Example support letters from a Mentor, Chair, Chief, and Dean are also available online here: https://www.lacats.org/research-funding/roadmap-scholars/instructions/#supportletters

Inhaled iloprost, dynamic hyperinflation, and oxidative stress in COPD patients

Nominee: [redacted], MD
Assistant Professor of Medicine
Section of Pulmonary and Critical Care Medicine
Louisiana State University Health Sciences Center

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors in the order listed on Form Page 2.

Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME [redacted]	POSITION TITLE Assistant Professor of Medicine
eRA COMMONS USER NAME (credential, e.g., agency login)	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
Bucknell University	BS	06/01	Biology
Temple University School of Medicine	MD	05/05	Medicine
Temple University Hospital	Residency	05/08	Internal Medicine
Temple University Hospital	Fellowship	05/12	Pulmonary and Critical Care

A. Personal Statement

Current treatment of COPD is focused on relieving airway obstruction and inflammation in order to improve symptoms. Development of a novel approach to therapy focusing on the pulmonary vasculature will significantly expand our therapeutic armamentarium for this common and disabling lung disease. The goal of the present project is to investigate the effects of a treatment directed at the pulmonary vasculature in patients with COPD. Specifically, the effect of inhaled iloprost, a prostacyclin analogue, will be investigated, with an emphasis on mechanisms of improvement including a reduction in dynamic hyperinflation and oxidative stress. Additionally, a more detailed mechanistic investigation will be conducted by administering inhaled iloprost in an experimental murine model of COPD. The preliminary data generated through this research project would be used to apply for a K23 NIH grant. After demonstrating the short term effects and safety of inhaled iloprost with the current project, the focus for the K23 application would be on a more detailed investigation of the mechanisms of improvement as well as the long-term effects of treatment with inhaled iloprost, with potential amelioration of emphysema progression. This exciting approach would have a high degree of clinical applicability and high impact if it was shown that a new therapeutic strategy would benefit COPD patients. This research will advance the main mission of the LACaTS Center because it will focus on the care and research of one of the most important chronic diseases in this country, COPD. It also will benefit an underserved population, as COPD disproportionately affects those below the poverty level, especially in Louisiana. Additionally, it will foster fruitful collaboration between clinician-investigators and basic scientists. The protected time to conduct research, the structured mentorship, and the Master of Science in Clinical Research curriculum provided as a LACaTS Roadmap Scholar would be instrumental in the advancement of my career development into an independent and funded researcher.

I have the combination of motivation, experience in the field, and excellent mentorship to make this research project and career development plan successful and productive. I demonstrated productivity during fellowship, with 5 abstracts, 3 poster presentations, 2 book chapters and 3 publications in peer-reviewed journals. Of particular relevance to this project, I published in the field of dynamic hyperinflation and exercise in COPD; additionally, I currently have three papers on this topic submitted for publication. Since joining the faculty at LSUHSC, I

have brought two large multi-center COPD trials to LSUHSC (the LOTT and STATCOPE trials); we will be participating as a satellite facility and will begin enrolling soon.

The mentorship team that I have assembled for this project will be critical to my success. Dr. Bennett deBoisblanc is a recognized expert in pulmonary vascular disease and a noted clinical investigator who is a PI for the ARDSNet studies. He has given me his full support and has offered excellent guidance in the application process thus far. Dr. Hamid Boulares will provide mentorship into the translational science of the project; he is particularly suited for this collaboration due to his experience in oxidative stress, vascular disease, and lung disease. Also, he has a proven record of mentorship, including providing guidance to clinicians. By collaborating with Dr. Boulares on this project, I will gain a deeper understanding of the translational science that is the foundation for research as well as to learn basic laboratory techniques, both of which will be essential as I move forward in my career. Dr. Judd Shellito is the Section Chief of Pulmonary and Critical Care Medicine and Vice-Chair for Basic Research in the Department of Medicine at LSUHSC. He also is an accomplished researcher who is the PI of a Program Project Grant from the NHLBI. Dr. Shellito is an experienced physician-scientist, and his mentorship will allow me to bring together the basic and clinical sciences. Drs. Shellito and Boulares have dedicated research funds for completing the proposed study. In summary, the combination of my motivation and experience, outstanding mentors in pulmonary vascular disease, COPD, and translational science, and the support of the LACaTS center will allow me to conduct this study, which has the potential to impact patients with COPD as well as generate data needed to compete successfully for an NIH K23 grant. Additionally, the support offered under the Roadmap Scholar program will facilitate my career development, expediting my growth into an independent investigator.

B. Positions and Honors

Positions and Employment

2008-2009	Clinical Instructor in Internal Medicine, Temple University Hospital, Philadelphia, PA
2012-present	Assistant Professor of Medicine, Louisiana State University Health Sciences Center, New Orleans, LA

Professional Memberships

2001-present	Phi Beta Kappa
2005-present	Alpha Omega Alpha
2008-present	American Thoracic Society
2008-present	American College of Chest Physicians
2011-present	Clinical Problems Assembly, American Thoracic Society
2012-present	Pulmonary Circulation Assembly, American Thoracic Society

Honors and Awards

2005	Emmanuel M. Weinberger Award, Temple University School of Medicine (Outstanding Achievement in Pulmonary and Critical Care)
2005	Most Outstanding Resident, Temple University Hospital
2008	Chief Medical Resident, Temple University Hospital
2009-2010	Fellow Education Award, Temple University Hospital

C. Selected Peer-reviewed Publications

1. [redacted], Ciccolella D, Marchetti N, Kohler M, Criner GJ. Increased oxygen pulse after lung volume reduction surgery is associated with reduced dynamic hyperinflation. *Eur Respir J* 2012; 40(4):837-43

2. [redacted], Panetta N, Vega ME. Airway bypass stents for emphysema, algorithm to exclude precapillary pulmonary hypertension, and sildenafil for pulmonary hypertension in heart failure with preserved ejection fraction. *Am J Resp Crit Care Med* 2012;85(12):1323-1324

3. Remakus CB, Cordova F, Ciccolella D, Mamary AJ, [redacted], Shenoy KV, Grabianowski CL, Gaughan JP, Criner GJ. Outcomes of COPD exacerbations treated with corticosteroids, antibiotics, or both. *ISRN Pulmonology* 2011; vol. 2011, Article ID 157693, 6 pages, 2011. doi:10.5402/2011/157693

4. [redacted], Wurzel J, and Criner G. Pulmonary tumor embolism. *Lung* 2010; 188(5):441-443

5. [redacted] and Mover DV. *Candida krusei* lung abscess in an immunocompetent male. *Infectious Diseases in Clinical Practice* 2009; 17(1):58-60

D. Research Support

No current research support

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors in the order listed on Form Page 2.

Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME Shellito, Judd E.	POSITION TITLE Lowenstein Professor of Medicine Professor of Microbiology, Immunology, and Parasitology
eRA COMMONS USER NAME JSHELL	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Johns Hopkins University, Baltimore, MD	B.A.	1970	Pre-Med
Tulane University School of Medicine	M.D.	1974	Medicine

A. Personal Statement

As Chief of the LSUHSC Section of Pulmonary and Critical Care Medicine, I have a long track record of mentoring pulmonary fellows and junior faculty in research career development. My personal research deals with pulmonary host defense against infection and I am currently PI of a Program Project Grant from the NHLBI. In that capacity, I have experience with group meetings to discuss experimental results, plan research design, and strategize for grant applications. As Section Chief, I will ensure that clinical expertise is available to [redacted] for bronchoscopy and pulmonary evaluations as necessary. And as LSUHSC Co-Director of the Clinical Resources Key Component for the recently funded IDEA award (LA Clinical and Translational Science Center), I will bring these resources to the project including space and facilities for research subject interviews and examinations.

B. Positions and Honors

Positions and Employment

1974-1978 Internship/Residency, Internal Medicine, Northwestern University School of Medicine, Evanston Hospital, Evanston, Illinois

1978-1980 Pulmonary Fellow, Department of Medicine, Pulmonary Division, University of New Mexico School of Medicine

1980-1982 Research Fellow, Laboratory of H. Benfer Kaltreider, M.D., Cardiovascular Research Institute, University of California San Francisco

1982-1989 Assistant Chief, Respiratory Care Section
Director, Chest Clinic, Veterans Administration Medical Center, San Francisco, California

1982-1989 Assistant Professor of Medicine in Residence, University of California San Francisco

1988-1989 Member, Associate Staff, Cardiovascular Research Institute, University of California San Francisco

1989-1990 Associate Professor of Medicine in Residence, University of California San Francisco

1990-1993 Associate Professor of Medicine, LSU Medical Center, New Orleans, Louisiana

1990-1993 Associate Professor of Microbiology, Immunology, and Parasitology, LSU Medical Center, New Orleans, Louisiana

