BIOGRAPHICAL SKETCH

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NAME: Majka, Susan M., Ph.D.

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POSITION TITLE: Associate Professor of Medicine, Cell & Developmental Biology, Vanderbilt University

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
Rutgers University, New Jersey	B.S.	06/92	Animal Science
Rutgers University, New Jersey	B.S.	06/92	Biotechnology
Colorado College, Colorado Springs		06/93	Advanced Immunology Course
Cold Spring Harbor Laboratories		07-08/94	Advanced Molecular Cloning & Expression of Eukaryotic Genes
University of New Mexico, New Mexico	Ph.D.	06/97	Cellular and Molecular Biology

A. Personal Statement

I am a midcareer scientist at Vanderbilt University, where I was recruited to the PAH group 3 years ago for my expertise in Cell, Vascular and Stem Cell biology. While establishing my research program at the University of Colorado, as the Director of Stem Cell Research in the Cardiovascular Pulmonary Research Group (CVP), my lab identified and characterized the ABCG2 Lung MSC as a novel non-contractile pericyte population, important in the regulation of microvascular homeostasis. We have been funded by the NIH and the AHA since 2003. My laboratory specializes in vascular mesenchymal stem cell biology related to lung disease and disease of mesenchymal-derived tissue. I have developed techniques to isolate, differentiate and analyze mesenchymal stem cell phenotype, proliferation, inflammation, migration and matrix synthesis both *in vitro* and *in vivo*. More recently my laboratory has developed a method for mesenchymal, endothelial and smooth muscle differentiation of murine and human iPS cells.

This application proposes to employ a combination of novel *in vitro* and *in vivo* modes to manipulate ABCG2 MSC function elucidate the underlying Wnt signaling mechanisms that regulate the contribution of lung MSC to pulmonary microvascular dysfunction and remodeling during PF. The synergy between these powerful technologies allows us to define the underlying mechanisms regulating lung MSC cell fate and function, which is paramount to identifying therapeutic interventions for many pulmonary vascular diseases and promoting improved repair, with the overall goal of functional tissue regeneration. The current application is an extension of our previous work. Our experience and strong collaboration in these areas will allow us to make rapid progress in meeting the goals of this application.

B. Positions, Honors and Employment

1997-1998 Postdoctoral Fellow, Department of Pathology, University of New Mexico Health Sciences Center, Albuquerque, New Mexico

1998-2000 Post-Doctoral Fellow, Departments of Surgery, Cell Biology and Physiology, University of New Mexico Health Sciences Center, Albuquerque, New Mexico

2000-2002 NIH Postdoctoral Fellow, Center for Cell and Gene Therapy, Baylor College of Medicine, Houston, Texas

2002-2010 Assistant Professor

2010-2012 Associate Professor, Cardiovascular Pulmonary/Cardiology Division, University of Colorado Health Sciences Center, Denver, Colorado
Director of Stem Cell Research in the Cardiovascular Pulmonary Research Group
Member, University of Colorado Cancer Center

Denver Veterans Administration Medical Center, Critical Care Division
Gates Center for Regenerative Medicine and Stem Cell Biology

2012-Pres. Associate Professor of Medicine (with tenure), Departments of Medicine; Cell and Developmental Biology; Pathology, Microbiology and Immunology; Vanderbilt University School of Medicine, Nashville, Tennessee

