BIOGRAPHICAL SKETCH

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NAME: Nicholas W. Morrell

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

POSITION TITLE: British Heart Foundation Professor of Cardiopulmonary Medicine

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
Charing Cross and Westminster Medical School	BSc	071984	Medical Science
Charing Cross and Westminster Medical School	MB, BS	07/1987	Medicine
University of London	MD	10/1993	Medicine
Royal College of Physicians UK	FRCP	06/2001	Medicine

A. Personal Statement

I have been involved in the field of pulmonary circulation research for nearly twenty years. I have published over 120 articles in this field. Recently, my group has contributed to understanding how mutations in the bone morphogenetic protein type II receptor (BMPR-II) cause the majority of cases of heritable pulmonary arterial hypertension (PAH) via loss of function in BMP signalling. Our work includes the use of mouse genetic models of disease and human and mouse cells and tissues, including progenitor cells and induced pluripotent stem cells. I am the Research Director of the Pulmonary Vascular Diseases Unit at Papworth Hospital, Cambridge, a national referral centre for patients with pulmonary arterial hypertension. I am Theme Lead for Cardiovascular Medicine in the Cambridge National Institute of Health Research Biomedical Research Center and Director of the BHF Cambridge Centre for Cardiovascular Research Excellence. I am a National Institute of Health Research Senior Investigator. I was elected to the Fellowship of the Academy of Medical Sciences in 2011.

Four publications that highlight my contribution to the BMPR-II and PAH fields are listed below:

1. Trembath RC, Thomson JR, Machado RD, Morgan NV, Atkinson C, Winship I, Simonneau G, Galie N, Loyd JE, Humbert M, Nichols WC, **Morrell NW**. Clinical and molecular genetic features of pulmonary hypertension in hereditary hemorrhagic telangiectasia. **New England Journal of Medicine** 2001;345:325-334.
2. Yang X, Long L, Southwood M, Rudarakanchana N, Upton PD, Jeffery TK, Atkinson C, Chen H, Trembath RC, **Morrell NW**. Dysfunctional Smad signaling contributes to abnormal smooth muscle cell proliferation in familial pulmonary arterial hypertension. **Circulation Research** 2005;96:1053-1063.
3. Long L,Yang X, Southwood M, Lu J, Marciniak SJ, Dunmore BJ, **Morrell NW**. Chloroquine prevents progression of experimental pulmonary hypertension via inhibition of autophagy and lysosomal bone morphogenetic protein type II receptor degradation. **Circulation Research** 2013 2;112:1159-70.
4. Long L, Ormiston ML, Yang XD, Southwood M, Graf S, Machado RD, Mueller M, Kinzel B, Yung LM, Wilkinson JM, Moore SD, Drake KM, Aldred MA, Yu PB, Upton PD, **Morrell NW**. Selective enhancement of endothelial BMPR-II with BMP9 reverses pulmonary arterial hypertension**. Nature Medicine** 2015;21(7):777-85. PMCID: PMC4496295

B. Positions and Honors

Positions

1987 to 1988	House physician	Charing Cross Hospital, London
1988 to 1988	House surgeon	Queen Elizabeth Hospital, King's Lynn
1988 to 1990	Senior House Officer rotation	Charing Cross and Westminster Medical School
1990 to 1993	Research Fellow	Charing Cross and Westminster Medical School, London
1993 to 1995	British Heart Foundation Fellow	University of Colorado Health Sciences Center, Denver
1996 to 1998	Senior Registrar/Lecturer	Royal Postgraduate Medical School, London
1998 to 2000	MRC Clinician Scientist	Imperial College School of Medicine, London
2000 to 2004	University Lecturer	University of Cambridge School of Clinical Medicine,
2004 to 2007	Reader in Respiratory Medicine	University of Cambridge School of Clinical Medicine
2007 to present	Professor of Cardiopulmonary Medicine	University of Cambridge School of Clinical Medicine

Honors

1984	MRC Intercalated Award
1993	Physiological Society Rushton Fund Travel Award
1993	Scadding-Morriston Davies Respiratory Fellowship
1993 to 1995	BHF International Fellowship
1998 to 2000	MRC Clinician Scientist Fellowship
2009	Awarded British Heart Foundation Chair in Cardiopulmonary Medicine
2018	ScD University of Cambridge

