BIOGRAPHICAL SKETCH

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NAME: **Rabinovitch, Marlene**

eRA COMMONS USER NAME (credential, e.g., agency login): RABINOVITCH.MARLENE

POSITION TITLE: 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
McGill University	B.Sc.	06/1967	Physiology/Psychology
McGill University	M.D.	06/1971	Medicine
Harvard Medical School	Post Doc	06/1976	Pediatric Cardiology

A. Personal Statement

We investigate mechanisms leading to pulmonary arterial hypertension (PAH) with the long-range view that we might better treat this progressively debilitating condition that has no cure except for lung transplantation. Our studies also address congenital heart and vascular disorders that cause severe stenoses in pulmonary arteries that can result in progressive right-sided elevated pressure and heart failure. Bioinformatic and multi-omic approaches are used that incorporate single cell transcriptomic and proteomic analyses in genetically modified murine and human cells including vascular, immune, and differentiated induced pluripotent stem cells. Penetrance of the BMPR2 mutation was modeled in iPSC-endothelial cells (EC) (1). We discovered that neutrophil elastase contributes to loss of pre-capillary vessels and proliferation of smooth muscle cells that occlude the pulmonary arterial (PA) lumen in PAH and showed that an elastase inhibitor, elafin, can amplify signaling of BMPR2 to reverse the pathological features of this disease (2). This has led to a Phase I Elafin Clinical Trial. We recently discovered that myeloid cells have amplified expression of endogenous retroviral elements, the products of which induce an innate immune response perpetuating vascular inflammation associated with heightened elastase activity in PAH, and we are addressing the mechanism leading to this myeloid cell dysregulation. EC-smooth muscle cells (SMC) co-cultures elucidate metabolic and epigenetic sequelae of dysfunctional BMPR2, including impaired Notch activation and EC regeneration in response to injury (3). We are studying mechanisms underlying mitochondrial and genomic DNA damage associated with impaired recovery from oxidant injury and have elucidated a role of PPARγ in DNA damage sensing and repair (4). In our new studies assessing the response to flow and high shear stress in hereditary, idiopathic and congenital heart disease associated PAH we use integrative omics to understand the role of remodeling of chromatin related to specific transcription factors and metabolites. A new focus is on the mechanism of exosome release and the role of exosomes as therapeutic or pathologic vehicles.

1. Gu M, Shao N-Y, Silin Sa S, Li D, Termglinchan V, Ameen M, Karakikes I, Sosa G, Grubert F, Lee J, Cao A, Taylor S, Ma Y, Zhao Z, Chappell J, Hamid R, Austin ED, Gold JD, Wu JC, Snyder MP, **Rabinovitch M**. Patient-Specific iPSC Derived Endothelial Cells Uncover Pathways that Protect Against Pulmonary Hypertension in BMPR2 Mutation Carriers. *Cell Stem Cell.* 2017 Apr 6;20(4):490-504. *(PMCID: PMC5500296)*
2. Nickel NP, Spiekerkoetter E, Gu M, Li CG, Li H, Kaschwich M, Diebold I, Hennigs JK, Kim KY, Miyagawa K, Wang L, Cao A, Sa S, Jiang X, Stockstill RW, Nicolls MD, Zamanian RT, Bland RD, **Rabinovitch M.** Elafin Reverses Pulmonary Hypertension via Caveolin-1 Dependent Bone Morphogenetic Protein Signaling. *Am J Respir Crit Care Med.* 2015 Jun 1;191(11):1273-86. *(PMCID: PMC4476518)*
3. Miyagawa K, Shi, Chen P-I, Hennigs JK, Zhao Z, Wang M, Li CG, Saito T, Taylor S, Sa S, Cao A, Wang L, Snyder MP, **Rabinovitch M**. Smooth Muscle Contact Drives Endothelial Regeneration by BMPR2-Notch1 Mediated Metabolic and Epigenetic Changes. *Circulation Research* 2019; Jan 18;124(2):211-224. *(PMCID: PMC6400637)*

4. Li CG, Mahon C, Sweeney NM, Verschueren E, Katamani V, Li D, Hennigs JK, Marciano DP, Diebold I, Abu-Halawa O, Elliott M, Sa S, Guo F, Wang L, Cao A, Guignabert C, Sollier J, Nickel NP, Kaschwich M, Cimprich KA, **Rabinovitch M**. PPARγ Interaction with UBR5/ATMIN Promotes DNA Repair to Maintain Endothelial Homeostasis. *Cell Reports.* 2019 Jan 29;26(5):1333-1343. (*PMCID: PMC6436616)*

B. Positions and Honors

Positions and Employment (current)