Professional Service and Memberships

2014 NIH/NHLBI IMST 15 SBIR/STTR: Cell, Molecular, and Computational Biology Nov. 6
2013 FAMRI Weizmann Center of Excellence, Institute Site Review, Israel, December
2013 NIH/NHLBI Chair, SBIRZRG1 CVRS-M-11 Nov
2013 Session Chair Origins of Cells that Contribute to Pulmonary Epithelial and Vascular Remodeling. Experimental Biology 2013, April 20-24, Boston, MA- Respiration Section/Featured Topic
2012 Special Emphasis Panel:R15 AREA ZRG1 BST-U (90), June
2012 K18 Career Enhancement in Stem Cell Research - ZHL1 CSR-R (O2) 1
2012 NIH/NHLBI: Reviewer RFA HL-11-032- ZHL1 CSR-Q (M2) 1 Feb28
2012-2014 Editor AJP: LCMP
2012-2015 APS Conference Committee
2011 NIH/NHLBI ZRG1 CVRS G (03) M October 18-19
2011 NIH/NHLBI Special Emphasis Panel/Scientific Review Group NIH-CSR-SB RES-ZRG1 RES-C (11) B July 14-15
2011 NIH/NHLBI Special Emphasis Panel/Scientific Review Group CSR-SB RES-ZRG1 RES-C (11) B March 24-25
2010 Grant Reviewer for Asthma UK Foundation, UK
2009 Review of Challenge Grant Applications by Special Emphasis Panel, ZRG1 CVRS-B(58) R
2009 Grant Reviewer for Asthma UK Foundation, UK
2007-2008 Grant Reviewer for the Sheffield Hospitals Charitable Trust Medical Research Committee. Sheffield, UK
2007 NIH/NHLBI Special Emphasis Panel/Scientific Review Group 2007/08 ZHL1 CSR-I (S1) (R)-Cell Therapy for Lung Disease
2006-Pres. American Heart Association – CPCC Council Member
2005-Pres. International Society for Stem cell Research: Committee: Public Policy and Education
2004-Pres. Federation of American Societies for Experimental Biology
2004-Pres. The American Physiological Society
2002-Pres. American Thoracic Society

Selected Awards & Honors

2000 NIH Postdoctoral Fellow, Baylor College of Medicine
2001 Pediatric Postdoctoral Fellow Research Award, Baylor College of Medicine
2006 Teaching Scholars Program – UCD-HSC
2007 Travel Award AHA – CPCC
2007 Finalist The Cournand & Comroe Young Investigator Prize In CPCC-AHA
2008 Mentor: UCD Chancellors Award for Excellence in Undergraduate Research
2014 Mentor: Poster Award FASEB conference. Lung Epithelium in Health & Disease

C. Significant Contribution to Science

Public URL for my NCBI Bibliography:
http://www.ncbi.nlm.nih.gov/pubmed/?cmd=historysearch&querykey=4

1. The use of ABCG2 as a marker to define adult Vascular Stem Cells.

During my postdoc at Baylor College of Medicine, I trained with a leading expert in pericyte and vascular Biology, Dr. Karen Hirschi (Fellow of Pat D'Amore and Judha Folkman). My project was the result of collaboration with Dr. Margaret Goodell, who discovered the hematopoietic stem cell population/marker "side population (SP)" at the Whitehead Inst. We combined vascular biology with the newly emergent field of stem cell biology in the early 2000s. In these collaborative projects I used Hoechst ^{low} dye staining and flow

cytometry to isolate and characterize bone marrow and skeletal muscle Hoechst ^{low} ABCG2 ^{pos} cells as hemangioblasts and vascular precursors. Their stem cell phenotype and function was evaluated using murine models of injury. Therefore, having identified Abcg2 positive vascular stem cells in muscle and bone marrow, I applied this technology to an open area of study in the lung when beginning my independent research career in 2002. This training formed the basis for the current research being performed in my laboratory.

- **Majka SM**, Jackson, K.A. Kienstra KA, Majesky MW, Goodell MA, Hirschi KK. Distinct progenitor populations in skeletal muscle are bone marrow derived and exhibit different cell fates during vascular regeneration. *J Clin Invest*. 111(1):71-9, 2003. PMCID: PMC151835
- **Majka SM***, Jackson KA*, Wang H, Pocius J, Hartley CJ, Majesky MW, Entman ML, Michael LH, Hirschi KK, Goodell MA. Regeneration of ischemic cardiac muscle and vascular endothelium by adult stem cells. *J Clin Invest*. 107(11):1395-402, 2001. (*Co-First Author). PMCID: PMC209322
- Goodell MA, Jackson KA, **Majka SM**, Mi T, Wang H, Pocius J, Hartley CJ, Majesky MW, Entman ML, Michael LH, Hirschi KK. Stem cell plasticity in muscle and bone marrow. *Ann N Y Acad Sci*. 938:208-18, 2001. PMID: 11458510

2. Lung MSC are important in the maintenance of pulmonary microvascular structure and when dysfunctional following the MyoFB transition, they exacerbate the development of PAH and PF.

