BIOGRAPHICAL SKETCH

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NAME: Cristina Maria Alvira ORCID ID: 0000-0002-6921-0001

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POSITION TITLE: Associate 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

I am a physician scientist with a translational research program that aims to elucidate the molecular mechanisms that promote alveolarization, the final stage of lung development occurring primarily during postnatal life. My ultimate goal is to translate this knowledge into novel therapies to treat infants and children with acute and chronic lung diseases. As a pediatric critical care physician, I became very interested in the immaturity of the lung during early childhood, and how this immaturity both heightens susceptibility to injury, but also confers a greater capacity for repair and regeneration. This motivation led me to pursue rigorous postdoctoral fellowship training with Dr. Marlene Rabinovitch, a preeminent vascular biologist, and Dr. Richard Bland, and expert in aberrant lung development. During my postdoctoral training, my work was the first to establish a previously undescribed role for nuclear factor kappa-B (NFκB) in protecting the immature lung from endotoxin-mediated injury-a function opposite what is observed in the mature lung. As I transitioned to independence, my lab extended our understanding of maturational differences in NFκB signaling by identifying that endogenous activation of NFκB is required for postnatal angiogenesis and alveolarization. My most recent work has employed single cell RNA-sequencing to profile the immune, mesenchymal, and endothelial landscape of the mouse lung during late embryonic and early postnatal development, with a focus on identifying how lung cell diversity changes across a period of rapid growth and how distinct subpopulations respond to injury. My lab has been supported by continuous NIH funding since 2014, including a recently awarded R01 (HL1R01HL155828-01) that aims to determine the role of a transcriptionally distinct, resident lung macrophage population on regulating pulmonary vascular growth and remodeling. My combined expertise in endothelial cell biology, intracellular signaling, mouse models of disrupted alveolarization, and single cell transcriptomics leaves me well positioned to serve as a Principal Investigator on the proposed project.

Ongoing projects that I would like to highlight include:

R01 HL155828-01 (PI: Alvira) 04/01/2021-03/31/2025
NIH/NHLBI
"Diverse Homeostatic Roles for Distinct Macrophages in the Developing Lung Vasculature"
The major goals of this project are to determine if a transcriptionally unique lung macrophage population in the embryonic regulates vascular development, identify the signals that promote macrophage and lung endothelial cell interactions, and define hyperoxia impairs EC-macrophage signaling at single cell resolution.

a. Domingo-Gonzalez R, Zanini F, Che X, Liu M, Jones RC, Swift MA, Quake SR, Cornfield DN, and **Alvira CM**. Diverse homeostatic and immunomodulatory roles of immune cells in the developing mouse lung at single cell resolution. Elife. 2020 Jun 2;9:e56890 PMID: 32484158

b. Zanini F, Che, Knutsen C, Liu M, Suresh N, Domingo-Gonzalez R, Dou S, Jones RC, Cornfield DN, Quake SR, and **Alvira CM**. Phenotypic diversity and sensitivity to injury of the pulmonary endothelium during a period of rapid postnatal growth. BioRxiv. 10.1101/2021.04.27.441649

c. Zanini F, Che X, Suresh N, Knutsen C, Klavina P, Xia Y, Domingo-Gonzalez R, Jones RC, Quake SR, **Alvira CM**, and Cornfield DN. Progressive increases in mesenchymal cell diversity modulate lung development and are attenuated by hyperoxia. BioRxiv. 10.1101/2021.05.19.444776

B. Positions, Scientific Appointments 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
2010-2019	Assistant Professor of Pediatrics, Stanford University School of Medicine
2019-present	Associate Professor of Pediatrics, Stanford University School of Medicine

Other Experience and Professional Memberships:

2012-present	Member, Society for Pediatric Research
2012	NIH Peer Review- NHLBI-Respiratory Integrative Biology and Translational Research (RIBT) Study Section
2013	NIH Peer Review- NHLBI-Lung Injury, Repair, Remodeling (LIRR) Study Section
2014-present	Editorial Board Member, American Journal of Physiology- Lung Cellular and Molecular Physiology
2018-2021	Council Member, Society for Pediatric Research
2016-present	Associate Director of Basic Research, Stanford Center for Excellence in Pulmonary Biology
2019-present	Director, Bridge to K Instructor Program, Stanford University Department of Pediatrics

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
2020-present	Crandell Endowed Faculty Scholar