2002-present Professor of Pediatrics; Research Faculty, Cancer Biology Program, Cardiovascular Institute, Endowed Dunlevie Chair in Pediatric Cardiology, Stanford University

2018-present Director, Basic Science and Engineering Program, Betty Irene Moore Children's Heart Center, Stanford University School of Medicine, Stanford, California

Other Experience and Professional Memberships

2000-2005 Associate Editor, Circulation Research
2001-2005 Research Advisory Committee, Burroughs Wellcome, Clinical Scientist Awards
2002-2005 Scientific Advisory Board, Gairdner Foundation
2006-present External Advisory Board, NIH PPG's & Training Grants, UCSF, U. Penn
2007-2012 National Heart, Lung, Blood Institute Advisory Council, NIH
2009-present Association of American Physicians
2010-2016 Cardiovascular Section Editor, Annual Review of Physiology
2013-2017 Max Planck Scientific Advisory Board
2013-2018 Advisory Committee NIH-NHLBI Lung Repair and Regeneration Consortium
2014-2016 Chair, Distinguished Scientist Awards Committee, American Heart Association

Honors

2000 Canadian Institutes of Health Research Distinguished Scientist Award
2002 Paul Dudley White Lecturer, American Heart Association
2003 Gill Heart Institute Award for Outstanding Contributions to Cardiovascular Research
2004 Canadian Institute of Health Research, Distinguished Lecturer and Prize
2004 The American Heart Association Basic Research Prize
2005 Dickinson-Richards Lecturer, AHA 2005
2006 The American Heart Association Distinguished Scientist Award
2008 American Thoracic Society, Recognition Award for Scientific Accomplishment
2010 Louis and Artur Lucian Award for Research in Circulatory Diseases, McGill University
2011 Innaugural Lois T Ellison Lectureship, Georgia Health Sciences University, Augusta, GA
2012 Judith Pool Mentoring Award, Northern California Chapter of American Women in Science
2015 Mentor Award of Excellence, Department of Pediatrics, Stanford University
2016 J. Burns Amberson Lecturer, ATS International Conference, San Francisco, CA
2016 Robert F Grover Prize, Assembly on Pulmonary Circulation, American Thoracic Society
2017 Distinguished Scientist Lecture, American Heart Association

C. Contributions to Science

1. Diagnosis and Prognosis of Pulmonary Arterial Hypertension: Our group first described quantitative structural changes in pulmonary arteries that correlated with hemodynamics prior to surgery and with hemodynamic outcome one year after repair of a congenital heart defect. We demonstrated that these changes could be diagnosed on a frozen section lung biopsy and by quantitative wedge angiography. Further contributions were made to our understanding of the pulmonary abnormalities in congenital heart defects when we defined the origins and points of stenosis in of systemic collateral arteries in patients with tetralogy of Fallot, indicating how this knowledge would influence surgical procedures. We also identified pulmonary arterial abnormalities in patients with absent pulmonary valve affecting distal lung airways and respiratory function.

a. **Rabinovitch M**, Herrera-DeLeon V, Castaneda AR, Reid L. Growth and development of the pulmonary vascular bed in patients with tetralogy of Fallot with and without pulmonary atresia. *Circulation.* 1981 Dec; 64(4):1234-49. *(PMID: 7296796)*

b. **Rabinovitch M**, Keane JF, Fellows KE, Castaneda AR, Reid L. Quantitative analysis of the pulmonary wedge angiogram in congenital heart defects: A correlation with hemodynamic data and morphometric findings in lung biopsy tissue. *Circulation.* 1981 Jan; 63(1):152-64. *(PMID: 7470217)*

c. **Rabinovitch M**, Grady S, David I, Van Praagh R, Sauer U, Buhlmeyer K, Castaneda AR, Reid L. Compression of intrapulmonary bronchi by abnormally branching pulmonary arteries associated with absent pulmonary valves. *Am J Cardiol.* 1982 Oct;50(4):804-13. *(PMID: 7124639)*

d. **Rabinovitch M**, Keane JF, Norwood WI, Castaneda AR, Reid L. Vascular structure in lung biopsy tissue correlated with pulmonary hemodynamic findings after repair of congenital heart defects. *Circulation.* 1984 Apr;69(4):655-67. *(PMID: 6697454)*