C. Contribution to science

1. My early publication in the field of PAH documented the role and importance of the renin-angiotensin system in the pathobiology of PAH and the potential to treat PH with angiotensin receptor antagonists.

a. **Morrell NW**, Grieshaber SS, Danilov SM, Majack RA, Stenmark KR. Developmental regulation of angiotensin converting enzyme and angiotensin type 1 receptor in the rat pulmonary circulation. ***Am J Respir Cell Mol Biol.*** 1996;14:526-37.

b. **Morrell NW**, Morris KG, Stenmark KR. Role of angiotensin-converting enzyme and angiotensin II in development of hypoxic pulmonary hypertension. ***Am J Physiol.*** 1995;269:H1186-94

c. **Morrell NW**, Atochina EN, Morris KG, Danilov SM, Stenmark KR. Angiotensinconverting enzyme expression is increased in small pulmonary arteries of rats with hypoxia-induced pulmonary hypertension. ***J Clin Invest***. 1995;96:1823-33.

2. Since the discovery of mutations in the bone morphogenetic protein type 2 receptor (BMPR2) as the commonest genetic cause of PAH I have studied the role of this pathway in disease biology. Our lab were the first to identify abnormal responses of pulmonary vascular cells derived from patients with PAH to BMPs and TGF-beta. In addition we were the first to identify that non-genetic forms of PAH are characterized by reduced expression of BMPR2. Furthermore we described the functional consequences of a range of different BMPR2 mutations and the activation of pro-proliferative pathways.

a. **Morrell NW**, Yang X, Upton PD, Jourdan KB, Morgan N, Sheares KK, Trembath RC. Altered growth responses of pulmonary artery smooth muscle cells from patients with primary pulmonary hypertension to TGF-b1 and bone morphogenetic proteins. **Circulation** 2001;104:790-795.

b. Atkinson C, Stewart S, Upton PD, Machado R, Thomson J, Trembath RC, **Morrell NW**. Primary pulmonary hypertension is associated with reduced pulmonary vascular expression of BMPR-II. **Circulation** 2002;105:1672-1678.

c. Rudarakanchana N, Flanagan JA, Chen H, Upton PD, Machado R, Patel D, Trembath RC, **Morrell NW**. Functional analysis of bone morphogenetic protein type II receptor mutations underlying primary pulmonary hypertension. **Human Molecular Genetics** 2002;11:1517-25.

d. Yang J, Davies RJ, Southwood M, Long L, Yang X, Sobolewski A, Upton PD, Trembath RC, **Morrell NW**. Mutations in bone morphogenetic protein type II receptor cause dysregulation of Id gene expression in pulmonary artery smooth muscle cells: implications for familial pulmonary arterial hypertension. **Circulation Research** 2008;102(10):1212-21.

3. We have focused our attention of approaches to target the dysfunctional BMPR2 pathway in PAH as a therapeutic approach in this disease and have shown proof of concept for the restoration of BMPR2 signalling in a series of studies.

a. Sobolewski A, Rudarakanchana N, Upton PD, Yang J, Crilley TK, Trembath RC, **Morrell NW**. Failure of bone morphogenetic protein receptor trafficking in pulmonary arterial hypertension: potential for rescue. **Human Molecular Genetics**. 2008;17:3180-90.
b. Hurst LA, Dunmore BJ, Long L, Crosby A, Al-Lamki R, Deighton J, Southwood M, Yang X, Nikolic MZ, Herera B, Inman CJ, Bradley JR, Rana AA, Upton PD, Morrell NW. TNFα drives pulmonary arterial hypertension by suppressing the BMP type-II receptor and altering NOTCH signaling. ***Nat Commun*** 2017;8:14079. PMCID: PMC5241886
c. Long L, Yang X, Southwood M, Lu J, Marciniak SJ, Dunmore BJ, **Morrell NW**. Chloroquine prevents progression of experimental pulmonary hypertension via inhibition of autophagy and lysosomal bone morphogenetic protein type II receptor degradation. ***Circ Res***. 2013;112(8):1159-70.
d. Yang J, Li X, Al-Lamki RS, Southwood M, Zhao J, Lever AM, Grimminger F,Schermuly RT, **Morrell NW**. Smad-dependent and smad-independent induction of id1 byprostacyclin analogues inhibits proliferation of pulmonary artery smooth muscle cells in vitro and in vivo. ***Circ Res***. 2010;107(2):252-62.