My Independent Research Program has defined a novel population of lung cells, the ABCG2^{positive} MSC, and has begin to elucidate their role in tissue homeostasis as well as chronic disease, including pulmonary arterial hypertension and fibrosis using novel murine models, patient tissue and primary human MSC lines.

We have documented that the CD45 negative ABCG2 positive side population of cells in lung is a mesenchymal stem cell population. In the distal lung tissue the lung MSC function as a specialized non-contractile pericyte population, supporting the alveolar – capillary network. Our recent data establishes that the lung MSC are a multipotent precursor population capable of vascular differentiation (MyoFB, pericyte and EC). This population has the capacity to participate in vascular homeostasis by regulating microvessel stability as well as to contribute to disease by participation in pathologic microvascular and interstitial remodeling.

These studies highlight an important role for microenviromental regulation of multipotent MSC function as well as their potential to contribute to tissue remodeling. Understanding these processes are crucial to define the role lung MSC play during normal microvascular tissue function and pathological pulmonary remodeling which exacerbates PAH which may be applied to other chronic adult lung diseases.

- Marriott S, Baskir R, Gaskill C, Menon S, Carrier E, Talati M, Baskir R, Kropski J, Austin E, Lama V, Loyd J, Wheeler L, Grayck E, West J, **Majka SM.** ABCG2pos lung mesenchymal stem cells are a novel pericyte subpopulation that contributes to fibrotic remodeling. *Am J Physiol.: Cell Physiol*. 307(8):C684-98, 2014. PMCID: PMC4200000
- Chow K, Fessel JP, Ihida-Stansbury K, Schmidt EP, Gaskill C, Alvarez D, Graham B, Harrison DG, Wagner D Jr, Nozik-Grayck E, West K, Klemm DJ, **Majka SM**. Dysfunctional resident lung mesenchymal stem cells contribute to pulmonary microvascular remodeling. *Pulm Circ*. 3(1):31-49, 2013. PMCID: PMC3641738
- Chow K, Jun D, Helm K, Wagner D, **Majka SM.** Isolation and Characterization of Mouse Lung Mesenchymal Stem Cells. *J Vis Exp*. 2011 Oct;(56):e3159, 2011. PMCID: PMC3227187
- Martin J, Helm K, Ruegg P, Garcia M, Burnham E, **Majka S**. Adult lung side population cells have mesenchymal stem cell potential. *Cytotherapy*. 10:140-151, 2008. PMID: 18368593
- Irwin D, Helm K, Campbell N, Imamura M, Fagan K, Harral J, Carr M, Young KA, Klemm D, Gebb S, Dempsey EC, West J. **Majka S**. Neonatal lung side population cells demonstrate endothelial potential and are altered in response to hyperoxia-induced lung simplification. *Am J Physiol.: Lung Cell Mol Physiol*. 293(4):L941-51, 2007. PMID: 17693487

An additional study performed to elucidate the role of MSC replacement during PF was also performed. These results were the first to demonstrate that lung Mesenchymal stem cells (MSC) possess antiinflammatory properties, similar to bone marrow MSC, which attenuate pulmonary tissue fibrosis. Also significant in that the work demonstrates that loss of lung MSC correlates with pulmonary disease and replacement of the “lost or absent” MSC with exogenously administered cells attenuated disease progression.

- Jun D, Garat C, West J, Thorn N, Chow K, Cleaver T, Sullivan T, Torchia E, Childs C, Shade T, Tadjali M, Lara A, Nozik-Grayck E, Malkoski S, Sorrentino B, Meyrick B, Klemm D, Rojas M, Wagner DH Jr, **Majka S**. The pathology of bleomycin induced fibrosis is associated with loss of resident lung

mesenchymal stem cells which regulate effector T-cell proliferation. *Stem Cells*. 29(4):725-35, 2011. PMCID: PMC3322548

3. The Use of Induced Pluripotent Stem cells in Regenerative Medicine & Modeling of Human Disease

Recent studies in my lab demonstrated the significant utility of inducible pluripotent stem cell (iPS) technology to differentiate bone grafts as well as employed the first heritable pulmonary arterial hypertension (HPAH) patient specific iPS derived mesenchyme, endothelium and smooth muscle to study the underlying cell and molecular mechanisms of disease.