2. Elastin and Elastase in Pulmonary Arterial Hypertension and Fibronectin in the Ductus Arteriosus: We made the observation that there was degradation of elastin very early in PAH pathogenesis later attributed to a neutrophil elastase produced by vascular smooth muscle cells (SMC). This enzyme was elevated in PAH and in mice where we showed the development of extensive neointimal lesions as a result of viral inoculation. Degradation of the extracellular matrix by elastase released mitogenic factors, and caused clustering and activation of growth factors receptors as a consequence of altered integrin signaling. Elastase inhibition not only prevented but also induced regression of experimental pulmonary hypertension. We described the process causing formation of a neointima required for ductus arteriosus (DA) closure in the late gestation lamb as resulting from increased EC production of hyaluronan and SMC production of fibronectin; both features are critical in SMC migration. We related increased fibronectin to LC3 mediated RNA binding and mRNA translation, a novel property of this autophagy protein. Blocking fibronectin using a gene therapy approach targeting the RNA binding domain of the mRNA prevented DA closure, a potential lifesaving measure in patients with a duct-dependent congenital heart defect, and a demonstration of the possibility of gene therapy in this condition.

a. Jones PL, Crack J, **Rabinovitch M**. Regulation of tenascin-C, a vascular smooth muscle cell survival factor that interacts with the $\alpha_v\beta_3$ integrin to promote epidermal growth factor receptor phosphorylation and growth. *J Cell Biol.* 1997 Oct 6;139(1):279-93. *(PMCID: PMC2139818)*

b. Zhou B, Boudreau N, Coulber C, Hammarback J, **Rabinovitch M**. Microtubule-associated protein 1 light chain 3 is a fibronectin mRNA-binding protein linked to mRNA translation in lamb vascular smooth muscle cells. *J Clin Invest.* 1997 Dec 15;100(12):3070-82. *(PMCID: PMC508520)*

c. Mason CAE, Bigras J-L, O'Blenes SB, Zhou B, McIntyre B, Nakamura N, Kaneda Y, **Rabinovitch M**. Gene transfer in utero biologically engineers a patent ductus arteriosus in lambs by arresting fibronectin-dependent neointimal formation. *Nat Med.* 1999 Feb;5(2):176-82. *(PMID: 9930865)*

d. Cowan KN, Heilbut A, Humpl T, Lam C, Ito S, **Rabinovitch M**. Complete reversal of fatal pulmonary hypertension in rats by a serine elastase inhibitor. *Nat Med.* 2000 Jun;6(6):698-702. *(PMID: 10835689)*

3. Inflammation and Environmental Factors in Cardiovascular Disease: The importance of elastase went beyond pulmonary hypertension as we showed that we could use elastase inhibitors to prevent and arrest progression of experimental models of viral myocarditis, vein graft atherosclerosis, transplant arteriopathy, restenosis, and cardiac dysfunction following myocardial ischemia. Vascular elastase was pro-inflammatory and loss of BMPR2, could lead to impaired assembly of elastin fibers and could also amplify an inflammatory response by inducing exaggerated mRNA translation of cytokines including GMCSF. This cytokine is instrumental in recruiting activated macrophages in response to pulmonary hypertension producing stimuli such as chronic hypoxia. Environmental factors can perturb normal oxygen sensing and mitochondrial function. We related increased expression of endogenous retroviral elements to a chronic innate immune response. Therapeutic approaches are currently being developed by high throughput screening using iPSC-induced EC.

a. Sawada H, Saito T, Nickel NP, Alastalo TP, Glotzbach JP, Chan R, Haghighat L, Fuchs, G, Januszyk M, Cao A, Lai YJ, de Jesus Perez VA, Kim YM, Wang L, Chen PI, Spiekerkoetter E, Mitani Y, Gurtner GC, Sarnow P, **Rabinovitch M**. Reduced BMPR2 expression induces GM-CSF translation and macrophage recruitment in humans and mice to exacerbate pulmonary hypertension. *J Exp Med.* 2014 Feb 10;211(2):263-80. (*PMCID: PMC3920564)*

b. Tojais NF, Cao A, Lai YJ, Wang L, Chen PI, Alcazar MAA, de Jesus Perez V, Hopper RK, Rhodes CJ, Bill MA, Sakai LY, Rabinovitch M. Codependence of Bone Morphogenetic Protein Receptor 2 and Transforming

