BIOGRAPHICAL SKETCH

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NAME: Nicolls, Mark

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

POSITION TITLE: Professor of Pulmonary & Critical Care Medicine and Immunology and Rheumatology

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
University of Portland, Portland, OR	BS	05/1987	Biology
Stanford School of Medicine, Stanford, CA	MD	05/1993	Medicine

A. Personal Statement

I am an Associate Dean for Research at Stanford Medical School, the Stanford Professor and Endowed Chair of Pulmonary and Critical Care Medicine, and Chief of the Pulmonary, Allergy and Critical Care Medicine Division at Stanford University. I also am the Director of Lung Immunology at Stanford, a member of the Stanford Institute of Immunity, Transplantation, and Immunology, a board member for the Wall Center for Pulmonary Vascular Research, as well as the Cardiovascular Institute at Stanford University. I have a joint appointment with Immunology and Rheumatology at Stanford. My VA/PAVIR lab focuses on the interaction between immune system and vasculature as it pertains to lymphedema, pulmonary hypertension, lung transplantation, and emphysema. I have >30 years of experience working in immunology, creating the first non-lytic anti-CD3 monoclonal antibody as a tolerizing transplant immunotherapy. I was a member of Bruce Hall's team at Stanford in the early 1990s when Tregs were first characterized by his group and have continued since that time to perform research on immune regulation and vascular disorders. My most recent projects focus on the role of immune dysregulation in the evolution of lymphedema[1,2], pulmonary hypertension[3,4], as well as why preserving microvascular health may prevent chronic rejection in solid organ transplant recipients[5]. On the clinical side, I care for lung transplant patients, Co-Chaired the 1st Aspen Lung Conference focused on lung transplantation, and was the Co-Chair, communicating, and senior author for the NHLBI Consortium and Consensus Statement on pre-clinical models in lung transplantation. I led an NIH-funded multicenter trial with 26 participating sites focused on B cell depletion for the treatment of systemic sclerosis-associated pulmonary hypertension[4]. I am also the communicating PI for a recent NIH lung transplant consortium U01 award to study immune responses in lung transplant recipients. A significant aspect of our group portfolio is understanding the biology underpinning lymphatic disease which we perform at the VA Palo Alto/PAVIR, assisting with clinical lymphatic studies with Dr. Stan Rockson. I have been a PI on a K12 training grant, and am the communicating PI for the Pulmonary Biology T32, and am dedicated to the training of clinician-scientists and basic science researchers.

Citations:

1. Kim D, Tian W, Wu TT, Xiang M, Vinh R, Chang J, Gu S, Lee S, Zhu Y, Guan T, Schneider EC, Bao E, Dixon JB, Kao P, Pan J, Rockson SG, Jiang X, **Nicolls MR**. Abnormal lymphatic S1P signaling aggravates lymphatic dysfunction and tissue inflammation. Circulation. 2023;148(16):1231-1249. PMCID: PMC10592179

2. Tian W, Rockson SG, Jiang X, Kim J, Begaye A, Shuffle EM, Tu AB, Cribb M, Nepiyushchikh Z, Feroze AH, Zamanian RT, Dhillon GS, Voelkel NF, Peters-Golden M, Kitajewski J, Dixon JB, **Nicolls MR**. Leukotriene B4 antagonism ameliorates experimental lymphedema. Sci Transl Med. 2017 May 10;9(389). PMID: 28490670

3. Tian W, Jiang X, Sung YK, Shuffle E, Wu TH, Kao PN, Tu AB, Dorfmüller P, Cao A, Wang L, Peng G, Kim Y, Zhang P, Chappell J, Pasupneti S, Dahms P, Maguire P, Chaib H, Zamanian R, Peters-Golden M, Snyder MP; Voelkel NF, Humbert M, Rabinovitch M, **Nicolls MR**. Phenotypically-silent bone morphogenetic protein receptor

2 (Bmpr2) mutations predispose rats to inflammation-induced pulmonary arterial hypertension by enhancing the risk for neointimal transformation. Circulation 2019 Oct 22; 140(17): 1409–1425. PMCID: PMC6803052

4. Zamanian RT, Badesch D, Chung L, Domsic RT, Medsger T, Pinckney A, Keyes-Elstein L, D'Aveta C, Spychala M, White RJ, Hassoun PM, Torres F, Sweatt AJ, Molitor JA, Khanna D, Maecker H, Welch B, Goldmuntz E, **Nicolls MR**; NIH ASC01 Study Group. Safety and Efficacy of B-Cell Depletion with Rituximab for the Treatment of Systemic Sclerosis Associated Pulmonary Arterial Hypertension: A Multi-center, Double-blind, Randomized, Placebo-controlled Trial. Am J Respir Crit Care Med. 2021 Jul; 204(2): 209–221. PMCID: PMC8650794