Our data were the first: 1. To illustrate the utility of iPS derived osteoblasts in the formation of bone grafts; and 2. To illustrate that cytoplasmic BMPR2 mutation regulates the Wnt signaling pathway and that the degree is dependent on the cell type evaluated. These studies were published and highlighted in *Stem Cells* and the *American Journal of Physiology.* The second study was nominated for manuscript of the year (2014).

- West JD, Austin ED, Gaskill C, Marriott S, Baskir RS, Bilousova G, Jean JC, Hemnes AR, Menon S, Bloodworth N, Fessel J, Matthews M, Kropski J, Irwin D, Ware L, Wheeler L, Hong CC, Meyrick B, Loyd JE, Bowman A, Ess K, Klemm DJ, Young PP, Merryman D, Kotton D, **Majka SM**. Identification of a common genetic signature across multiple cell types in Pulmonary Arterial Hypertension. *Am J Physiol.: Cell Physiol*. 307(5):C415-30, 2014. PMCID: PMC4154073
- Bilousova G, Jun du H, King KB, De Langhe S, Chick WS, Torchia EC, Chow KS, Klemm DJ, Roop DR, **Majka SM**. Osteoblasts derived from induced pluripotent stem cells form calcified structures in scaffolds both *in vitro* and *in vivo*. *Stem Cells*. 29(2):206-16, 2011. PMCID: PMC3321731
- **Majka S,** Hagen M, Harral J, Gendron R, Paradis H, Grayck E, Stenmark DR, West J. Endothelial – Physiologic and molecular consequences of endothelial Bmpr2 mutation. *Respir Res*. 12:84, 2011. PMCID: PMC3141420
- Hemnes A, Austin E, **Majka S**. Modeling PAH with pluripotent stem cells. In: *Lung Stem Cells in the Epithelium and Vasculature*. Firth, Amy, Yuan, Jason X.-J. (Eds.) Springer, 2015. ISBN 978-3-319-16231-7
- Ikonomou L, Hemnes AR, Bilousova G, Hamid R, Loyd J, Hatzolpoulos A, Kotton D, **Majka SM**, Austin E. Programmatic change: lung disease research in the era of induced pluripotency. (Invited Perspective). *Am J Physiol.: Lung Cell Mol Physiol*. 301(6):L830-5, 2011. PMCID: PMC3233828

4. Stem Cell Biology (Adipose, Lung and Skeletal Muscle)

With a team of collaborators, I contributed to the documentation of significant findings in stem cell biology, outside my immediate field of study in adipose tissue, lung and skeletal muscle. In collaboration with Dr. Klemm, our results were the first to demonstrate BM-HSC myeloid derived cell contribution to adipose tissue, gender specific differences and fat depot specific differentiation. With Dr. DeLanghe, we demonstrated the existence of epithelial stem cell niche within smooth muscle. In studies with the skeletal muscle expert, Dr. Olwin, we further characterized the skeletal muscle side population as a muscle progenitor population.

- **Majka SM**, Miller HL, Sullivan T, Erickson PF, Kong R, Weiser-Evans M, Nemenoff R, Moldovan R, Morandis SA, Davis JA, Klemm DJ. Adipose lineage specification of bone marrow-derived myeloid cells. *Adipocyte*. 1(4):215–229, 2012. PMCID: PMC3609111
- Dill E, Campbell A, Volckaert T, Tiozzo C, **Majka S**, Bellusci S, De Langhe S. Parabronchial smooth muscle constitutes an airway epithelial stem cell niche in the mouse lung after injury. *J Clin Invest*. 121(11):4409-4419, 2011. PMCID: PMC3204843
- **Majka S,** Fox KE, Psilas JC, Helm KM, Childs CR, Acosta AS, Janssen RCX, Friedman JE, Woessner BT, Shade TR, Varella-Garcia M, Klemm DJ. De novo generation of white adipocytes from the myeloid lineage via mesenchymal intermediates is age, adipose depot, and gender specific. *Proc Natl Acad Sci USA*. 107(33):14781-6, 2010. PMCID: PMC2930432
- Crossno J, **Majka S**, Grazia T, Gill R, Klemm D. Rosiglitazone promotes formation of multilocular adipocytes from bone marrow progenitor cells. *J Clin Invest.* 116:3220-3228, 2006.
- Tanaka KK, Cornelison D, Hall JK, **Majka SM,** Olwin BB. Syndecan-4 expressing muscle progenitor cells in the SP engraft as satellite cells during muscle regeneration. *Cell Stem Cell*. 4:217-225, 2009. PMCID: PMC3142572