1990-1998 Director, Pulmonary/Critical Care Fellowship Program, LSU Medical Center, New Orleans, Louisiana
1994-present Professor of Medicine, LSU Medical Center, New Orleans, Louisiana
1994-present Professor of Microbiology, Immunology, and Parasitology, LSU Medical Center, New Orleans, Louisiana
2003-2004 Acting Director, LSUHSC Gene Therapy Program, LSU Health Sciences Center, New Orleans, LA
2008-present Section Chief, LSUHSC Section of Pulmonary/Critical Care Medicine, LSU Health Sciences Center, New Orleans, LA
2009-present Vice-Chair for Basic Research, Department of Medicine, LSU Health Sciences Center, New Orleans, LA

Other Experience and Professional Memberships
1991-present Southern Society for Clinical Investigation
1993-2009 Editorial Board, *Southern Medical Journal*
1998-2001 Member, NIH Lung Biology Study Section
2001-2006 Director, Center for Lung Biology and Immunotherapy
2006-2012 Deputy Editor, *Proceedings of the American Thoracic Society*
2012–present Member, VA Pulmonary Merit Review Panel

C. Selected peer-reviewed publications

1. Shellito J, Suzara V, Blumenfeld W, Beck J, Steger H, Ermak T. A new model of Pneumocystis carinii infection in mice selectively depleted of helper T lymphocytes. J Clin Invest 1990;85:1686-1693. PMC209424

2. Beck JM, Warnock ML, Curtis JL, Sniezek MJ, Arraj-Peffer SM, Kaltreider HB, Shellito J. Inflammatory responses to *Pneumocystis carinii* in mice selectively depleted of helper T lymphocytes. Am J Respir Cell Mol Biol 1991;5:186-197.

3. Beck JM, Liggitt HD, Brunette EN, Fuchs HJ, Shellito JE, Debs RJ. Reduction in intensity of *Pneumocystis carinii* pneumonia in mice by aerosol administration of interferon-gamma. Infection and Immunity 1991;59:3859-3862.

4. Kolls J, Beck J, Nelson S, Shellito J. Alveolar macrophage release of tumor necrosis factor during murine *Pneumocystis carinii* pneumonia. Amer J Respir Cell Mol Biol 1993;8:370-376.

5. Shellito JE, Tate C, Ruan S, Kolls J. Murine CD4+ T-lymphocyte subsets and host defense against Pneumocystis carinii. J Infec Dis 2000;181:2011-7.

6. Steele C, Zheng M, Young E, Marrero, Shellito JE, Kolls JK. Host Resistance Against Pneumocystis carinii Pneumonia in gamma delta T Cell-Deficient Mice: Protective Role of IFN-γ and CD8 T cells. Infection and Immunity 2002;70:5208-5215. PMC128275

7. Happel KI, Dubin PJ, Zheng M, Ghilardi N, Lockhart C, Quinton LJ, Odden AR, Shellito JE, Bagby GJ, Nelson S, Kolls JK Divergent roles of IL-23 and IL-12 in host defense against Klebsiella pneumoniae J Exp Med 2005;202:761-769. PMID: 16157683

8. Zheng M, Ramsay AJ, Robichaux MB, Norris KA, Kliment C,Crowe C, Rapaka RR, Steele C, McAllister F, Shellito JE, Marrero L, Schwarzenberger P, Zhong Q, and Kolls JK. CD4+ T cell-independent DNA vaccination against opportunistic infections J. Clin. Invest., 2005; 115: 3536 – 3544 PMC1288835

9. McAllister F, Steele C, Zheng M, Shellito JE, Kolls JK. In vitro effector activity of *Pneumocystis*-specific T cytotoxic-1 CD8+ T-cells: role of GM-CSF. Infec Immun 2005;73:7450-7457.

10. McAllister F, Ruan S, Kolls JK, Shellito JE. CXCR3 and IP-10 Pneumocystis pneumonia. J. Immunology 2006;177:1846-1854.

11. Rudner XL, Happel KI, Young EA, Shellito JE. The IL-23/IL-17 cytokine axis in murine Pneumocystis infection. Infection and Immunity 2007;75:3055-3061. PMC1932856

12. Happel KI, Rudner X, Quinton LJ, Clark C, Odden AR, Movassaghi JL, Zhang P, Bagby GJ, Nelson S, Shellito JE. Acute alcohol intoxication suppresses the pulmonary ELR negative CXC chemokine response to lipopolysaccharide. Alcohol 2007;41:325-333. PMC2044567

13. Ruan S, McKinley L, Zheng M, Rudner X, Kolls J, Shellito JE. Interleukin-12 and host defense against murine Pneumocystis pneumonia. Infection and Immunity 2008;76: 2130-2137. PMCID: PMC2346719

14. Shi X, Lecapitaine N, Rudner X, Shellito JE. Lymphocyte apoptosis in murine Pneumocystis pneumonia. Respiratory Research 2009;10:57. PMCID: PMC2714500

15. Kelly MN, Shellito JE. Current understanding of Pneumocystis immunology. Future Microbiology. 2010;5:43-65. PMCID: NIHMS171835(NHMSID)

16. Shi X, Zhang P, Sempowski GD, Shellito JE. The Thymopoietic and Bone Marrow Response to Murine *Pneumocysitis* Pneumonia. Infection and Immunity 2011;79:2031-2042.

17. Kelly M, Zheng M, Ruan S, Kolls JK, D'Souza A, Shellito JE. Memory CD4+ T cells are required for optimal NK cell effector functions against the opportunistic pathogen, Pneumocystis murina. In Press, J. Immunology

18. D'Souza A, Desai S, Rudner X, Kelly M, Ruan S, Shellito JE. Suppression of the Macrophage Proteasome by Ethanol Impairs MHC Class I Antigen Processing and Presentation. PLOS ONE 2013;8(2):1-10.

D. Research Support

Ongoing Research Support

P01 HL076100 Shellito (PI) 12/1/03-7/31/16
National Heart Lung and Blood Institute
Host Defense against HIV-related pulmonary infections
This Program Project grant investigates novel immune therapies for HIV-related pulmonary infections.

T32 Bagby (PI) 3/01/00-8/31/14
National Institute on Alcohol Abuse and Alcoholism
Biomedical Alcohol Research Training Program
This training grant provides a focused postdoctoral training program in alcohol-related research to MD and PhD trainees as part of the LSUHSC Alcohol Research Center.
Role: Co-Investigator

P20 RR021970 (COBRE Grant; Augusto Ochoa, PI) 8/01/10-6/30/15
NCRR/NIH
"Mentoring Translational Researchers in Louisiana"
This COBRE grant will provide mentorship and career advancement support to junior investigators at LSU Health Sciences Center.
Role: Mentor

Institutional Development Award (IDeA) for Louisiana Clinical and Translational Research (W. Cefalu, PI) 8/1/12-7/30/17
Co-Key Component Leader, Clinical Research Resources and Facilities
National Center for Research Resources (NIH)
This CTSA type grant provides comprehensive infrastructure support for clinical/translational research for LSUHSC, Tulane Health Sciences Center, and Pennington Biomedical Research Center. The Clinical Research Resources component will establish clinical research offices at each institution and provide young investigators access to clinical trials support as well as other components of the overall award.

Completed Research Support

RO1 AI51677 01-05 Shellito (PI) 5/01/02-4/30/09 (No-cost extension)
National Institute of Allergy and Infectious Disease/RO1
IL-17, and Klebsiella Pneumonia
This project investigates the host defense role of the cytokine, IL-17 against bacterial pneumonia.

P01 HL076100 Shellito (PI) 2/10/04-1/31/10 (No-cost extension)
National Heart Lung and Blood Institute
Host Defense against HIV-related pulmonary infections
This Program Project grant investigates novel immune therapies for HIV-related pulmonary infections.

P01 HL075161 Prockop (PI) 7/18/05-6/30/10
National Heart Lung and Blood Institute
Homing and Differentiation of Adult Stem Cells to Lung
Project 3 investigates bone-marrow-derived stem cells in the repair of emphysema.
Role: Project leader, Project 3

LSUHSC Translational Grant 1/7/07 – 1/6/09
"Chemokine Gradients and HIV-Associated Pneumonia"
Louisiana Board of Regents
This project attempts to validate measurement of chemokines in exhaled breath condensate of patients with pneumonia with simultaneous measurement in lavage fluid.
Role: Co-Investigator (Lee Engels, PI)

P60 AA09803 Nelson (PI) 12/01/03-11/30/09
National Institute of Alcoholism and Alcohol Abuse
Alcohol, HIV Infection, and Host Defense
Project 4 addresses the effect of alcohol consumption on the cytokine, IL-17 in bacterial pneumonia.
Role: PI, Research Component 4

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors in the order listed on Form Page 2.

Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME deBoisblanc, Bennett P	POSITION TITLE Professor of Medicine and Physiology
eRA COMMONS USER NAME (credential, e.g., agency login)	Mentor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
Louisiana State University, Baton Rouge	BS	1976	Zoology
LSU School of Medicine, New Orleans	MD	1981	Medicine
Charity Hospital, New Orleans		1981-1985	Internal Medicine
LSU Affiliated Hospitals/New Orleans		1985-1988	Pulmonary/Critical Care

A. Personal Statement

For the purposes of Dr. [redacted]s LACaTS Roadmap Scholar Award application, I will serve as his co-mentor. I was active in recruiting Dr. [redacted] to join the faculty at LSUHSC and we have developed a close working relationship. I am a physician clinical investigator with experience as a principal or a co-investigator in over 120 clinical trials, many in COPD or pulmonary vascular disease, which has direct applicability to Dr. [redacted]'s proposed research. I have personally been involved in the development of most of the therapies that we currently use to treat pulmonary hypertension, including iloprost which will be used in the current proposal. Through over 25 years of clinical trials experience, I have developed a thorough understanding of the ethical principles and federal regulations that guide clinical research. I will mentor Dr. Lammi on the principal investigator responsibilities, good clinical practice guidelines, clinical trials design, patient recruitment strategies, interactions with the IRB, data management, records keeping, working with research pharmacists, and management of protected health information. Because I am also currently funded by the NIH to perform clinical trials in ARDS, I have the knowledge and experience to help Dr. [redacted] obtain extramural funding for his next award.

B. Positions and Honors

Academic Positions Held

Assistant Professor of Medicine and Physiology, LSU Medical School, 1989-1994
Associate Professor of Medicine and Physiology, LSU Medical School, 1994-1999
Professor of Medicine and Physiology, LSU Medical School, 1999-present

Board Certification

Diplomate American Board of Internal Medicine, Sept. 1985, #104598, recertification 2000
Subspecialty Pulmonary Diseases, Nov. 1988, #104598, recertification 2000
Subspecialty Critical Care Medicine, Nov. 1989, #104598, recertification 2011

Honors and Awards

Alpha Omega Alpha, 1981
NIH National Research Service Award, 1987-1988
Fellow College of Chest Physicians, 1990-present

Fellow American College of Physicians, 1998-present
Fellow American College of Critical Care Medicine, 1998-present
Secretary-Treasurer Louisiana Thoracic Society, 1995-1996
Vice President Louisiana Thoracic Society, 1996-1997
President Louisiana Thoracic Society, 1998-2000
Southern Society of Clinical Investigation, 1995
Society for Critical Care Medicine, Critical Care Clinical Investigation Network, 1996-1999
Best Doctors in New Orleans, Best Doctors in Louisiana, Best Doctors in America (multiple years)
Director Critical Care Services, MCLNO 1995-present
Co-Director LSU-Ochsner Pulmonary Vascular Diseases Clinic, 2006-present

C. Selected Peer-reviewed Publications

1. Guery BPH, **deBoisblanc BP**, Sarphy TG, Nelson S, Beaucaire G, Summer WR, Mason CM. Pulmonary stress injury within physiological ranges of airway and vascular pressures. J Crit Care 13:58-66, 1998.
2. Nelson S, Belknap S, Carlson R, Dale D, **deBoisblanc BP**, Farkas S, Fotheringham N, Ho H, Marrie T, Movahhed H, Root R, Wilson J, and the CAP study Group. Filgrastim in the treatment of hospitalized patients with community-acquired pneumonia (CAP). J Infect Dis 178:1075-1080, 1998.
3. Pellett AA, Johnson RW, Morrison GG, Champagne MS, **deBoisblanc BP**, Levitzky MG. A comaprison of pulmonary arterial occlusion algorithms for estimation of pulmonary capillary pressure. Am J Respir Crit Care Med 160:162-168, 1999.
4. Welsh DA, Summer WR, **deBoisblanc BP**, Thomas D. Hemodynamic consequences of mechanical ventilation. Clin Pulm Med 6:52-65, 1999.
5. East TD, Heermann LK, Bradshaw MS, Lugo A, Sailors RM, Ershler L, Wallace CJ, Morris AH, McKinley B, Marquez A, Tonnesen A, Parmley L, Shoemaker W, Meade P, Thaut P, Hill T, Young M, Baughman J, Olterman M, Gooder V, Quinn B, Summer W, Valentine V, Carlson J, Bonnell B, **deBoisblanc BP**, McClarity Z, Cachere J, Kovitz K, Gallagher E, Pinsky M, Angus D, Cohen M, Hudson L, Steinberg K. Efficacy of computerized decision support for mechanical ventilation: results of a prospective multi-center randomized trial. Proc / AMIA Ann Sym :251-5, 1999.
6. Welsh DA, Guery BPH, **deBoisblanc BP**, Dobard EP, Creusy C, Mercante D, Nelson S, Summer WR, Mason CM. Keratinocyte growth factor attenuates hydrostatic pulmonary edema in an isolated perfused rat lung model. Am J Physiol Heart Circ Physiol 280(3):H1311-H1317, 2001.
7. Wunderink RG, Leeper K, Schein R, Nelson S, **deBoisblanc BP**, Fotheringham N, Logan E. Filgrastim in patients with pneumonia and severe sepsis or septic shock. Chest 119:523-529, 2001.
8. Pellett AA, Lord K, Champagne MS, **deBoisblanc BP**, Johnson RW, Levitzky MG. Pulmonary capillary pressure during acute lung injury in dogs. Crit Care Med 30:403-409, 2002.
9. **deBoisblanc BP**, Pellett AA, Johnson RW, Champagne MS, McClarity E, Dhillon G, Levitzky MG. Estimation of pulmonary artery occlusion pressure by an artificial neural network. Crit Care Med 31(1)261-6, 2003.
10. **deBoisblanc BP**, Girod-Espinoza A, Welsh D, Taylor D. Hemodynamic monitoring in ALI/ARDS. Respir Care Clin 9:457-479, 2003.
11. Rizvi K, **deBoisblanc BP**, Truwit JD, Dhillon G, Arroliga A, Fuchs BD, Guntupalli KK, Hite D, and D. Hayden for the NIH/NHLBI ARDS Clinical Trials Network. Effect of airway

pressure display on inter-observer agreement in the assessment of vascular pressures in patients with acute lung injury and ARDS. Crit Care Med (in press)
12 Pellett A, **deBoisblanc BP**, Welsh D. Low positive end-expiratory pressure does not exacerbate nebulized-acid lung injury in dogs. J Crit Care 20:97-105, 2005.
13. Bierre S, Kumari R, **deBoisblanc BP**. The endocrine system during sepsis. Am J Med Sci 328(4),2004.
14. **deBoisblanc BP**. Black Hawk please come down: reflections on Charity Hospital's struggle to survive in the wake of Hurricane Katrina. Am J Respir Crit Care Med 172(10):1239-40, 2005.
15. **deBoisblanc BP.** Acute lung injury: new insights from computed tomography. Crit Care Med 33:900-901, 2005.
16. Wiedemann HP, Wheeler AP, Bernard GR, Thompson BT, Hayden D, **deBoisblanc B**, Connors AF, Hite RD, Harabin AL, National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network. Comparison of two fluid-management strategies in acute lung injury. New England Journal of Medicine. 354(24):2564-75, 2006.
17. Wheeler AP, Bernard GR, Thompson BT, Schoenfeld, D, Wiedemann HP, **deBoisblanc B**, Connors AF, Hite RD, Harabin AL, National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network. Pulmonary-artery versus central venous catheter to guide treatment of acute lung injury. New England Journal of Medicine. 354(21):2213-24, 2006.
18. Brierre, S, **deBoisblanc BP**,. Common pitfalls in the use of the pulmonary artery catheter. http:// www.chestnet.org. PCCU 20:13, 2006.
19. Wheeler AP, Bernard GR, Thompson BT, Schoenfeld, D, Wiedemann HP, **deBoisblanc B**, Connors AF, Hite RD, Harabin AL, National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network. Pulmonary-artery versus central venous catheter to guide treatment of acute lung injury. New England Journal of Medicine. 354(21):2213-24, 2006.
20. Jain S, Venura H, **deBoisblanc BP**. Pathophysiology of pulmonary hypertension. Sem Cardiothoracic Vasc Anesthes 11:104-109; 2007.
21. Jain S, **deBoisblanc BP**. Pulmonary Vascular Diaseases. in: *Pulmonary Pathophysiology*. Ali J, Summer WR, Levitzky MG, eds. McGraw-Hill, New York, 2009
22. Walkey AJ, Rice T, Konter J, Ouchi N, Shibata, R, Walsh K, **deBoisblanc BP**, Summer R. Plasma. Adiponectin and Clinical Outcomes in Critically Ill Subjects with Respiratory Failure. Crit Care Med 38(12) 2329-2334, 2010.
23. Rice TW, Wheeler AP, Thompson BT, **deBoisblanc BP**, Steingrub J, Rock P, and the NHLBI ARDS Clinical Trials Network. Enteral omega-3 fatty acid, gamma-linolenic acid, and antioxidant supplementation in acute lung injury. JAMA 306(14):1574-1581, 2011.
24. ARDSnet Investigators. Initial trophic vs full enteral feeding in patients with acute lung injury. JAMA 307(8):795-803, 2012.

D. Research Support

Ongoing Federal Principal Investigator:
Louisiana Critical Care Clinical Center (CCCC) within the NIH-NHLBI ARDSnet 2002-present. The goals of ARDSnet are to test novel therapies for the prevention or treatment of ALI/ARDS. A randomized trial of rosuvastatin for acutely injured lungs in sepsis ("SAILS").