Growth Factor-β in Elastic Fiber Assembly and Its Perturbation in Pulmonary Arterial Hypertension. *Arterioscler Thromb Vasc Biol.* 2017 Aug;37(8):1559-69. *(PMCID: PMC5593082)*

c. Chen P-I, Cao A, Miyagawa K, Tojais NF, Hennigs JK, Li CG, Sweeney NM, Inglis AS, Wang L, Li D, Ye M, Feldman BJ, and **Rabinovitch M.** Amphetamines Promote Mitochondrial Dysfunction and DNA Damage in Pulmonary Hypertension. *JCI Insight.* 2017 Jan 26;2(2):e90427. *(PMCID: PMC5256132)*

d. Saito T, Miyagawa K, Chen SY, Tamosiuniene R, Wang L, Sharp O, Samayoa E, Harada D, Moonen JAJ, Cao A, Chen PI, Hennigs JK, Gu M, Li CG, Leib RD, Li D, Adams CM, Del Rosario PA, Bill MA, Haddad F, Montoya JG, Robinson W, Fantl WJ, Nolan GP, Zamanian RT, Nicolls MR, Chiu CY, Ariza ME, **Rabinovitch M**. Upregulation of HERV-K is Linked to Immunity and Inflammation in Pulmonary Arterial Hypertension. *Circulation.* 2017 Nov 14;136(20):1920-35. *(PMCID: PMC5685911)*

4. The BMPR2-PPARγ Axis, Mitochondrial Dysfunction and Pulmonary Hypertension: We have used high throughput drug screening and bioinformatics to find novel therapies that improve BMPR2 function. The immunosuppressant, FK506, was found on a high throughput drug screen for agents that activate BMPR2 and is now going into a Phase II clinical trial. We identified PPARγ as a nuclear transcription factor activated by BMPR2 in smooth muscle cells (SMC), and apolipoprotein E as a target of transcription and showed that loss of PPARγ in SMC could induce smooth muscle proliferation and pulmonary hypertension, In SMC, tandem activation of Wnt signaling pathways downstream of BMPR2 is necessary for migration. In EC, BMPR2 hijacks Wnt activation to induce canonical and non-canonical signaling pathways that are essential for pulmonary (PA) EC proliferation and migration related to vascular regeneration. In EC, Wnt (β–catenin) forms a transcription factor complex with PPARγ to regulate genes that regenerate vessels, suppress SMC proliferation and counteract inflammation. Mice with loss of BMPR2 in EC, show mitochondrial hyperpolarization, glycolysis, increased ATP and activation of a p53, PGC1α-TFAM cascade inducing an inflammasome response. The stress of hypoxia and reoxygenation in these BMPR2 negative EC, causes loss of glycolytic reserve and ATP, reduced mitochondrial membrane potential via suppression of the p53-PGC1α, cascade, mitochondrial DNA deletion and a pro-apoptotic phenotype. iPSC-EC have been used to model both idiopathic and BMPR2-mutant PAH.

a. de Jesus Perez VA, Ali Z, Alastalo TP, Ikeno F, Sawada H, Lai YJ, Kleisli T, Spiekerkoetter E, Qu X, Rubinos LH, Ashley E, Amieva M, Dedhar S, **Rabinovitch M**. BMP promotes motility and represses growth of smooth muscle cells by activation of tandem Wnt pathways. *J Cell Biol.* 2011 Jan 10;192(1):171-88. (*PMCID: PMC3019546)*

b. Spiekerkoetter E, Tian X, Cai J, Hopper RK, Sudheendra D, Li CG, El-Bizri N, Sawada H, Haghighat R, Chan R, Haghighat L, de Jesus Perez V, Wang L, Reddy S, Zhao M, Bernstein D, Solow-Cordero DE, Beachy PA, Wandless TJ, Ten Dijke P, **Rabinovitch** M. FK506 activates BMPR2, rescues endothelial dysfunction, and reverses pulmonary hypertension*. J Clin Invest.* 2013 Aug;123(8):3600-13. *(PMCID PMC3726153)*

c. Diebold I, Hennigs JK, Miyagawa K, Li CG, Nickel NP, Kaschwich M, Cao A, Wang L, Reddy S, Chen P-I, Nakahira K, Alejandre Alcazar MA, Hopper RK, Ji L, Feldman BJ, **Rabinovitch M**. BMPR2 preserves mitochondrial function and DNA integrity during reoxygenation to promote endothelial survival and reverse pulmonary hypertension. *Cell Metab.* 2015 Apr 7; 21(4):596-608. *(PMCID: PMC4394191)*

d. Sa S, Gu M, Chappell J, Shao NY, Ameen M, Elliott KA, Li D, Grubert F, Li CG, Taylor S, Cao A, Ma Y, Fong R, Nguyen L, Wu JC, Snyder MP, **Rabinovitch** M. Induced pluripotent stem cell model of pulmonary arterial hypertension reveals novel gene expression and patient specificity. *Am J Respir Crit Care Med.* 2017 April 1;195(7):930-41. *(PMCID: PMC5387706)*

Complete List of Published Work in My Bibliography:

https://www.ncbi.nlm.nih.gov/sites/myncbi/1LeG-lt9VrJkK/collections/48079734/public/