5. Jiang X, Khan MA, Tian W, Beilke J, Natarajan R, Yoder MC, Semenza GL, **Nicolls MR**. Adenovirus-mediated HIF-1α gene transfer promotes repair of mouse airway allograft microvasculature and attenuates chronic rejection. J Clin Invest. 2011 Jun;121(6):2336-49. PMCID: PMC3104770

The ongoing projects that I would like to highlight include:

5R01HL138473 (NIH/NHLBI) Nicolls, MR, Rabinovitch M (PIs) 07/01/17-06/30/2028
BMPR2, Monocytes and Macrophages in Pulmonary Artery Hypertension/ We investigate the innate immune mechanism underlying the activated circulating monocyte in pulmonary arterial hypertension and its role in orchestrating adverse vascular remodeling through its derivatives, the monocyte derived dendritic cell and the monocyte derived macrophage.**(*5th percentile)**

U01 HL163124-01 (NIH/NHLBI) Nicolls, MR, Dhillon G, Pulendran (PIs) 08/05/2022–07/31/2027
Vaccination responses in lung transplant recipients.
The creation of a national lung transplant consortium is permit team-based investigations. Stanford will investigate lung transplant patient responses to vaccines using big data approaches.

I01 BX005628 (VA) Nicolls, MR (PI) 06/01/2021–06/30/2026
BMPR2 mutations, Neointimal Transformation and Pulmonary Arterial Hypertension. This proposal explores how genetic and environmental triggers may lead to neointimal formation and PAH at the cellular and molecular levels; proposed studies also search for druggable targets driving EC transformation following TGF-β treatment. (***4.5th percentile**)

R01 HL158714 (NIH/NHLBI) Nicolls, MR (PI) 07/01/2021–07/31/2025
Regulatory T Cells and Pulmonary Hypertension. This proposal investigates how genetic (*BMPR2* mutations) and environmental (pulmonary inflammation) risk factors contribute to Treg derangements and a predisposition to PAH, and how Treg infusion can treat active disease. Proposed studies address a previously undocumented role of BMPR2 signaling in adaptive immune cells. (***4th percentile**)

R01 HL095686 (NIH/NHLBI) Nicolls, MR (PI) 04/01/2010–05/31/2025
Critical Role for Microvasculature in Airway Transplantation. Goals: Transplantation is the only treatment available for a number of advanced diseases but is limited by a high rate of organ failure. This competitive renewal focuses on airway lymphatics in transplanted airways. (***1st percentile**)

R01 HL141105-01A1 (NIH/NHLBI) Nicolls, MR (PI) 01/21/2019–12/31/2024
A Critical Role for Leukotriene B4 in Lymphedema. The goal of this study is to determine the mechanistic basis of LTB4 injury to the lymphatics in lymphedema. (***3rd percentile**)

T32 HL129970-01A1 (NIH/NHLBI) Nicolls, MR, Cornfield DN (PIs) 07/01/2016–06/30/2026
Stanford Training Program in Lung Biology**.** The goal of this training program is to train clinician-scientists in adult/pediatric pulmonary medicine.

B. Positions, Scientific Appointments, and Honors

Positions and Employment

2023 -	**Associate Dean for Research**, Stanford University School of Medicine
2016 -	Professor of Pulmonary & Critical Care Medicine and Immunology and Rheumatology with tenure, Stanford University School of Medicine, Stanford, CA
2016 -	Medical Director, Pulmonary, Allergy & Critical Care Medicine Service Line
2015 - 2018	Executive Steering Committee, Sean N. Parker Center for Allergy and Asthma, Stanford