Ongoing Non-Federal Principal Investigator:

1. A randomized, double blind, placebo-controlled, multi-center study of first line Ambrisentan and Tadalafil combination therapy in subjects with pulmonary arterial hypertension; GS-US-300-0140/AMB112565 . 2010.
2. A phase 2 randomized double blind placebo controlled multicenter dose ranging study of cicletanine in subjects with pulmonary arterial hypertension;GS-US-235-0101 Gilead. 2009
3. A multicenter, double-blind, placebo-controlled Phase 3 study to demonstrate the efficacy and safety of ACT-293987 in patients with pulmonary arterial hypertension; Actelion AC-065A-302 Griphon 302. 2010
4. Long-term single-arm open-label study, to assess the safety and tolerability of ACT 293987 in patients with pulmonary arterial hypertension; Actelion AC-065A-303 Griphon 303. 2010
5. Prospect: Registry to prospectively evaluate use of room temperature stable epoprostenol for injection in patients with pulmonary arterial hypertension; Actelion AC-066A-501. 2011

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors in the order listed on Form Page 2.

Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME Boulares, A. Hamid	POSITION TITLE Associate Professor
eRA COMMONS USER NAME (credential, e.g., agency login)	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
University of Sciences and Technology at Algiers and the Pasteur Institute, Algiers, Algeria	B.S.	1983-1987	Microbiology
University of Connecticut, Storrs, CT	M.S.	1990-1992	Microbiology
University of Connecticut, Storrs, CT	Ph.D.	1992-1997	Biochemistry
Georgetown University, Washington, DC	Post. Doc.	1997-2000	Biochemistry

A. Personal Statement

I am writing to express my strong support of Dr. [redacted]'s LaCATS Roadmap Scholar Award application. His project entitled "*Inhaled iloprost, oxidative stress and dynamic hyperinflation in COPD patients*" is timely with high clinical significance. I will serve as a co-mentor for Dr. [redacted] and put my extensive experience in mentoring along with that of Drs. deBoisblanc and Shellito in the Pulmonary and Critical Care section of LSUHSC to serve and benefit his training in research. [redacted] and I have met in person repeatedly and discussed the details of the project. In addition to studying the clinical effects of inhaled iloprost on oxidative stress parameters and dynamic hyperinflation in patients with COPD, he will also explore mechanisms underlying the potential benefit of this medication in an animal model of the disease. This model is well-established in the laboratory. We also have an *in vitro* model of the disease using cigarette smoke extracts with primary human lung epithelial cells. My research expertise in the inflammatory processes including asthma and COPD and the molecular intricacies associated with these diseases makes me uniquely qualified to guide Dr. [redacted] in this area. I plan on providing [redacted] with mentorship and guidance in the translation of clinical research into a laboratory environment. I will also provide him with allocated laboratory space and expert assistance in running the needed experiments. Lastly, through this research project [redacted] will gain a more in-depth knowledge of oxidative stress in lung disease as well as basic laboratory techniques.

Over the past 15 years I have mentored several junior faculty members, postdoctoral researcher/fellows, and many graduate, MD/Ph.D., and undergraduate students. I have trained several junior faculty members, close to fifteen postdoctoral researchers and six graduate students, two of whom have already graduated. Most of the postdocs I have trained were successful in getting extramural funds while in my laboratory and went on to become independent scientists with major independent funding. [redacted] will receive the same attention. He will benefit from repeated informal interaction with me and members of my lab as well as scheduled weekly laboratory meetings. [redacted] is a highly energetic junior faculty with a highly inquisitive and independent mind. I am very sure that this support will help him generate critical data that will be the basis for future extramural grant application.

B. Positions and Honors

Professional Experience:

1992-1995	Teaching Assistant for Fundamentals of Microbiology and Pathogenic Microbiology (UCONN)
1995-1997	Head of Teaching Assistants for Microbiology (University of Connecticut)
1997- 2000	Research Associate at Georgetown University Medical Center
2000-2002	Assistant Professor (Research Track) at Georgetown University Medical Center, Department of Molecular Biology, Washington, DC.
2002-2008	Assistant Professor (Tenure Track) at LSUHSC, Dept. Pharmacology, New Orleans, LA.
2002-2008	Adjunct Assistant Professor, Stanley Scott Cancer Center, LSUHSC, New Orleans, LA
2008-Present	Associate Professor (tenured) at LSUHSC, Dept. of Pharmacology, New Orleans, LA.
2008-Present	Associate Professor at LSUHSC, Dept. of Pathology, New Orleans, LA.
2008-Present	Adjunct Associate Professor, Stanley Scott Cancer Center, LSUHSC, New Orleans, LA

Other Experience and Professional Memberships

1995-96	Member, American Society of Virology
1995-2001	Member, Northeast Society of Toxicology
2000	Member, Society of Toxicology
2004-	Member, American Heart Association
2006-	Member, American Association of Immunologists
2008-	Member, European Respiratory Society
2009-	Member, American Society for Pharmacology and Experimental Therapeutics (ASPET)
2009-	Member, Society for Leukocyte Biology
2010-	Member, *Editorial Board of the J Clinical and Experimental Cardiology*

Honors

1996	Dissertation Proposal Award/Research Foundation of the Univ. of Connecticut,
1997	The Graduate Student Teaching Excellence Award, Univ. of Connecticut,
2000	Board of Publications Award:Best Paper in *Toxicological Sciences* (Boulares et al. 1999 *Toxicol. Sci.* 48:264-274) at the Society of Toxicology 39th annual meeting.
2009	*Outstanding Scientific Achievement* (Signaling Program)/ The Louisiana Cancer Research Consortium Second Annual Scientific Retreat
2009	American Cancer Society Scholar

Ad Hoc member:

2007-	*Member, Peer Review Committee*, American Heart Association: Southern and Ohio Valley 2A; Study group: Lipoproteins, Lipid Metabolism and Nutrition, Thrombosis, and Vascular Wall Biology.
2009	NIH/ZRG1 CVRS B Study Section
2010-	NIH/F10A study section (2010-present)
2010	NIH/LCMI study section
2010	The Research Netherlands Asthma Foundation
2011	Co-Chair NIH/RIBT study section
2012	*Member, Peer Review Committee*, Italian Ministry of Health
2012	NIH/Atherosclerosis and Inflammation of the Cardiovascular System (AICS)

C. Selected Peer-reviewed Publications (Most relevant to the current application; selected from 56 peer-reviewed publications)

1. Oumouna M, Datta, R, Oumouna-Benachour, K., Suzuki, Y., Hans, C., Matthews, K., Fallon, K. and **Boulares AH***. PARP-1 Inhibition Prevents eosinophil recruitment by Modulating Th2 Cytokines in a Murine Model of Allergic Airway Inflammation: a Potential Specific Effect on IL-5. *J. Immunol.* (2006) 177(9):6489-96.
2. Kanai, M., Hanashiro, K, Kim, S, Hanai, S, **Boulares**, AH, Miwa, M, and Fukasawa, K. (2007). Inhibition of Crm1-p53 Interaction and Nuclear Export of p53 by Poly(ADP-ribosyl)ation. *Nature Cell Biol.* **9**(10):1175-83
3. Oumouna-Benachour K, Hans, C, Suzuki, Y, Naura, A., Datta, R, Belmadani, S., Woods, C, and **Boulares, H***. PARP-1 Inhibition Reduces Atherosclerotic Plaque Size and Promotes Factors of Plaque Stability in ApoE-Deficient Mice: Effects on Macrophage Recruitment, NF-κB Nuclear Translocation, and Foam Cell Death. (2007) *Circulation* **115** (18): 2442.
4. Zerfaoui M, Suzuki Y, Naura A, Hans C, and **Boulares AH***. (2007). Nuclear translocation of p65 NF-κB is sufficient for VCAM-1, but not ICAM-1, expression in TNF-stimulated smooth muscle cells: differential requirement *for PARP-1 expression and interaction (2008). Cellular Signalling 20(1):186-94.*
5. Naura A, Hans C, Zerfaoui M, You D, Cormier S, Oumouna M, and **Boulares AH***. (2008). Post-allergen Challenge Inhibition of PARP Harbors Therapeutic Potential for Treatment of Allergic Airway Inflammation. Clin. Exp. Allergy;38(5):839-46
6. Hans, PC., Zerfaoui, M., Naura, AS., Catling, A., and **Boulares, AH***. Differential Effects of PARP Inhibition on Vascular Cell Survival and ACAT-1 Expression Favoring Atherosclerotic Plaque Stability. 2008. *Cardiovascular Res. 78(3):429-39*
7. Naura A S, R Datta, C P. Hans, M Zerfaoui, Y Errami, B. M. Rezk, M Oumouna, K. Matrougui, and **A H Boulares***. (2009) Reciprocal regulation of iNOS and PARP-1 during allergen-induced eosinophilia. *Eur Respir.* 33:252-262.
8. Zerfaoui M, Errami, Y, Naura, AS, Suzuki, Y, Kim, H, Ju, J, Liu, T, Hans, CP, Kim, JG, Abd Elmageed, Z, Koochekpour, S, Catling, A, **Boulares, AH***. *PARP-1 is a determining factor in Crm1-mediated nuclear export of p65 NF-κB and retention upon TLR4 stimulation: A novel mechanism of regulating NF-κB-dependent gene expression. J Immunol.* 2010;185(3):1894-902.
9. Naura, A; Zerfaoui, M; Kim, H; Abd Elmageed, Z; Rodriguez, P; Hans, C; Ju, J; Errami, Y; Park, J; Ochoa, A; and **Boulares,AH***. *Requirement for iNOS in chronic allergen exposure-induced pulmonary fibrosis but not inflammation. J Immunol.* 2010; 185(5):3076-85.
10. Zerfaoui, M, Suzuki, Y, Naura, A, Hans, C, and **Boulares, AH***. (2007). Nuclear translocation of p65 NF-κB is sufficient for VCAM-1, but not ICAM-1, expression in TNF-stimulated smooth muscle cells: differential requirement for PARP-1 expression and interaction (2008). *Cellular Signalling **20**(1):186-94.*
11. Ju, J; Naura, AS.; Zerfaoui, M; Kim, H; Errami, Y; Kim, JG., and **Boulares, AH***. Phosphorylation of p50 NF-κB at a single serine residue by DNA-dependent protein kinase is critical for VCAM-1 expression upon TNF treatment *J. Biol. Chem. 2010;285(52):41152-60.*
12. *Kim H, Naura AS, Errami Y, Ju J, **Boulares AH***. Cordycepin blocks lung injury-associated inflammation and promotes BRCA1-deficient breast cancer cell killing by effectively inhibiting PARP. Mol Med. 2011 Sep-Oct;17(9-10):893-900*
13. Errami Y, Naura AS, Kim H, Ju J, Suzuki Y, El-Bahrawy AH, Ghonim MA, Hemeida RA, Mansy MS, Zhang J, Xu M, Smulson ME, Brim H, **Boulares AH***. *Apoptotic DNA fragmentation may be a cooperative activity between caspase-activated DNase and the PARP-regulated DNAS1L3, an ER-localized endonuclease that translocates to the nucleus during apoptosis. J. Biol. Chem. 2013. 288(5):3460-8.*
14. Yadav UC, Naura AS, Aguilera-Aguirre L, Boldogh I, **Boulares AH**, Calhoun WJ, Ramana KV, Srivastava SK. Aldose Reductase Inhibition Prevents Allergic Airway Remodeling through PI3K/AKT/GSK3β Pathway in Mice. *PLoS One. 2013;8(2):e57442.*

