pp60^{Src}$ signaling and its role in the development of the pulmonary vascular disease associated with pulmonary over-circulation.
Role: PI

Completed Research Support (Selected)

R01HL060190 (PI: Black) 04/01/1998-04/30/2019
NIH/NHLBI
Perinatal Regulation of Endothelial NOS
This application will elucidate the mechanisms by which sustained increases in shear stress utilizes H_2O_2 to reduce NO signaling. Based on pilot data, the central hypothesis we will test is that a key event in the disruption of NO signaling in children born with congenital heart disease and increased pulmonary blood flow is a shear stress-mediated decrease in L- arginine.
Role: PI

UAHS Multidisciplinary Program Feasibility Award (Co-PIs: Black/Zhang) 07/01/2016-06/30/2018
UA U54 CounterAct development
This support is to help with the revised application to the NIH Counteract Program to develop a U54 Center of Excellence at the University of Arizona. This is a multi-disciplinary award with investigators from both the College of Medicine and Pharmacy participating.
Role: Co-PI