2015 - 2022	Chairman of the Board, Palo Alto Veterans Institute for Research (PAVIR), VA Palo Alto
2013 -	Executive Committee, Cardiovascular Institute, Stanford University School of Medicine
2010 -	Steering Committee, Vera Moulton Wall Center for Pulmonary Vascular Disease, Stanford
2010 -	**Chief, Division of Pulmonary, Allergy & Critical Care Medicine, Stanford Medical School**
2009 - 2010	Program Director, Stanford Pulmonary/Critical Care Medicine Fellowship, Stanford, CA
2007 - 2016	Associate Professor of Pulmonary & Critical Care Medicine and Immunology and Rheumatology, Department of Medicine, Stanford University School of Medicine, Stanford, CA
2007 -	**Director of Lung Immunology, Stanford University School of Medicine, Stanford, CA**
2007 -	Faculty, Multidisciplinary Program in Immunology, Stanford University, Stanford, CA
2007 -	Associate Member, Institute for Immunity, Transplantation and Infection, Stanford, CA
2007 -	Staff Physician, Department of Pulmonary Medicine, VAPAHCS, Palo Alto, CA
2006 - 2007	Associate Professor of Medicine and Immunology, University of Colorado, Aurora, CO
2000 - 2006	Assistant Professor of Medicine and Immunology, University of Colorado
1996 - 1999	Fellowship, Pulmonary and Critical Care Medicine, University of Colorado
1993 - 1996	Internship and Residency, Stanford University Hospital, Stanford, CA

Other Experience and Professional Memberships

2017	Inventor, Methods of improving microvascular integrity (lung transpl.). Patent No. 9682071
2015 -2021	Member, Respiratory Integrative Biology and Translational Research (RIBT) Study Section
2012 -2018	Editorial Board, European Respiratory Journal
2009 -	Director, Stanford Remodeled Airways Tissue Bank
2000	No. 168206, Diplomate in Critical Care Medicine
1999	No. 168206 (recertified until 2019), Diplomate in Pulmonary Disease
1996	No. 168206, American Board of Internal Medicine

Honors

2021	Dickinson W. Richards Memorial Lecturer, AHA
2020	**Elected, Member of the Association of American Physicians (AAP)**
2016	**Endowed Chair, The Stanford Professor of Pulmonary & Critical Care Medicine**
2015	VA Palo Alto Award for Outstanding Research/Clinical Innovation, VA Palo Alto
2014	**Elected, Member of the American Society of Clinical Investigation (ASCI)**
2013	Sullivan SPARK Scholar (For Translational Research), Stanford School of Medicine
2000	Harry Shwachman Cystic Fibrosis Clinical Investigator Award, Cystic Fibrosis Foundation
1999	Young Investigator's Award, American Society of Transplantation
1998	Clinician Scientist Award, Barbara Davis Center
1993	Research Honors (Transplantation Immunology), Stanford University
1988	Stanford University Medical Scholar Award, Stanford University

C. Contributions to Science

1. While it is standard of care to target the adaptive immune response during acute rejection with high-dose steroids, we discovered that complement-dependent antibody activity and CD4+ T cells are independently sufficient to destroy microvessels and cause chronic rejection of transplanted airways. These processes can be addressed with targeted therapeutics to prevent chronic rejection, the leading problem of solid organ transplant recipients. More recently, we have evaluated how CD4+ T cells interact directly with lymphatic vessels to mediate lymphatic vascular injury in lymphedema generation.

a. Kim D, Tian W, Wu TT, Xiang M, Vinh R, Chang J, Gu S, Lee S, Zhu Y, Guan T, Schneider EC, Bao E, Dixon JB, Kao P, Pan J, Rockson SG, Jiang X, **Nicolls MR**. Abnormal lymphatic S1P signaling aggravates lymphatic dysfunction and tissue inflammation. Circulation. 2023;148(16):1231-1249. PMCID: PMC10592179

b. Khan MA, Maasch C, Vater A, Klussman S, Morser J, Leung LL, Atkinson C, Tomlinson, S, Heeger, PS, **Nicolls MR**. Targeting complement component 5a promotes vascular integrity and limits airway remodeling. Proc Natl Acad Sci U S A. 2013 Apr 9;110(15):6061-6. PMCID: PMC3625314

c. Khan MA, Jiang X, Dhillon G, Beilke J, Holers VM, Atkinson C, Tomlinson S, **Nicolls MR**. CD4+ T cells and complement independently mediate graft ischemia in the rejection of mouse orthotopic tracheal transplants. Circ Res. 2011 Nov 11;109(11):1290-301. PMCID: PMC3243047

d. Babu A, Murakawa T, Thurman JM, Miller EJ, Henson P, Zamora MR, Voelkel NF, **Nicolls MR**. Microvascular destruction identifies murine allografts that cannot be rescued from airway fibrosis. J Clin Invest. 2007 Dec;117(12):3774-85. PMCID: PMC2096438