15. Naura AS, Kim H, Ju J, Rodriguez PC, Jordan J, Catling AD, Rezk BM, Abd Elmageed ZY, Pyakurel K, Tarhuni AF, Abughazleh MQ, Errami Y, Zerfaoui M, Ochoa AC, **Boulares AH***. *Minocycline blocks asthma-associated inflammation in part by interfering with the TCR-NF-κB-GATA-3-IL-4 axis with a prominent effect PARP. J. Biol. Chem. 2013. 288(3):1458-68.*

D. Research Support

Ongoing Research Support

R01HL072889- Boulares (PI) 2/2011-11/2015
Participation of PARP in asthma pathogenesis
The goals are to study the roles of PARP-1 in the pathogenesis of asthma-associated lung inflammation and its role in regulating key inflammatory factors such as NF-κB, iNOS, adhesion molecules and cytokines.
Role: PI

Amer Cancer Society RSG-116608 Boulares (PI) *07/2009-06/2013*
Roles of PARP-1 and DFF in colon tumorigenesis
The goal is to test the hypothesis that the DNA fragmentation factor (DFF) and PARP-1–mediated amplification phase of apoptosis (proposed by us) plays an important role in physiological turnover of the colonic epithelium, and that alterations in one or more of the components of this phase provide a growth advantage to cells with genomic abnormalities and promote their development into colon tumors.
Role: PI

1P20RR18766 Kapusta (PD) 09/2008-08/2013

Mentoring in cardiovascular Biology
The goal of this COBRE grant is to train junior investigator in the field of cardiovascular research to increases their chances of getting independent extramural funding
Role: Mentor

1P20GM103501 Augusto Ochoa- PD 08/2010 - 07/2015
Mentoring in Translational Research in Louisiana
Role: Mentor

NIH/NRSA Fellowship *Student: Rahul Datta* *7/2009-6/2012*
The goal is to determine the mechanism by which PARP-1 regulates IL-5 during lung inflammation.
Role: Mentor

American Heart Association Postdoc Fellowship PI: Jihang Ju *7/2011-6/2013*
The goal is to determine the mechanism by which DNA-PK regulates NF-κB and expression of associated genes during vascular wall inflammation.
Role: Mentor

Fellowship from the Egyptian Embassy/Higher education ministry *Student:* M Ghonim
Role: Mentor 6/2012-5/2014

Fellowship from the Egyptian Embassy/Higher education ministry *Student:* A Hassan
Role: Mentor 8/2012-7/2014

Fellowship from the Libyan Ministry of Higher Education and Scientific Research/the Canadian Bureau for International Education *Student:* A Tarhuni 10/2012-5/2015

Role: Mentor

Abstract

This is an application for the LACaTS Roadmap Scholar Award for Dr. [redacted], a pulmonary and critical care faculty member at LSUHSC. This award will provide Dr. [redacted] with the support necessary to achieve the following goals: (1) develop an independent patient-oriented translational research career focused on the pulmonary vasculature in COPD; (2) generate sufficient preliminary data for a successful K23 NIH submission at the end of 18 months; (3) become skilled at basic laboratory techniques that will be used in future research studies; (4) gain expertise in epidemiology and biostatistics by courses taken towards a Master of Science in Clinical Research. In order to accomplish these goals, an outstanding mentorship team of Drs. Judd Shellito, Bennett deBoisblanc, and Hamid Boulares has been assembled which will combine clinical and basic science expertise in the areas of pulmonary vascular disease and oxidative stress. The proposed research project will explore the role of the pulmonary vasculature in COPD by expanding on recent data which have shown: (1) histological changes and endothelial dysfunction are nearly ubiquitous findings and play a central role in early pathogenesis in COPD; (2) oxidative stress, in part arising from the pulmonary vasculature, is a critical component in the initiation and progression of COPD and has been linked to dynamic hyperinflation; (3) prostacyclin analogues, such as inhaled iloprost, have been found to alter emphysema development in experimental models; (4) inhaled iloprost reduces oxidative stress in other disease states. The proposed research has 3 components: (1) To test the hypothesis that inhaled iloprost will reduce dynamic hyperinflation, a placebo-controlled crossover study will be conducted in 24 COPD patients undergoing exercise testing. (2) To test the hypothesis that inhaled iloprost will reduce oxidative stress in COPD, markers of oxidative stress will be measured in these same 24 patients before and after inhaled iloprost. (3) To more comprehensively explore the effect of inhaled iloprost on lung physiology and biology, an experimental mouse model of COPD will also be utilized. The aims are consistent with the goals of LACaTS, as COPD is a critically important chronic disease that disproportionately affects residents of Louisiana. The proposed study and subsequent work may lead to a new treatment strategy that is desperately needed in COPD. Additionally, the career development plan will foster the growth of Dr. Lammi into an independent translational investigator.

Proposed performance sites

- Clinical testing will take place at the Interim Louisiana Hospital in New Orleans. This includes pulmonary function testing, exercise testing, and arterial blood gas analysis.
- Echocardiography will take place at the School of Allied Health Professionals in New Orleans.
- Animal experiments will be performed at the Louisiana Cancer Research Center in New Orleans in the lab of Dr. Hamid Boulares. This will also be the site for assays involving oxidative stress and inflammation obtained during the human study.

Mentors

Judd Shellito, MD. Dr. Shellito is a Professor of Medicine and Microbiology, Immunology, and Parasitology at Louisiana State University Health Sciences Center. He is also the Section Chief of Pulmonary and Critical Care Medicine and is the Vice Chair for Research in the Department of Medicine at LSUHSC. Additionally, he has extensive experience in translational research and is the PI of an NIH Program Project Grant investigating novel immune therapies in HIV-related pulmonary infections.

Dr. Shellito was responsible for recruiting me to LSUHSC and has been extremely supportive of my growth since the beginning of my appointment. I am confident that this support will continue and grow through the formal mentorship offered in the LACaTS program. His guidance will be particularly valuable, as he is truly a physician-scientist through whom I will learn the role of the clinician in translational science. I will meet on a weekly basis with Dr. Shellito to discuss the progress of my research and career development.

Bennett deBoisblanc, MD. Dr. deBoisblanc is a Professor of Medicine and Physiology in the Section of Pulmonary and Critical Care Medicine at Louisiana State University Health Sciences Center. Dr. deBoisblanc is an experienced clinical researcher who is a Principal Investigator of the NIH ARDSNet study. He is also co-director of Ochsner-LSU Pulmonary Vascular Disease Clinic, which is a regional referral center for patients with pulmonary hypertension. He has extensive experience in conducting clinical trials in patients with pulmonary vascular disease.

