BIOGRAPHICAL SKETCH

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NAME: Cristina Maria Alvira

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

POSITION TITLE: Assistant Professor of Pediatrics

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
Tufts University, Medford, MA	BS	1995	Biology
Tufts University School of Medicine, Boston, MA	MD	1999	Medicine
Stanford University School of Medicine	Residency	1999-2002	Pediatrics
Stanford University School of Medicine	Fellowship	2002-2005	Critical Care Medicine

A. Personal Statement

My goal of my research program is to identify novel mechanisms that regulate angiogenesis in the developing lung. As a postdoctoral fellow, I trained in the laboratory of Dr. Marlene Rabinovitch, a preeminent vascular biologist, and studied the role of vascular inflammation in models of lung and cardiac disease. During this time I gained proficiency in a wide range of state of the art technologies, including the use of genetically modified mice, the isolation of primary murine endothelial cells, and molecular strategies to achieve gain and loss of function both *in vivo* and *in vitro*. Collaboration with Dr. Richard Bland, an expert in bronchopulmonary dysplasia, allowed me to acquire additional skills in lung development, including morphometric analysis. In developing my independent line of investigation, I choose to explore the role of the transcription factor, nuclear factor kappa B during late lung development. I developed a model to inhibit NFκB in mice at the onset of alveolarization, and showed that constitutive activation of NFκB promotes pulmonary angiogenesis and alveolarization, in part through the direct transcriptional regulation of the pro-angiogenic receptor, vascular endothelial growth receptor-2 (VEGFR2).

1. **Alvira CM**, Abate A, Yang GB, Dennery PA, and Rabinovitch M. "Nuclear Factor-κB Activation In Neonatal Mouse Lung Protects Against Lipopolysaccharide-Induced Inflammation." *Am J Respir Crit Care Med* 2007; 175(8):805-15. PMID: 17255561

2. Iosef C, Alastalo TP, Iosef C, Hou Y, Chen C, Ahn Y, Chen C, Lyu SC, Adams ES, Cornfield DN, and **Alvira CM**. "Inhibiting Nuclear Factor Kappa-B (NFκB) in the Developing Lung Disrupts Angiogenesis and Alveolarization." *Am J Physiol Lung Cell Mol Physiol* 2012 May 15;302(10):L1023-36. PMID: 22367785. ***Faculty of 1000 Recommended***

3. **Alvira CM.** "Nuclear Factor-Kappa-B Signaling in Lung Development and Disease: One Pathway, Numerous Functions." *Birth Defects Res A Clin Mol Teratol* 2014 Mar;100(3):202-16. Epub 2014 Mar 1 PMID: 24639404

4. Hou Y, Liu M, Husted C, Chen C, Thiagarajan K, Rao SP, and **Alvira CM.** "Activation of the Nuclear factor Kappa-B Pathway During Postnatal Lung Inflammation Preserves Alveolarization by Suppressing Macrophage Inflammatory Protein-2." *Am J Physiol Lung Cell Mol Physiol.* 2015 Jul 10 [Epub ahead of print]. PMID: 26163511

B. Positions and Honors

Positions and Employment:

2005-2009	Instructor of Pediatrics, Stanford University School of Medicine
2009-2010	Acting Assistant Professor of Pediatrics, Stanford University School of Medicine
2010-Present	Assistant Professor of Pediatrics, Stanford University School of Medicine

Other Experience and Professional Memberships:

2014-present	Editorial Board Member, American Journal of Physiology- Lung Cellular and Molecular Physiology
2013	NIH Peer Review- NHLBI-Lung Injury, Repair, Remodeling (LIRR) Study Section
2012	NIH Peer Review- NHLBI-Respiratory Integrative Biology and Translational Research (RIBT) Study Section
2012-present	Society for Pediatric Research

Honors:

1998	Alpha Omega Alpha National Honor Society
1999	Louise Weinstein Prize for Excellence in Clinical Medicine
2004	Western Society for Clinical Investigation Travel Award
2004	Society of Pediatric Research Travel Award
2007	Pediatric Clerkship Honor Roll for Teaching
2008	AHA Fellow to Faculty Transition Award
2012	SPR Young Investigator Coaching Program
2013	AJP-Lung Outstanding Junior Investigator Award
2015-2020	Tashia and John Morgridge Faculty Scholar in Pediatric Translational Medicine

C. Contributions to Science:

1. Endothelial cell dysfunction has been implicated in vascular diseases marked by abnormal vascular remodeling and dysregulated vascular tone. My work in this field has focused on cross talk between the endothelial and vascular smooth muscle cells, and the importance of endothelial cell dysfunction in promoting the pathologic smooth muscle cell contraction and proliferation occurring in pulmonary hypertension. My publications in this arena have identified a novel regulator of nitric oxide production in the pulmonary endothelium (VDAC2), delineated endothelial specific effects of the Rho kinase pathway on modulating pulmonary vascular tone, and demonstrated that dysfunctional paracrine signaling from endothelial cells lacking PPARγ increases vascular smooth muscle proliferation and results in pulmonary hypertension.

