A. Personal Statement

As the PIs on this project, I believe I have the expertise to carry this project to completion. First through years of being mentored by successful NIH funded scientists and myself being a recipient of an NHLBI K08, I have acquired the necessary skills to design and carry out the proposed studies. Second as the Chief of Thoracic Surgery and the Surgical Director of Lung Transplantation at the University of Virginia, my clinical interest parallels and complements this proposal. My research laboratory has had a long standing interest in adenosine analogs and lung transplant injury, and I have been part of the team of researchers at UVA performing the preclinical studies with these agents in lung transplantation. My K08 where we studied in preclinical models the role of adenosine in lung transplant injury and repair was mentored by two of the members of this team (Drs. Joel Linden and Irving Kron). I am currently a co-investigator of a R01 with this group (Dr’s Laubach, Kron, and Sharma) studying adenosine analogs and ex-vivo lung perfusion in preclinical models. Our group has published extensively on our preclinical data and now with this current proposal we plan to take decades of work into the clinical arena. Since the previous submission of this proposal we have had an additional paper accepted for publication and an additional abstract accepted for presentation [Stone ML, Sharma AK, Mas VR, Gehrau RC, Mulloy DP, Zhao Y, Lau CL, Kron IL, Laubach VE. Ex vivo Lung Perfusion with Adenosine A2A Receptor Agonist Enhances Rehabilitation of Murine Non-Heart-Beating Donor Lungs. J Thorac Cardiovasc Surg 2015 (accepted); Wagner CE, Pope, NH, Charles, EJ, Hueter ME, Salmon MD, Carter BT, Lau CL, Laubach VE, Kron IL. Adenosine agonist administration during ex vivo lung perfusion of non-heart-beating donor lungs subjected to an extended cold preservation time decreases ischemia-reperfusion injury after transplant in a preclinical porcine model (abstract AATS 95th Annual Meeting, April 2015; J Thorac Cardiovasc Surg (submitted)].

This initial clinical study is a safety and feasibility trial of an adenosine analog, regadenoson in human lung transplantation. It is highly innovative because it addresses our overarching goal of improving the success of lung transplantation by addressing the problem from two totally different directions (donor lungs and recipient response) and thus increases the likelihood of a positive substantial clinical impact. The aim of this proposal is to generate sufficient data to perform a larger multi-institutional trial to show the benefits of adenosine analogs (specifically adenosine 2A receptor agonists) in prevention and treatment of lung transplant injury. This proposal has been in the works for years, and I hope if you have followed our team’s preclinical studies you will see the timing is ideal as the groundwork has been laid for this study to begin.

B. Positions and Honors

Professional Experience:

<table>
<thead>
<tr>
<th>Year</th>
<th>Position Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>2002-2005</td>
<td>Assistant Professor of Surgery, University of Michigan, Ann Arbor, MI</td>
</tr>
<tr>
<td>2007-2010</td>
<td>Assistant Professor of Surgery, University of Virginia, Charlottesville, VA</td>
</tr>
<tr>
<td>2009-present</td>
<td>Surgical Director of Lung Transplantation, University of Virginia, Charlottesville, VA</td>
</tr>
<tr>
<td>2010-present</td>
<td>Associate Professor of Surgery, University of Virginia, Charlottesville, VA</td>
</tr>
<tr>
<td>2014-present</td>
<td>Chief, Section of Thoracic Surgery</td>
</tr>
</tbody>
</table>

Honors and Awards:

Janet M. Glasgow Memorial Award, 1st in Medical School Class 6/1995
Junior AOA, Dartmouth Medical School 5/1994
President AOA - Alpha, NH Chapter
Syvertsen Scholar, Dartmouth Medical School 4/1994
Arthur Naitove Surgical Scholar Award, Dartmouth Medical School 6/1995
Association for Academic Surgery Award 6/1995
Founding Member of the Mosenthal Surgical Society, Dartmouth Medical School 6/1995
Weck/Duke University Medical Center Department of Surgery Award for Excellence in Clinical & Basic Science Lung Transplantation 6/1998
Washington University School of Medicine Pulmonary Medicine Training Grant (T32HL07317) 7/2002-7/2003
AATS John W. Kirklin Fellow 7/2006-6/2008
Detroit's Top Doctors (Hour Detroit Magazine) 2007
Leadership in Academic Medicine 2010
Leadership Fellowship Darden MBA 2010-2012
US News and World Report Top Doctor 2011
Top Doctor in Thoracic Surgery and Cancer 2011-2013

C. Selected publications most relevant to current application from 120 articles, 35 book chapters, 5 patents; 1 invited review


D. Research Support

Current Research Funding
R01 HL119218  (MPI: Laubach/Kron) 8/1/2013 – 7/31/2018
NIH/NHLBI
Ex vivo perfusion in a lung box for rehabilitation of donor lungs
This project tests the hypothesis that ex vivo lung perfusion (EVLP) with adenosine A2A agonist or combined adenosine A2A agonist + adenosine A2B antagonist will extend warm and cold ischemic times of NHBD lungs using a porcine lung transplantation model as well as human (previously rejected) donor lungs.
Role: Co-Investigator

IIR WS2331368 (PI: Lau) 12/01/2012 – 11/30/2014
Pfizer
Prevention of Chronic Allograft Rejection through Fibrocytes and mTOR Inhibition
The goal of this study is to study the role of fibrocytes in chronic rejection.

Past Research Funding
Research Grant  (PI: Kron) 4/1/2012 – 3/31/2014
Roche Organ Transplant Research Foundation, Meggen, Switzerland
Improving Lung Transplantation with Immediate Ex Vivo Perfusion
This project studies the role of immediate versus delayed ex vivo lung perfusion for the rehabilitation of donor lungs for transplantation using a porcine model.
Role: Co-Investigator

5K08HL094704 (PI: Lau) 01/01/2009 – 12/31/2013
NIH/NHLBI
Adenosine 2A Receptor Signaling in Lung Transplant Injury and Rejection
The major goal of this study is to determine the kinetics, magnitude of effect, and cellular mechanisms of A2AR signaling in the pathogenesis of bronchiolitis obliterans.

PI- Lau, C.L. 07/01/2009 – 6/30/2014
Thoracic Surgery Foundation for Research and Education
Matching Funds for K08
These are matching funds for the K08.