In preparation for this award submission, Dr. deBoisblanc has already offered extensive guidance in study design of the project. Due to his experience with clinical trials, I will learn about the recruitment and retention of study subjects as well as the responsible conduct of research. Additionally, he will offer guidance in manuscript preparation/submission and grant writing. Regularly scheduled meetings will be conducted every week to formalize and solidify these topics. I have found Dr. deBoisblanc to be an outstanding mentor to me thus far in my academic career and firmly believe that his mentorship is instrumental to my future success.

Hamid Boulares, PhD. Dr. Boulares is an Associate Professor of Pharmacology at the Louisiana State University Health Sciences Center. Dr. Boulares is an independently funded researcher who has extensive research experience in the fields of oxidative stress, lung disease, and vascular disease, which makes him an ideal mentor for this project. He also has a long and successful track record of mentoring PhD's and MD's.

Dr. Boulares has been extremely forthcoming and generous in his time and guidance in preparing for this award submission. Dr. Boulares is a well-published NIH-funded investigator and therefore will offer guidance in manuscript preparation and submission, along with successful grant writing. I will also learn basic science techniques in his lab, which will be critical in gaining a more in-depth understanding of translational research, so that I may take ideas from the clinical realm to the lab, and vice versa. Regularly scheduled meetings every week will be conducted to formalize and solidify these topics.

Specific Aims

Chronic obstructive pulmonary disease (COPD), the 3rd leading cause of death in the US, is a progressive disorder for which new treatments are urgently needed, as existing therapies are focused primarily on symptom relief. Oxidative stress, in part arising from inducible nitric oxide synthase (iNOS) released by the pulmonary vasculature, is critical for the development and progression of COPD; a treatment strategy focused on the pulmonary vasculature is hypothesized to be beneficial in COPD patients. This will be studied with the use of an inhaled prostacyclin analogue, iloprost, which has been approved for pulmonary hypertension and investigated in small studies of COPD patients. Potential mechanisms include reductions in dynamic hyperinflation during exercise in COPD patients (Aim 1) or improvements in oxidative stress and/or inducible nitric oxide synthase expression (Aims 2 and 3). We will define these mechanisms by pursuing the following Specific Aims:

Hypothesis 1: The acute administration of inhaled iloprost to COPD patients reduces minute ventilation requirements and dynamic hyperinflation during exercise.

Aim 1: Determine the effect of acutely administered inhaled iloprost on dead space ventilation, metabolic isotime minute ventilation, and inspiratory capacity during maximal cardiopulmonary exercise testing in COPD patients.

Hypothesis 2: Acutely administered inhaled iloprost reduces oxidative stress in COPD patients.

Aim 2: Determine the effect of acutely administered inhaled iloprost on serum markers of oxidative stress and inflammation in COPD patients.

Hypothesis 3: In a murine model of COPD, the administration of inhaled iloprost reduces oxidative stress, the expression of inducible nitric oxide synthase (iNOS), and bronchial hyperresponsiveness.

Aim 3: Determine the effect of inhaled iloprost on oxidative stress, iNOS, and bronchial hyperresponsiveness in a murine model of COPD and airway inflammation induced by LPS and elastase. The use of an animal model with acute and repeated challenges of iloprost will be required for a more comprehensive functional and biologic assessment.

The long-term result of this line of work may be a new treatment strategy focused on the pulmonary vasculature and oxidative stress in COPD patients. To achieve the goals of this study, an integrative approach will be taken that includes human COPD patients, an animal model of this condition, and molecular techniques. The proposed work is highly innovative because it would constitute the first clinical study addressing the relationship between the effects of inhaled iloprost on oxidative stress and dynamic hyperinflation in COPD patients as well as addressing the effect(s) of the drug in an animal model of pre-existing emphysema and airway inflammation. At the completion of this project, I will have the necessary preliminary data to successfully compete for extramural funding.

Significance: COPD is an inflammatory disorder of the lungs that is the 3rd leading cause of death in the U.S. and a major cause of morbidity and mortality worldwide. Although cigarette smoking is the proximal etiology of most cases of COPD, the disease often progresses after smoking cessation due to self-amplifying loops of apoptosis, oxidative stress (OS), and inflammation[1]. Current treatments are primarily focused on symptom relief and a therapeutic strategy to disrupt the cycle of physiologic and functional decline is desperately needed.

Clinical pulmonary hypertension (PH) is present in approximately 20% of COPD patients[2], but early histopathologic changes and endothelial dysfunction in pulmonary arteries are central features in most patients[3,4]. Exercise limitation in COPD has an important connection to the pulmonary circulation, as blood flow regulation and ventilation/perfusion matching determines minute ventilation needs. Exercise dyspnea results directly from dynamic hyperinflation, a temporary and variable increase in end-expiratory lung volume (i.e. gas trapping) during increased minute ventilation[5]. ***Inhaled iloprost, a synthetic analogue of***

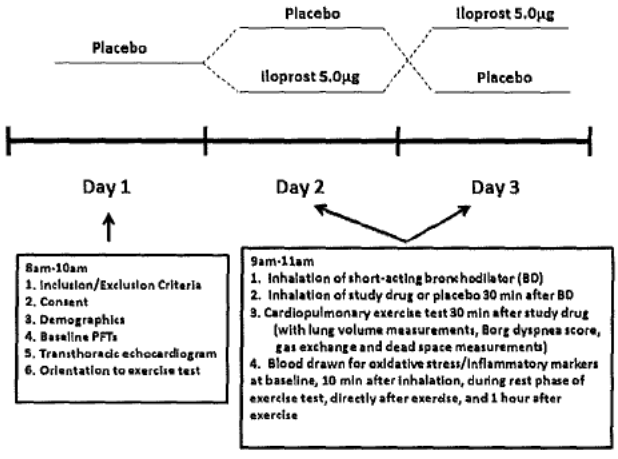
prostacyclin used clinically for pulmonary arterial hypertension, may be efficacious in the treatment of COPD since it directly regulates the pulmonary vasculature and has been shown in other disease states to reduce oxidative stress.

Treatment of the pulmonary vasculature and oxidative stress has been found in animal studies to halt progression or even cause reversal of emphysema[6,7]; it appears that these remarkable findings were caused by decreases in inducible nitric oxide synthase (iNOS). Iloprost has further been shown to decrease cigarette smoke extract (CSE)-induced pulmonary arterial endothelial cell apoptosis[8]. Beraprost, another prostacyclin analogue, was found to abrogate CSE-induced apoptosis, proteolytic enzyme and inflammatory cytokine release, oxidant activity, and emphysema development[9]. ***Iloprost has antioxidant effects in other disease states, which may explain its long-term benefit despite its short-term hemodynamic properties.*** Iloprost has been found to decrease oxidative stress in experimental models of LPS-induced lung injury[10] and myocardial ischemia[11]. In humans, iloprost decreases oxidative stress in critical limb ischemia[12] and scleroderma[13,14].

A randomized trial of iloprost in COPD-PH was planned by the manufacturer but was recently terminated due to low enrollment because of restrictive inclusion criteria focusing on severe PH. Acutely administered inhaled iloprost was investigated in two small studies of COPD patients with PH. One study reported a significant improvement in 6-minute walk distance[15], while the other showed no overall effect on exercise tolerance, although several patients responded favorably[16]. Importantly, both studies showed a significant beneficial decrease in minute ventilation with one[15] also finding decreased dead space. It is likely that inhaled iloprost increases blood flow to areas of the lung with high ventilation/perfusion ratios thereby decreasing dead space and required minute ventilation during exercise. ***In our study, the expected effect of inhaled iloprost would be a decrease in dynamic hyperinflation and exercise dyspnea independent of the presence of concomitant PH.***

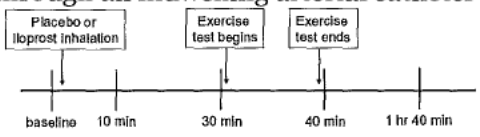
Innovation: Our proposal contains many innovative aspects. (1) This would be the first study to quantify the effects of iloprost on oxidative stress in COPD patients and (2) the first to determine the effects of iloprost on exercise dynamic hyperinflation. Although the ability of prostacyclin analogues to modify emphysema *development* in experimental models has been demonstrated, (3) no study to date has evaluated the effect of iloprost on *pre-existing* emphysema in mice. The preliminary data generated through these experiments would lead to further investigation into treatments directed at the pulmonary vasculature, which may represent a new approach to treating COPD.

Research Approach: In order to accomplish Aims 1 and 2, a 24 patient, single-center, prospective, randomized, placebo-controlled, double-blind crossover study will be conducted. The co-primary outcomes studied will be dynamic hyperinflation (DH) during maximal cardiopulmonary exercise testing (CPET) and 8-isoprostane, a marker of oxidative stress (OS). Secondary outcomes will include peak oxygen consumption and exercise time, dead space ventilation during CPET, Borg dyspnea score, safety and oxygenation, and other markers of oxidative stress and inflammation. Patients will be included if they are >40 years old with a ≥10 pack-year history of smoking and have a physician diagnosis of moderate-severe COPD confirmed by spirometry ($FEV_1/FVC<0.7$ and FEV_1). Key exclusion



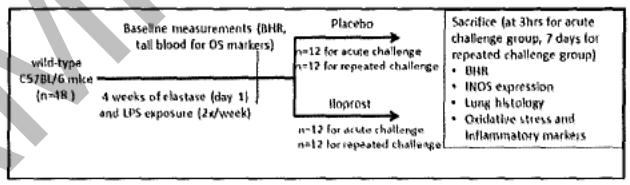
criteria include COPD exacerbation within 30 days, known inflammatory disease other than COPD, the need for oxygen therapy, active smoking or oral corticosteroid use. I will recruit patients from outpatient clinics and through a database of 483 COPD patients who have agreed to be contacted about clinical studies.