a. Guignabert C, **Alvira CM**, Alastalo TP, Sawada H, Hansmann G, Zhao M, Wang L, El-Bizri N, Rabinovitch M. "Tie2-Mediated Loss of Peroxisome Proliferator-Activated Receptor-g in Mice Causes PDGF-Receptor b-Dependant Pulmonary Arterial Muscularization. *Am J Physiol Lung Cell Mol Physiol* 2009; Oct 2. PMID: 19801450

b. **Alvira CM**, Sukovich DJ, Lyu SC, Umesh A, Cornfield DN. "Rho Kinase Activity Modulates Postnatal Adaptation of the Pulmonary Circulation through Separate Effects on Pulmonary Artery Endothelial and Smooth Muscle Cells." *Am J Physiol Lung Cell Mol Physiol.* 2010 Dec; 299(6):L872-8. PMID: 20709731 ***Faculty of 1000 Recommended****

c. **Alvira CM**, Umesh A, Iosef C, Ying L, Hou Y, Lyu SC, Nowak J, and Cornfield DN. "Voltage-Dependent Anion Channel-2 Interaction with NOS Enhances Pulmonary Artery Endothelial NO Production." *Am J Respir Cell Mol Biol* 2012 Jul 27. PMID: 22842492

2. An additional area of focus during my postdoctoral fellowship training in vascular biology was centered upon the molecular pathways leading to extracellular matrix degradation in inflammatory aneurysms. My main study in this arena explored the role of TGF-β in inflammatory aneurysm formation. At the time of that study, excessive TGF-β had been identified as key to the pathogenesis of aneurysm formation in Marfan syndrome,

and there was great interest in extrapolating the potential benefits of TGF-β antagonists to other aneurysmal diseases. However, my study demonstrated that TGF-β signaling was protective in inflammatory aneurysms, and suggested that therapeutic strategies to block TGF-β would likely be detrimental in this form of aneurysm. While completing these studies, I gained expertise in extracellular matrix biology, and continued to build proficiency in the use of genetically modified mouse models. While my current research program is not centered upon aneurysm formation, my work in this area resulted in a productive, ongoing collaboration with the laboratory of Michael Fischbein, a vascular biologist and cardiovascular surgeon here at Stanford with an interest in the mechanisms leading to aneurysm formation in Marfan syndrome.

a. **Alvira CM**, Guignabert C, Kim YM, Wang L, Duong TT, Yeung RS, Li D, Rabinovitch M. "Transforming Growth Factor Beta Inhibition Increases Matrix Metalloproteinase-9 Activity and Enhances Elastin Degradation in a Murine Model of Kawasaki Disease." *Am J Pathol.* 2011 Mar; 178(3):1210-20
PMID: 21356372

b. Merk DR, Chin JT, Dake BA, Maegdefessel L, Miller MO, Kimura N, Tsao PS, Iosef C, Berry GJ, Mohr FW, Spin JM, **Alvira CM**, Robbins RC, and Fischbein MP. "miR-29b Participates in Early Aneurysm Development in Marfan Syndrome." *Circ Res* 2012 Jan 20;110(2)312-24. PMID 22116819

c. Emrich FC, Okamura H, Dalal AR, Merk DM, Raaz U, Hennings JK, Chin JT, Miller MO, Blankenberg FG, Connolly AJ, Rabinovitch R, **Alvira CM**, Mohr FW, Robbins RC, and Fischbein MP. "Enhanced Caspase Activity Contributes to ECM Remodeling and Early Aneurysm Development in a Murine Model of Marfan Disease." Accepted for publication in *Arterioscler Thromb Vasc Biol.* 2014 Oct 30 [Epub ahead of print]. PMID: 25359856

3. Pulmonary angiogenesis is essential for alveolarization, the final stage of lung development that begins just before term birth and extends through the first decade of life. During this stage, septation of the alveolar sacs markedly increases the gas exchange surface area of the lung. Disrupted alveolarization and pulmonary angiogenesis is a hallmark of bronchopulmonary dysplasia, a chronic lung disease of infancy that is a common complication of prematurity. My dual interests in lung development/injury and pulmonary angiogenesis have been the impetus for pursuing studies exploring experimental models of disrupted alveolarization, with the long-term goal of translating this knowledge into potential therapies to reactivate developmental pathways in order to stimulate lung growth after injury.

a. Baker CD **and Alvira CM.** "Disrupted lung development and bronchopulmonary dysplasia: opportunities for lung repair and regeneration." *Curr Opin Pediatr.* 2014 Jun;26(3):306-14.
PMID: 24739494

b. Hilgendorff A, Reiss I, Ehrhardt H, Eickelberg O, **Alvira CM.** "Chronic lung disease in the preterm infant: Lessons learned from animal models." *Am J Respir Cell Mol Biol* 2014 Feb;50(2):233-45.
PMID 24023524

c. Mokres LM, Parai K, Hilgendorff A, Ertsey R, **Alvira CM**, Rabinovitch M, Bland RD. "Prolonged mechanical ventilation with air induces apoptosis and causes failure of alveolar septation and angiogenesis in lungs of newborn mice." *Am J Physiol Lung Cell Mol Physiol* 2010 Jan;298(1):L23-35. Epub 2009 Oct 23. PMID: 19854954.

d. Bland RD, Ertsey R, Mokres LM, Xu L, Jacobson BE, Jiang S, **Alvira CM**, Rabinovitch M, Shinwell ES, and Dixit A. "Mechanical ventilation uncouples synthesis and assembly of elastin and increases apoptosis in lungs of newborn mice. Prelude to defective alveolar septation during lung development?" *Am J Physiol Lung Cell Mol Physiol. 2008 Jan;294(1):L3-14* PMID: 17934062.