5. Reactive Oxygen species and PAH

With a team of collaborators, I contributed to significant findings in PAH with an emphasis on reactive oxygen species. In collaboration with Drs. Grayck and Klemm we evaluated the effects of ROS on remodeling of the pulmonary vasculature and interstitium in murine models of PAh as well as PH with associated PAH and demonstrated that EC-SOD was an important antioxidant enzyme necessary for response to lung injury. Antioxidants also present pulmonary artery smooth muscle hypertrophy.

- Nozik-Grayck E, Woods C, Taylor JM, Benninger RK, Johnson RD, Villegas LR, Stenmark KR, Harrison DG, **Majka SM**, Irwin D, Farrow KN.. Selective depletion of vascular EC-SOD augments chronic hypoxic pulmonary hypertension. *Am J Physiol: Lung Cell Molec Physiol*. 307(11):L868-76, 2014. PMCID: PMC4254965
- Van Rheen Z, Domarski S, **Majka S,** Klemm D, Stenmark KR, Nozik-Grayck E. Lung EC-SOD Lung extracellular superoxide dismutase overexpression lessens bleomycin-induced pulmonary hypertension and vascular remodeling. *Am J Respir Cell Mol Biol*. 44(4):500-508, 2011. PMCID: PMC3095923
- Klemm DJ, **Majka S,** Crossno JT Jr, Psilas JC, Reusch JE, Garat CV. Reduction of reactive oxygen species prevents hypoxia-induced CREB depletion in pulmonary artery smooth muscle cells. *J Cardiovasc Pharmacol*. 58(2):181-91, 2011. PMCID: PMC3095923

D. **Research Support**

Ongoing Research Support

5 R01 HL 116597-02 (PI:Majka; 60% effort) 08/01/13 - 05/31/17
NIH/NHLBI
"Role of Lung MSC in Emphysema"
To delineate the role of MSC in regulation of the microvascular-alveolar epithelial interactions in COPD.

5 P01 HL 108800-03 (Loyd) 09/01/12 - 06/30/17
NIH/NHLBI
"Hormonal, Metabolic and Signaling Interactions in PAH: Project 3, ACE2 Safety and Mechanism in Treatment of Pulmonary Arterial Hypertension"
To develop a new therapy for pulmonary arterial hypertension (PAH) based on interventions against cytoskeletal trafficking defects, which we believe are central to the pathology of both hereditary and idiopathic forms of disease.
Majka Role: CoI: 10% effort to provide feedback and protocols for *in vitro* modeling of PAH.

Completed Research Support

Vanderbilt Institute for Clinical and Translational Research (VICTR VR8655.1) (Majka)
"Gene Expression Profiling of Lung Mesenchymal Stem Cells in Pulmonary Disease" 03/06/14- 01/20/15
We will perform microarray analyses of multiple human MSC lines, from control and disease, as well as iPS derived MSC to validate them as disease models.

5 R21 DK 094132-02 (Majka) 09/15/12 - 08/31/15
NIH/NIDDK
"Induced pluripotent stem cell therapy for lipodystrophy"
The major goals of this project are to create a set of mouse iPS cell models of lipodystrophy using transgene-free approaches for the purpose of evaluating the differentiation potential of young versus aged derived iPS relative to BM-MSC to mesenchymal and adipose lineages and subsequent function. We will also test the ability of the iPS cell derived mesenchymal stem cells to rescue a mouse model of lipodystrophy relative to BM-MSC.

7 R01 HL 091105-05 (Majka) 08/01/09 - 07/31/14
NIH/NHLBI
"Fate of Lung Stem Cells During Pulmonary Disease"
The major goals of this project were to define and understand the role of lung mesenchymal stem cells and how they contribute to lesions during the progression of pulmonary hypertension.