This will be a 3-day study for each patient (see figure above). On day 1, consent will be obtained, followed by baseline pulmonary function testing (PFTs)[17] and echocardiography[18]. Days 2 and 3 will be identical except for the treatment given (saline placebo or 5.0μg inhaled iloprost over 10 minutes), the order of which will be determined randomly. Blood will be drawn through an indwelling arterial catheter at time intervals outlined in the figure below.



A maximal CPET will be conducted[19]; standard respiratory and metabolic measures will be collected, as well as inspiratory capacity[20] for measurement of DH and arterial blood gases every 2 minutes for calculation of dead space fraction (**Aim 1**). I will conduct measurements of serum IL-1β IL-6, IL-8, IL-10, IL-13 IL-18, TNF-α, 8-isoprostane, superoxide dismutase, catalase, nitrite, and plasma malondialdehyde by Bio-Rad multiplex analysis in Dr. Boulares' lab (**Aim 2**). Although our hypotheses are based on sound reasoning and data, we recognize that it is possible that inhaled iloprost will not have an overall favorable effect on this group of COPD patients. If this would occur, analyses will be performed to discover clinical and biologic phenotypes of responders that can be used in future studies. Other analyses, such as the relationship between DH and OS[21] or the influence of exercise on OS in COPD[22], can be conducted with data collected in this study.

In order to accomplish Aim 3, an animal study will be conducted for a more comprehensive analysis of the effect of inhaled iloprost on mice with LPS/elastase-induced COPD. Forty-eight 5 week old wild-type C57BL/6 mice will receive elastase and LPS[23] to induce a phenotype of COPD, as has been done successfully in Dr. Boulares' lab. After 4 weeks, I will make baseline measurements of bronchial hyperresponsiveness (BHR)[24] and oxidative stress markers (obtained from tail blood) by multiplex analysis[24]. Mice will be assigned randomly into 1 of 4 groups, each with 12 mice: single-dose placebo, single-dose inhaled iloprost (0.20μg delivered intratracheally[25]), repeated challenge of placebo (daily for 7 days), or repeated challenge of iloprost (daily for 7 days). Mice will be sacrificed at the end of their exposure period (3 hours for the single-dose group and 7 days for the repeated challenge group). Using protocols established in Dr. Boulares' lab, I will perform the following measurements in all groups: BHR[24], iNOS expression[26], markers of oxidative stress and inflammation[24], cytokines in bronchoalveolar lavage fluid[24], and histology with morphologic assessment of emphysema[27,7] (**Aim 3**). In this ideal situation we will have measurements of the same mice at baseline (after COPD induction) and then after exposure. If this were not feasible (e.g. inadequate blood obtained for analysis), an alternative approach would be to sacrifice a group of mice after 4 weeks of elastase/LPS for baseline measurements, and then have separate mice continue the exposure portion of the experiment.



This is a highly feasible study that will be accomplished in the 2-year time period. The human component is a short-term investigation and recruitment will be aided by the presence of a large COPD database, numerous patients seen in clinical practice, and established clinical trial infrastructure. The LPS-elastase murine model has an advantage over cigarette smoke models due to its shorter time for COPD phenotype induction. The investigators are skilled in the performance of CPETs and Dr. Boulares' lab is experienced in the conduct of all study protocols. In April, the protocols will be submitted to the IRB and IACUC for review; the IACUC review will be expedited, as it is an addendum to an established protocol.

References

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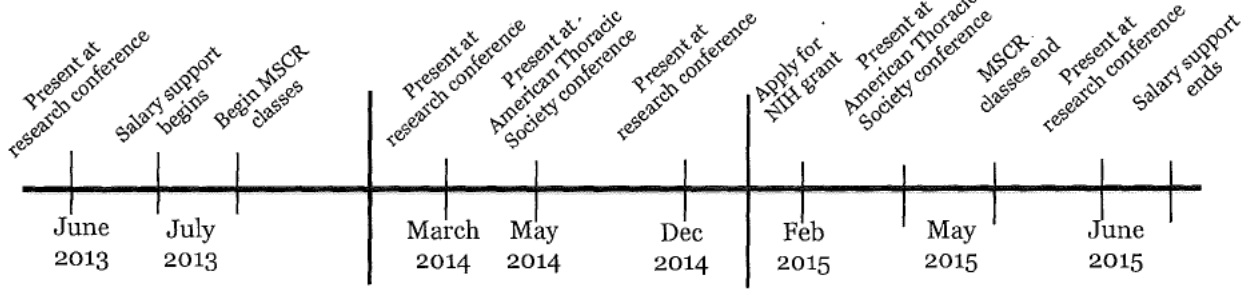
Career development plan

Being accepted as a LACaTS Roadmap Scholar would be instrumental in allowing me to attain my long-term academic goal of becoming a skilled, independent, funded clinical and translational investigator. My specific research goal for this proposal is to investigate the fascinating role of the pulmonary vasculature in limiting exercise capacity in patients with COPD. It is hoped that this area of investigation will lead to exciting new treatment strategies for this significant disease. Of equal importance, the methods employed in this proposal will provide me with invaluable experience in translational research that will propel my career as an academic physician-investigator.

My prior research and training experiences have ideally prepared me for this award. I trained at Temple University Hospital in Philadelphia under the mentorship of Dr. Gerard Criner, an internationally recognized clinical researcher in COPD, during which time a passion for clinical investigation was sparked. My prior clinical research experience was conducting experiments on dynamic hyperinflation and heart-lung interactions during exercise in COPD patients. This led to a publication in the European Respiratory Journal, with three more papers under consideration in peer-reviewed journals. Additionally, I completed two courses in the Master of Science in Clinical and Translational Medicine program at the Temple University School of Public Health. The lessons learned from these courses and my prior research experience have created a love for investigation and prepared me for the opportunities presented by this award.

The two years of protected support and mentored career development offered to LACaTS Roadmap Scholars would be invaluable in my progression from a new faculty member to an independent investigator. This structure would allow me to generate preliminary data towards a subsequent submission for a first extramural grant. Dedicated mentorship provided through the program will facilitate my development into an independent researcher. I will meet on a weekly basis with my mentors individually and monthly as a group to discuss and review my progress and future development. As outlined in the figure, formal research presentations will take place at Pulmonary Research Conference on a regular basis as well as at the American Thoracic Society International Conference yearly. When I joined the faculty at LSUHSC, obtaining a master's degree in clinical research was a short-term goal which would be facilitated and expedited by being accepted as a LACaTS Roadmap Scholar. Through the coursework I will expand my expertise in biostatistics and epidemiologic methods, the responsible conduct of research, protocol design and writing, and grant writing. All of these skills will greatly enhance my chances of successfully obtaining external research support. During the conduct of the proposed research project, I will develop specific technical skills working with experimental animal models of COPD and in vitro systems that will be applied to future research. These techniques will not only be related to the proposed experiments, but will allow me to develop a general laboratory approach to solve clinical problems. I have developed an interdisciplinary collaboration with a basic scientist (Dr. Boulares), which will lead to further collaborations (we are currently discussing a clinical trial of PARP inhibitors in patients with COPD).

In conclusion, being chosen as a LACaTS Roadmap Scholar would allow me to build upon my prior research experience and attain my goal of becoming an independent, externally-funded clinical and translational investigator. Through these interactions, I will able to take ideas from the clinic to the lab and vice versa, which is the ultimate goal of any successful physician scientist.



LSU Health Sciences Center
NEW ORLEANS
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Department of Internal Medicine

School of Medicine
School of Dentistry
School of Nursing
School of Allied Health Professions
School of Graduate Studies
School of Public Health

March 12, 2013

Paula Gregory, Ph.D.
Roy Weiner, M.D.
Directors, LACaTS Education and Career Development Core

RE: [redacted]
Road Map Scholar Applicant

Paula Roy

Dear Drs. Gregory and Weiner:

It is a pleasure to provide a letter of support for Dr. [redacted] in his application to become a LACaTS Road Map Scholar for 2013.

Dr. [redacted] is a newly appointed Assistant Professor in the Section of Pulmonary and Critical Care Medicine. He has strong motivation for a career in clinical research as attested to by his CV. I have reviewed his research plan and feel that he is a strong candidate for research training as a LACaTS Road Map Scholar.

I pledge the support of the LSUHSC Department of Medicine in the career development of Dr. [redacted] as a Road Map Scholar. Through the Section of Pulmonary and Critical Care Medicine, Dr. [redacted] will have 75 percent protected time for the first two years of this award and for up to an additional three years if he wins support for further training with a K award.