4. My group has contributed to understanding the genetic basis of PAH and importantly the role of the BMPR2/ALK1 receptor complex in this disease, allowing the identification of BMP9/10 as potential therapies.

a. Upton PD, Davies RJ, Trembath RC, **Morrell NW**. Bone morphogenetic protein (BMP) and activin type II receptors balance BMP9 signals mediated by activin receptor-like kinase-1 in human pulmonary artery endothelial cells. **Journal of Biological Chemistry** 2009;284:15794-804. PMCID: PMC2708876
b. Machado RD, Aldred MA, James V, Harrison RE, Patel B, Schwalbe EC, Gruenig E, Janssen B, Koehler R, Seeger W, Eickelberg O, Olschewski H, Elliott CG, Glissmeyer E, Carlquist J, Kim M, Torbicki A, Fijalkowska A, Szewczyk G, Parma J, Abramowicz MJ, Galie N, Morisaki H, Kyotani S, Nakanishi N, Morisaki T, Humbert M, Simonneau G, Sitbon O, Soubrier F, Coulet F, **Morrell NW**, Trembath RC. Mutations of the TGF-beta type II receptor BMPR2 in pulmonary arterialhypertension. ***Hum Mutat***. 2006;27(2):121-32.
c. Trembath RC, Thomson JR, Machado RD, Morgan NV, Atkinson C, Winship I, Simonneau G, Galie N, Loyd JE, Humbert M, Nichols WC, **Morrell NW**. Clinical and molecular genetic features of pulmonary hypertension in hereditary hemorrhagic telangiectasia. **New England Journal of Medicine** 2001;345:325-334.
d. Gräf S, Haimel M, Bleda M, …..Upton PD, Wilkins MR, Trembath RC, **Morrell NW**. Identification of rare sequence variation underlying heritable pulmonary arterial hypertension. ***Nat Commun.*** 2018;9:1416. PMCID: PMC5897357

A full list of my publications can be found here: http://www.ncbi.nlm.nih.gov/pubmed/?term=morrell-nw

D. Research Support

Ongoing Research Support

Programme grant RG/13/4/30107 (Morrell, NW, PI) 09/01/13-08/31/19
British Heart Foundation
Targeting the BMP signalling pathway for the treatment of pulmonary arterial hypertension
To explore approaches to target BMPR2 to treat PAH
Role: PI

Special Project no. SP/12/12/29836 (Morrell, NW, PI) 07/01/13-12/31/22
British Heart Foundation
National Cohort Study of heritable pulmonary arterial hypertension
To establish a research network of PAH patients for genetic, epidemiology and biomarker studies
Role: PI

Completed Research Support

Translatrantic Research Network (Morrell, NW & Bloch KD, PI) 01/01/10-12/31/15
Leducq Foundation
Multidisciplinary Program to Elucidate the Role of Bone Morphogenetic Protein Signaling in the Pathogenesis of Pulmonary and Systemic Vascular Diseases
Multi program to elucidate the role of bone morphogenetic protein signaling in the pathogenesis of pulmonary and systemic vascular diseases
Role: co-PI

Project Grant (Morrell, NW, PI) 04/30/14-03/31/17
British Heart Foundation
Development of induced pluripotent stem cell models to elucidate mechanism and develop treatment for pulmonary arterial hypertension.
To establish an iPSC model of BMPR2 mutation and PAH
Role: co-PI

Intermediate Basic Science Research Fellowship FS/12/39/29653 (Morrell, NW, PI) 01/01/12-12/31/16
British Heart Foundation
Elucidating the role of natural killer cells in the regulation of pathological pulmonary vascular remodelling
To determine the mechanisms by which BMPR2 regulates NK cell function and the role of these cells in PAH
Role: Supervisor

Experimental Challenge Award (Morrell, NW, PI) 06/01/13-05/31/18
Medical Research Council
Mechanism underlying the development of pulmonary arterial hypertension
To undertake whole genome sequencing and metabolomics studies in the UK cohort of patients with idiopathic PAH
Role: PI