2. Translational research of immune injury on the vasculature leads to NIH multicenter, double-blind, randomized, placebo-controlled trial of rituximab for systemic sclerosis PAH; the first trial of cell-depleting immunotherapy for PAH. Building our basic science models of lymphatic vascular disease, we conducted a few clinical trials of anti-inflammatory therapies for lymphedema. The JCI Insight study using ketoprofen (which antagonizes Leukotriene B_4) is the first medical therapy holding promise for this chronic condition. Finally, building on principles that we established in pre-clinical modeling of lung transplantation, we confirmed in a clinical study that lung transplant patient airways are relatively hypoxic, a finding attributable to the bronchial artery circulation not being restored at the time of transplantation.

a. Zamanian RT, Badesch D, Chung L, Domsic RT, Medsger T, Pinckney A, Keyes-Elstein L, D'Aveta C, Spychala M, White RJ, Hassoun PM, Torres F, Sweatt AJ, Molitor JA, Khanna D, Maecker H, Welch B, Goldmuntz E, **Nicolls MR**; NIH ASC01 Study Group. Safety and Efficacy of B-Cell Depletion with Rituximab for the Treatment of Systemic Sclerosis Associated Pulmonary Arterial Hypertension: A Multi-center, Double-blind, Randomized, Placebo-controlled Trial. Am J Respir Crit Care Med. 2021 Jul; 204(2): 209–221. PMCID: PMC8650794

b. Rockson SG, Tian W, Jiang X, Kuznetsova T, Haddad F, Zampell J, Mehrara B, Roche L, Kim J, **Nicolls MR**. Pilot studies demonstrate the potential benefits of anti-inflammatory therapy in human lymphedema. JCI Insight. 2018. Oct 18;3(20). PMCID: PMC623744

c. Tian W, Rockson SG, Jiang X, Kim J, Begaye A, Shuffle EM, Tu AB, Cribb M, Nepiyushchikh Z, Feroze AH, Zamanian RT, Dhillon GS, Voelkel NF, Peters-Golden M, Kitajewski J, Dixon JB, **Nicolls MR**. Leukotriene B4 antagonism ameliorates experimental lymphedema. Sci Transl Med. 2017 May 10;9(389). PMID: 28490670

d. Dhillon GS, Zamora MR, Roos JE, Sheahan D, Sista RR, Van der Starre P, Weill D, **Nicolls MR**. Lung Transplant Airway Hypoxia: A Diathesis to Fibrosis? American Journal of Respiratory and Critical Care Medicine 2010; 182: 230-236. PMCID: PMC3269232

3. Investigations into how the leukotriene B4 (LTB_4) and 5-LO immunity affects the vasculature. These pre-clinical efforts led to the ULTRA trial (the first multicenter double-blind, randomized placebo-controlled drug trial for lymphedema), HEAL trial (single center, double-blind, randomized placebo-controlled drug trial for secondary arm lymphedema), and the LIBERTY trial (for PAH). Our group were the first to demonstrate the protective role of regulatory T cells (Tregs) against harmful immunity in PAH. Our more recent efforts highlight the of sex and Treg biology in PAH.

a. Jiang X, Tian W, Granucci EJ, Tu AB, Kim D, Dahms P, Pasupneti S, Peng G, Kim Y, Lim AH, Espinoza FH, Cribb M, J. Dixon JB , Rockson SG, Semenza GL, **Nicolls MR**. Decreased lymphatic HIF-2α accentuates lymphatic remodeling in lymphedema. 2020 Journal of Clin Invest; Jul 16. PMCID: PMC7524470

b. Tamosiuniene R, Manouvakhova O, Mesange P, Saito T, Qian J, Sanayal M, Lin YC, Nguyen L, Luria A, Tu A, Sante J, Rabinovitch M, Fitzgerald DJ, Graham BB, Habtezion A, Voelkel NF, Aurelian L, **Nicolls MR**. A dominant role for regulatory T cells in protecting females against pulmonary hypertension. Circ. Res. 2018 Mar 15.117.312058. PMCID: PMC634071

c. Tian W, Jiang X, Sung YK, Shuffle E, Wu TH, Kao PN, Tu AB, Dorfmüller P, Cao A, Wang L, Peng G, Kim Y, Zhang P, Chappell J, Pasupneti S, Dahms P, Maguire P, Chaib H, Zamanian R, Peters-Golden M, Snyder MP; Voelkel NF, Humbert M, Rabinovitch M, **Nicolls MR**. Phenotypically-silent bone

morphogenetic protein receptor 2 (Bmpr2) mutations predispose rats to inflammation-induced pulmonary arterial hypertension by enhancing the risk for neointimal transformation. Circulation 2019 Oct 22; 140(17): 1409–1425. PMCID: PMC6803052

d. Tian W, Jiang X, Tamosiuniene R, Sung YK, Qian J, Dhillon G, Gera L, Farkas L, Rabinovitch M, Zamanian RT, Inayathullah M, Fridlib M, Rajadas J, Peters-Golden M, Voelkel NF, **Nicolls MR**. Blocking macrophage leukotriene b4 prevents endothelial injury and reverses pulmonary hypertension. Sci Transl Med. 2013 Aug 28;5(200):200ra117. PMCID: PMC4016764