C. Contributions to Science:

1. Identification of novel, physiologic functions for nuclear factor kappa B signaling in the developing lung. Alveolarization, the final stage of lung development that occurs almost exclusively during postnatal life, induces an exponential increase in gas exchange surface area. Prior work demonstrated that pulmonary

angiogenesis drives alveolarization, however the molecular mechanisms regulating pulmonary angiogenesis during alveolarization were not clearly defined. During my postdoctoral fellowship, I made the unexpected observation that the transcription factor, nuclear factor kappa-B (NFκB) serves an anti-inflammatory function in the neonatal mouse lung, in contrast to the well-established pro-inflammatory function in the adult mouse lung. This observation led us to hypothesize that NFκB may have distinct, physiologic functions in the developing lung. We explored this hypothesis, and established that NFκB is endogenously activated in the early alveolar pulmonary endothelium, yet quiescent in the adult pulmonary endothelium; and that blocking NFκB disrupts both pulmonary angiogenesis and alveolarization in neonatal mice. More recently, we have shown that suppression of endothelial NFκB signaling contributes to impaired alveolarization in experimental models of aberrant lung development, and identified IKKβ, an upstream activator of NFκB, as the primary activator promoting these protective responses. Taken together these studies were the first to identify an essential, developmental role for NFκB in the developing pulmonary circulation, and established NFκB as a new therapeutic target for strategies to enhance lung repair and regeneration.

a. **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

b. 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***

c. 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;309(6):L593-604. PMID: 26163511

d. Iosef C, Liu M, Ying L, Rao SP, Concepcion KR, Chan WK, Oman A, and **Alvira CM**. Distinct roles for IkappaB kinases alpha and beta in regulating pulmonary endothelial angiogenic function during late lung development. *J Cell Mol Med*. 2018 Sep;22(9):4410-4422. PMID: 29993183

2. Identification of molecular pathways that promote pathologic pulmonary vascular remodeling. 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. Hansmann G, de Jesus Perez VA, Alastalo, TP, **Alvira, CM**, Guignabert C, Bekke, JM, Schellong S, Urashima T, Wang L, Morrell NW, and Rabinovtich M. 2008. "An antiproliferative BMP-2/PPARgamma/apoE axis in human and murine SMCs and its role in pulmonary hypertension." *J Clin Invest* 2008; 118:1846-1857. PMID: 18382765.

b. 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-Dependent Pulmonary Arterial Muscularization. *Am J Physiol Lung Cell Mol Physiol* 2009; Oct 2. PMID: 19801450

c. **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***

d. **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

3. Identification of mechanisms that disrupt alveolarization and contribute to bronchopulmonary dysplasia. 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. Disrupted alveolarization and pulmonary angiogenesis are hallmarks of bronchopulmonary dysplasia, a chronic lung disease of infancy that is the most common complication of preterm birth. 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 reinvoke developmental pathways in order to stimulate lung growth after injury.

a. 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.

b. Ehrhardt H, Pritzke T, Oak P, Kossert M, Biebach L, Förster K, Koschlig M, **Alvira CM***, and Hilgendorff A. "Absence of TNF-α Results in Imbalanced Inflammatory Response in the Newborn Lung Undergoing Ventilation." *Am J Physiol Lung Cell Mol Physiol.* 2016 May 15;310(10):L909-18 PMID: 27016588

c. Dodson RB, Powers KN, Gien J, Rozance PJ, Seedorf GJ, Astling D, Jones KL, Crombleholme TM, Abman SH, and **Alvira CM.** "Intrauterine growth restriction decreases nuclear factor-kappa B signaling in fetal pulmonary artery endothelial cells of fetal sheep". *Am J Physiol Lung Cell Mol Physiol.* 2018 May 3. PMID: 29722560

d. Liu M, Iosef C, Rao S, Domingo-Gonzalez R, Fa S, Snider P, Conway SJ, Umbach GS. Heilshorn SC, Dewi RE, Dahl MJ, Null DM, Albertine KH, and **Alvira CM**. "Transforming growth factor induced protein promotes NF-κB mediated angiogenesis during postnatal lung development." *Am J Respir Cell Mol Biol.* 2020.

4. Identification of TRPV4 as novel therapeutic target to prevent preterm birth. Prematurity is the leading cause of neonatal mortality in the US, and the cause of 10% of neonatal mortality worldwide. The chronic lung disease, bronchopulmonary dysplasia (BPD) remains the most common complication of preterm birth. Thus, strategies to prevent preterm labor will effectively eliminate BPD. Limited understanding of the fundamental biology of myometrial contractility continues to constrain efforts to develop effective therapies, and to date, there are no effective therapies prevent or treat preterm labor. 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.

a. 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**

5. Identification of pathways to promote or prevent aneurysm formation. An additional area of focus during my postdoctoral fellowship 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, we 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 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

d. Okamura H, Emrich F, Trojan J, Chiu P, Dalal AR, Arakawa M, Sato T, Penov K, Koyano T, Pedroza A, Connolly AJ, Rabinovitch M, **Alvira C***, and Fischbein MP. "Long-term miR-29b Suppression Reduces Aneurysm Formation in a Marfan Mouse Model." *Physiol Rep.* 2017 Epub 2017 Apr 28

Complete List of Published Work in MyBibliography:
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