D. Research Support:

Ongoing Research Support:

R01 HL138473 (PIs: M Rabinovitch, MR Nicolls) **07/2017 - 06/2022**
NIH/NHLBI
Endothelial Injury, BMPR2 Dysfunction and Macrophage (MØ) Activation Cause EndMT and PAH

This project addresses the hypothesis that injured PAECs with dysfunctional BMPR2 signaling recruit and activate MØs that amplify LTB_4 and HERV-K; these immune factors work in concert to sustain inflammation and promote severe PAH by apoptosis and EndMT. Aim 1 evaluates how LTB_4 produced by injured PAECs, activates MØs to stimulate further LTB_4, causing PAEC apoptosis and EndMT when BMPR2 signaling is impaired. Aim 2 evaluates whether PAECs from PAH patients including those with reduced BMPR2 function, secrete factors in response to injury that amplify HERV-K expression in monocytes. Aim 3 investigates the vulnerability of BMPR2-deficient animals in developing severe PH and EndMT following endotracheal instillation of Ad-5LO to generate high LTB_4 levels, or intravenous administration of recombinant HERV-K dUTPase.

R01 HL074186 (PI: M Rabinovitch) **04/2004 - 01/2024**
NIH/NHLBI
Pulmonary Hypertension in Genetically Modified Mice
Genetically modified mice are used to dissect the contributions of aldehyde dehydrogenase enzymes in EC, SMC and monocytes as they relate to pulmonary hypertension.

P01 HL108797 (PI: M Rabinovitch) **08/2011 - 06/2022**
NIH/NHLBI
Elafin Therapy for Pulmonary Arterial Hypertension
This proposal pursues the mechanisms leading to a chronic inflammatory response as manifest in abnormal neutrophil activation and elastase release, and supports a Phase I and Phase II clinical trial using Elafin as a therapy for PAH. Preclinical GLP animal studies are also supported. An immunophenotyping Core develops biomarkers based upon CyTOF and MIBI analyses. Administrative Core and Data Coordinating Center coordinate bioassays, patient database and physiological studies.
Role: Program Director; PI, Project I; Core Leader, Administrative Core

R01 HL087118 (PI: M Rabinovitch) **12/2006 - 04/2023**
NIH/NHLBI
The BMP-PPARγ Axis and Pulmonary Hypertension
This project investigates pathological mechanisms altering phosphorylation of PPARγ in PAH, and their impact on DNA damage, gene expression, and vascular and monocyte cell phenotype.

R24 HL123767 (NIH Parent award PI: M Geraci) **09/2014 - 06/2018 (NCX to 06/2020)**
Indiana University, Indianapolis, IN (Prime Sponsor: NIH/NHLBI)
Pulmonary Hypertension Breakthrough Initiative. This Center harvests lungs from patients with idiopathic and secondary forms of PAH and control subjects. Blood and tissue and cell samples are archived for proteomic and genomic analyses, light and electron microscopy. Role: Stanford Transplant Preparation Ctr PI

Completed Research Support (last three years):

K12 HL120001 (PIs: M Rabinovitch, MR Nicolls, MP Snyder) **09/2013 - 05/2018 (NCX to 05/2019)**
NIH/NHLBI
Stanford Career Development Program in Omics of Lung Diseases
This multidisciplinary career development program equips new MD and PhD investigators with the knowledge and skills to integrate omic abnormalities that cause or predispose to lung diseases, focusing on PAH.

R01 HL122887 (PIs: M Rabinovitch, MR Nicolls, MP Snyder) **08/2015 - 05/2019**
NIH/NHLBI
Integrative Omics as a Discovery Tool for Pulmonary Hypertension
The project develops and applies innovative bioinformatics methods of analysis to integrate very large publicly available data sets with novel data sets derived from state-of-the-art transcriptomic and metabolomic technologies, to generate a powerful systems biology approach to characterize PAH.

U01 HL107393 (PIs: M Rabinovitch, MP Snyder, JC Wu) **07/2011 - 06/2016 (NCX to 06/2017)**
NIH/NHLBI
iPSC Derived EC as Surrogates Using Pulmonary Hypertension as a Prototype Disease. Native pulmonary arterial endothelial cells (PAEC) from IPAH vs. control lungs are compared to ECs transformed from induced pluripotent stem cells (iPSCs). Gene variants, DNA methylation (Methyl-Seq) and RNA expression (RNA-Seq) are related to cell phenotype. iPSCs are used to correct gene variants and iPSC-ECs to screen FDA approved drugs for potential benefit in pulmonary arterial hypertension.