Dr. [redacted] has my enthusiastic support in his application to become a LACaTS Road Map Scholar.

Sincerely,

Charles V. Sanders, M.D.
Edgar Hull Professor and Chair
Department of Medicine

LSUHealthNewOrleans
School of Medicine • Section of Pulmonary/Critical Care Medicine

March 15, 2013

Paula Gregory, PhD
Roy Weiner, MD
Directors, LACaTS Education and Career Development Core

RE: Road Map Scholar Applicant
[redacted], MD

Dear Drs. Gregory and Weiner,

It is a pleasure for me to provide a letter of support for [redacted] in his application to become a LACaTS Road Map Scholar for 2013.

[redacted] is relatively new to LSUHSC having joined the faculty in Pulmonary and Critical Care Medicine as Assistant Professor of Medicine in August of 2012. As you can see from his CV, [redacted] is exceedingly well trained. He received his MD at Temple in 2005 followed by residency and chief residency in Internal Medicine at the same institution. He has completed fellowship training in Pulmonary and Critical Care Medicine at Temple, where he was described as one of the best fellows ever to train there. While at Temple, [redacted] developed an interest in clinical research and clinical education. Taking advantage of a large population of COPD patients undergoing lung volume reduction surgery and mentorship from Gerald Criner, Section Chief, [redacted] initiated and carried through to publication a number of clinical research studies dealing with exercise evaluation and dynamic hyperinflation. In addition, [redacted] made regular abstract and oral research presentations at the international conference of the American Thoracic Society as well as numerous educational presentations to the faculty and fellows at Temple.

Since joining LSUHSC, [redacted] has rapidly integrated himself into Section activities and has proven to be an integral member of the Section of Pulmonary and Critical Care Medicine. Thoughtful and well-read, [redacted] is well-liked by the fellows and is a skilled educator. Consistent with his fellowship interest in COPD complications, we have assigned him to a pulmonary hypertension clinic along with Dr. deBoisblanc, who will serve as mentor for the proposed scholarship. [redacted] has also worked in concert with one of our rheumatologists, Leslie Saketkoo, to found a clinic in pulmonary hypertension for patients with connective tissue disease. In addition, [redacted] has also spearheaded a collaborative partnership with Temple University which we are particularly excited about. This partnership will allow LSUSHC to function as a satellite site for a multi-center COPD clinical research network.

I feel that we were fortunate to recruit [redacted] to join the LSUHSC Section of Pulmonary and Critical Care Medicine, and I want to do everything I can to assure that he continues his training and success in clinical research. To that end, I feel that [redacted] is an ideal candidate for training as a LACaTS Road Map Scholar. He is obviously committed to a career in clinical research. In the attached Research Plan, we plan to extend [redacted]'s expertise in COPD to a translational study

of pulmonary vasoregulation in COPD patients. This study will be done in concert with Hamid Boulares, PhD, from the Department of Pharmacology, and will address oxidant-antioxidant balance in the pulmonary vasculature of COPD patients. The human subject component of this project proposes to test inhaled eicosanoid therapy in COPD patients as a means of modulating this balance in human subjects. This is a novel and relatively untested form of therapy for COPD, and may well open up a completely new avenue of treatment for these patients. Mechanistic studies will take place in mice with the assistance of Dr. Boulares. The Pulmonary Section currently conducts a number of clinical trials in COPD and has 4 full-time research nurses on payroll. We have the subjects and the infrastructure to support Matt's research. We have identified LSUHSC Foundation funds to cover expenses of the proposed clinical research (recruitment fees, etc.). The inhaled vasodilator drug will be provided by the manufacturer. Matt has already applied for IRB approval for the clinical research component of the project.

Mentorship for [redacted]'s research will be provided by a mentorship team of Drs. Ben deBoisblanc, Hamid Boulares, and Judd Shellito. Dr. deBoisblanc is Professor of Medicine in the Pulmonary Section and PI for the NIH-funded ARDSNet at the LSUHSC site. ARDSNet is a multi-center network for clinical research in acute lung injury (ARDS). Ben is also PI for a number of clinical trials for investigational therapies in pulmonary hypertension and directs a weekly referral clinic for patients with pulmonary hypertension. He has expertise in the use of vasodilator therapies for pulmonary hypertension, such as those proposed for use by Dr. [redacted] in COPD patients. A copy of Dr. deBoisblanc's biosketch is attached. Hamid Boulares is Associate Professor of Pharmacology with a research focus on oxidative stress in asthma. Dr. Boulares will provide the basic science component of [redacted]s training and will help [redacted] translate findings related to oxidative stress to answer mechanistic questions related to pulmlonary vasoregulation. A copy of Dr. Boulares' biosketch is attached. I am the Lowenstein Professor of Medicine at LSUHSC and Chief of the Section of Pulmonary and Critical Care Medicine. I am PI of a Program Project Grant from the NHLBI dealing with development of novel vaccines for Pneumocystis pneumonia. I have experience fostering the academic development of junior faculty such as Dr. [redacted] A copy of my biosketch is attached as well. Ben, Hamid, and I have worked with [redacted] to develop his Research Plan with the goal of generating preliminary data for a K application within 18 months. The mentorship team plans to meet with [redacted] on a weekly basis to go over his research and to be sure he is given sufficient resources to meet his goals. In addition, [redacted] will receive mentorship support through LACaTS and will do coursework for a Masters of Science in Clinical Research. As LSUHSC Co-Director of the LACaTS Clinical Research Resources Key Component, I will work to assure that [redacted] is provided with sufficient resources to complete his clinical research at the LSUHSC site, and if feasible, at other sites within the LACaTS network.

I am well aware of the importance of protected time for young investigators and the requirement of 75% protected time as a LACaTS Road Map Scholar. It will be my responsibility to assure that [redacted]s time is so protected during the initial 5 years of his time on faculty and as a Road map Scholar. [redacted] will have clinical responsibilities but these will not consume greater than 25% of his time. When on clinical service, [redacted] will provide attending duties at Ochsner Kenner Hospital (full-time effort) and on the pulmonary consultation service at the Interim LSU Hospital in New Orleans (half-time effort). He will not be assigned as attending for the ICU at ILH during his first year. [redacted] will do one half-day of clinic per week. During that half-day, he will assist Dr. deBoisblanc in the Pulmonary Hypertension Clinic which is relevant to his research plan. I will limit his exposure to hospital or university committee work while [redacted] is a Road Map Scholar. I

am committed to providing sufficient protected time for [redacted] to complete his research plan as a Road Map Scholar, to complete his coursework for a Masters in Clinical Research, and to compete for a K award from the NIH.

In summary, [redacted] has my whole-hearted support for training as a LACaTS Road Map Scholar. I feel that he is an ideal candidate for this award, and that this training will pay off with the blossoming career of a talented and productive clinical investigator.
Thank you for your time and consideration.

Sincerely,

Judd Shellito, MD
Lowenstein Professor of Medicine
Chief, Section of Pulmonary and Critical Care Medicine
LSU Health Sciences Center, New Orleans

Mentorship Agreement

[1] ***Goals*** (what you hope to achieve as a result of this relationship; e.g., gain perspective relative to skills necessary for success in academia, explore new career opportunities/alternatives, obtain knowledge of organizational culture, networking, leadership skill development, etc.):

To gain knowledge in the design, deployment, and analysis/dissemination of translational research. Improve my clinical research productivity and grantsmanship. To gain a better practical knowledge of the logistics of developing a clinic-based pragmatic research project with the ultimate goal of becoming an independent

[2] ***Steps to achieving goals*** as stated above (e.g., meeting regularly, manuscripts/grants, collaborating on research projects, steps to achieving independence, etc.):

Corresponding regularly and meeting in person, specifically for the purpose of review of my work as well as progress on the current project. Frequent review of progress on manuscripts and grant proposals. Assistance in development of clinical program for future projects.

[3] ***Meeting frequency*** (frequency, duration, and location of meetings):

Every two weeks with both Drs. [redacted] and [redacted] present at [redacted]. Dr. [redacted] and Dr. [redacted] will join in when available by phone or in person.

[4] ***Confidentiality:*** Any sensitive issues that we discuss will be held in the strictest of confidence. Issues that are off limits for discussion include:

None

[5] Plan for ***evaluating relationship effectiveness*** (e.g., bi-annual review of mentorship meeting minutes, goals, and outcomes/accomplishments):

Formal bi-annual review of goals and progress. Ongoing monitoring of metrics established at previous meeting (e.g. meeting project benchmarks, manuscript productivity, grant composition progress) will occur during twice weekly meetings.

[6] ***Relationship termination clause****:* In the event that either party finds the mentoring relationship unproductive and requests that it be terminated, we agree to honor that individual's decision without question or blame.

[7] ***Duration****:* This mentorship relationship will continue as long as both parties feel comfortable with its productivity or until: June 30, 2021

Mentee's Signature [redacted] Mentor's Signature [redacted] Date [redacted]

Adapted from the Mentorship Agreement Template, University of Wisconsin-Madison Institute for Clinical and Translational Research