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 the Stanford 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 lab focuses on immune regulation as it pertains to lung transplantation, lymphedema, pulmonary hypertension, and emphysema. I have >25 years of experience working in transplant 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 pulmonary hypertension and lymphedema and why preserving microvascular health may prevent chronic rejection in solid organ transplant recipients. On the clinical side, I care for lung transplant patients, Co-Chaired the 1st Aspen Lung Conference focused on lung transplantation (PMCID: PMC5802624 (2017)) and was the Co-Chair, communicating and senior author for the NHLBI Consortium and Consensus Statement on pre-clinical models in lung transplantation (PMCID: PMC5414568 (2017)). 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 (PMID: 33651671(2021)). With this large-scale effort, the first placebo-controlled trial of an immunotherapy for pulmonary hypertension, we coordinated the collection of hundreds of blood samples from geographically-distant sites, matched samples with demographic information, coordinated the trial biorepository at the Stanford Human Immune Monitoring Center, and conducted machine-learning analysis that paired immunophenotyping to clinical outcomes. I recently submitted a thematically-related Lung Transplantation Consortium U01 grant (funding decision anticipated February 2022) focusing on *system biological evaluation of vaccine responses in lung transplant recipients*. I have trained numerous fellows in academic careers and am committed to fostering the careers of junior faculty. I am PI, with David Cornfield, overseeing the Stanford Combined Adult/Pediatric T32 Pulmonary Biology Training Grant.

The ongoing and completed projects that I would like to highlight include:

I01BX005628 (VA) Nicolls, MR (PI) 06/01/2021–05/31/2025

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**)

R01HL158714 (NIH/NHLBI) Nicolls, MR (PI) 07/01/2021–06/30/2026

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) 04/01/2010–03/28/2023
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**)

R01HL141105-01A1 (NIH/NHLBI) Nicolls, MR (PI) 01/21/2019–12/31/2022
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**)

R01HL138473-01 (NIH/NHLBI) Nicolls, MR, Rabinovitch M (PIs) 07/01/2017–04/30/2022
Endothelial injury, BMPR2 dysfunction and macrophage activation cause EndMT and PAH. The goal of this research is to determine how endothelial injury in conjunction with endogenous retrovirus and leukotriene B4 leads to endothelial mesenchymal transformation and pulmonary hypertension.

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

2016 -	Professor of Pulmonary & Critical Care Medicine and Immunology and Rheumatology with tenure, Stanford University School of Medicine, Stanford, CA
2016 -	Director, Center for Advanced Lung Disease, Stanford
2015 -	Executive Steering Committee, Sean N. Parker Center for Allergy and Asthma, Stanford
2015 -	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. 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]

2. 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 led efforts to help investigators by assembling the first NIH Consortium of science investigators in lung transplantation and published a consensus statement designed to assist researchers choose the best model system for their scientific questions regarding pulmonary allografts.

a. Lama VN, Belperio JA, Christie JD, El-Chemaly S, Fishbein MC, Gelman AE, Hancock WW, Keshavjee S, Kreise D, Laubach VE, Looney MR, McDyer JF, Mohanakumar T, Shilling RA, Panoskaltsis-Mortari A, Wilkes DS, Eu JP, **Nicolls MR**. Models of Lung Transplant Research: a consensus statement from the National Heart, Lung, and Blood Institute workshop. JCI Insight. 2017 May 4;2(9). [PMCID: PMC5414568]

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]

3. 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 trial of anti-inflammatory therapy for lymphedema. The JCI Insight study using ketoprofen (which antagonizes leukotrienes and COX-2) is the first medical therapy holding promise for this chronic condition. Finally, building on principles that we established in pre-clinical modelling 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 Mar 2. [PMID: 33651671]

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: PMC6237444]

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]

4. 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) 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: PMC6340714]

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 Aug 29 [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]

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