4. Prematurity is the leading cause of neonatal mortality in the US, and the cause of 10% of neonatal mortality worldwide. Premature infants are often hospitalized for extended periods of time, and additional costs arising from

special education, maternal health care, and diminished work productivity of adult survivors of prematurity result in an annual estimated cost of prematurity in the US to be greater than 26 billion dollars. Bronchopulmonary dysplasia (BPD) remains the most common complication of preterm birth. Thus, strategies to prevent preterm labor will effectively prevent BPD. Despite the clear importance of strategies to address preterm labor, limited understanding of the fundamental biology of myometrial contractility continues to constrain efforts to develop effective therapies. To date, there are no therapeutic strategies that reliably prevent preterm labor and delivery. We recently identified the transient receptor potential vanilloid-4 channel (TRPV4) as a previously unrecognized modulator of myometrial contractility, and a potential new drug target to address preterm labor.

1. Ying L, Becard M, Lyell D, Han X, Shortliffe L, Iosef-Husted C, **Alvira CM*** and Cornfield DN*. "The Transient Receptor Potential Vanilloid-4 Channel Modulates Uterine Tone During Pregnancy." *Sci Transl Med.* 2015 Dec 23;7(319):319ra204. PMID: 26702092
   ***Co-senior authors**

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/1T16bfwusk9QP/bibliography/47575276/public/?sort=date&direction=ascending

D. Research Support

Ongoing Research Support

National Institute of Health (NHLBI): R01HL122918-01 — Alvira (PI) — 05/01/14-04/30/19
"Novel Molecular Mechanisms Regulating Postnatal Angiogenesis"
The goal of this project is to identify factors present in the lung microenvironment that stimulate physiologic angiogenesis and alveolarization.
Role: Principal Investigator (PI)

Burroughs Wellcome Fund: Preterm Birth Initiative Program — Cornfield (PI) — 07/01/14-06/30/18
"Myometrial Smooth Muscle Cell TRPV Channel Activity Modulates Contractility"
The goal of this project is to determine the role of TRPV4 channel activity in modulating myometrial contractility and inflammation in an experimental model of preterm labor.
Role: Co-Investigator (Co-I)

Stanford Child Health Research Institute: Tashia and John Morgridge Faculty Scholar in Pediatric Translational Medicine — Alvira (PI) — 09/01/15-08/31/20
"Essential Physiologic Roles for Nuclear-Factor Kappa B During Lung Development"
The goal of this award is to provide salary and other research support to the junior faculty scholar to promote the pursuit of research activities related to innovation in child health.
Role: Faculty Scholar/ Principal Investigator

Completed Research Support

Stanford Child Health Research Institute: Transdisciplinary Initiative Program (TIP) — Alvira (PI) — 03/01/14-02/28/16
"Transforming Growth Factor Beta Induced Protein Promotes Pulmonary Angiogenesis in the Developing Lung by Activating NFκB and Wnt Signaling in the Pulmonary Endothelium"
The goal of this project is to develop novel microfluidic angiogenesis assays to test the whether TGFBI induces pulmonary angiogenesis by activating NFκB and Wnt signaling pathways.
Role: Principal Investigator (PI)

D. Research Support (Cont.)

Completed Research Support

American Heart Association: #14BGIA18980070 — Alvira (PI) — 01/01/14-05/01/14
"A Role for Nuclear Factor Kappa B in Promoting Pulmonary Angiogenesis"
The major goals of this project were to determine how the NFκB activating kinases IKKα and IKKβ differentially modulate pulmonary endothelial cell angiogenesis. *Award relinquished early due to scientific overlap with NIH R01HL122918-01*
Role: Principal Investigator (PI)

American Heart Association #0875001N — Alvira (PI) — 07/01/08-06/30/13
"The Role of Transforming Growth Factor Beta in Inflammatory Aneurysm Formation"
This career development award supported the transition of the PI from fellowship to faculty. The goals of the fellowship portion of the award were to define how disruption of TGF-β signaling by systemic inflammation leads to inflammatory aneurysm formation
Role: PI

P30 HL101315-01 — Cornfield (PI) — 09/30/09-08/31/12
"Postnatal Lung Development: Mechanisms of Molecular and Vascular Development"
The goal of this project was to create a new research focus concentrated on lung developmental biology, within the Center for Excellence in Pulmonary Biology at Stanford University School of Medicine. The goal was to be achieved by the recruitment and support of a newly independent investigator (NII), Dr. Cristina Alvira.
Role: NII