4. Discovery that protection of microvessels is key for preventing the development of chronic rejection and emphysema. The hypoxia-inducible factors (HIF-1α and HIF-2α) are differentially important regulators of microvascular health.

a. Pasupneti S, Tian W, Tu AB, Dahms P, Granucci E, Gandjeva A, Xiang M, Butcher EC, Semenza GL, Tuder RM, Jiang X and **Nicolls MR**. Endothelial HIF-2α as a key endogenous mediator preventing emphysema. Amer J Resp Crit Care Med. 2020 Jun 9. PMICD: PMC7528783

b. Jiang X, Tian W, Tu AB, Pasupneti S, Shuffle E, Dahms P, Zhang P, Cai H, Dinh TT, Liu B, Cain C, Giaccia AJ, Butcher EC, Simon MC, Semenza GL, **Nicolls MR**. Endothelial HIF-2α is required for the maintenance of airway microvasculature. Circulation 2019 Jan 22;139(4):502-517. PMCID: PMC6340714

c. Hsu JL, Manouvakhova OV, Clemons KV, Inayathullah M, Tu AB, Sobel RA, Tian W, Nazik H, Pothineni VR, Pasupneti S, Jiang X, Dhillon GS, Bedi H, Rajadas J, Haas H, Aurelian L, Stevens DA, **Nicolls MR**. Microhemorrhage-associated tissue iron enhances the risk for Aspergillus fumigatus invasion in murine tracheal transplantation. Sci Transl Med, 2018 Feb 21;10(429). PMCID: PMC5841257

d. Jiang X, Khan MA, Tian W, Beilke J, Natarajan R, Yoder MC, Semenza GL, **Nicolls MR**. Adenovirus-mediated HIF-1α gene transfer promotes repair of mouse airway allograft microvasculature and attenuates chronic rejection. J Clin Invest. 2011 Jun;121(6):2336-49. PMCID: PMC3104770

5. Early investigations from the PI resulted in the creation of the first non-mitogenic anti-CD3 monoclonal antibody later used as a general approach for promoting immune tolerance in autoimmune conditions including such as new-onset Type I diabetes. We were the first group to report how the combination of anti-LFA-1 and anti-CD40L antibodies was particularly tolerogenic; a combination strategy that was later widely adopted in immunology research. We showed the effectiveness of this approach in an experimental model of lung transplantation.

a. Murakawa T, Kerklo MM, Zamora MR, Wei Y, Gill RG, Grover FL, **Nicolls MR**. Simultaneous LFA-1 and CD40 ligand antagonism prevents airway remodeling in orthotopic airway transplantation: implications for the role of respiratory epithelium as a modulator of fibrosis. J Immunol. 2005 Apr 1;174(7):3869-79. PMID: 15778341

b. **Nicolls MR**, Coulombe M, Beilke J, Gelhaus HC, Gill RG. CD4-dependent generation of dominant transplantation tolerance induced by simultaneous perturbation of CD154 and LFA-1 pathways. J Immunol. 2002 Nov 1;169(9):4831-9. PMID 12391193

c. **Nicolls MR**, Coulombe M, Yang H, Bolwerk A, Gill RG. Anti-LFA-1 therapy induces long-term islet allograft acceptance in the absence of IFN-gamma or IL-4. J Immunol. 2000 Apr 1;164(7):3627-34. PMID: 10725719

d. **Nicolls MR**, Aversa G, Pearce N, Spinelli A, Berger M, Gurley K, Hall B. Induction of long-term specific tolerance to allografts in rats by therapy with an anti-CD3-like monoclonal antibody. Transplantation. 1993 Mar;55(3):459-68. PMID: 8456460

Complete List of Published Work in My Bibliography:
http://www.ncbi.nlm.nih.gov/myncbi/mark.nicolls.1/bibliography/40597408/public/?sort=date&direction=ascending