BIOGRAPHICAL SKETCH

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NAME Mark T. Gladwin	POSITION TITLE Chief, Pulmonary, Allergy and Critical Care Medicine Department, University of Pittsburgh Director, Vascular Medicine Institute, University of Pittsburgh School of Medicine
eRA COMMONS USER NAME mgladwin	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing,*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
University of Miami, Miami, FL. 6-year program	BSc-MD	1985-1991	Biochemistry, Medicine

A. Personal Statement

Mark Gladwin, MD, has a long history of leadership of translational projects and programs, having served as a principal or associate investigator on more than 30 human subjects protocols and having held more than seven FDA INDs for the use of investigational therapeutic medications, including IV nitrite, inhaled nitrite, carbon monoxide, L-NMMA, oxypurinol, acetylcholine, and sildenafil. Serving for more than 5 years as an Intramural Research Division Branch Chief, he has served as PI on two major phase II clinical trials, the DeNOVO trial of NO therapy for acute pain crisis in patients with sickle cell disease, which successfully enrolled 154 patients at 13 Centers, and the Walk-PHASST trial of sildenafil for pulmonary hypertension secondary to sickle cell disease. Dr. Gladwin's basic and translational research has led to the development and licensing of intravenous and inhaled nitrite as a human therapeutic, with recent completion of animal toxicology, GMP formulations, and phase Ia and Ib clinical trials. Phase II trials of inhaled nitrite are now underway.

Dr. Gladwin's research activities cover four areas of scientific investigation: (1) The discovery that the nitrite anion is a circulating storage pool for NO bioactivity (*PNAS* 2000) that regulates hypoxic vasodilation (*Nature Medicine* 2003) and the cellular resilience to low oxygen and ischemia (*JCI* 2005). (2) The discovery of a novel physiological function for hemoglobin as an electronically and allosterically-regulated nitrite reductase (*Nature Medicine* 2003; Huang *JCI* 2005). These studies reveal that nitrite is a potent vasodilator in humans and is bioactivated by reaction with deoxyhemoglobin (and myoglobin) to generate NO preferentially under hypoxic conditions; they also suggest that hemoglobin has an "enzymatic" property as a nitrite reductase that participates in hypoxic vasodilation. In related translational studies, Dr. Gladwin has demonstrated that inhaled nitrite reverses hypoxic neonatal pulmonary hypertension in sheep (*Nature Medicine* 2004), and that infused nitrite solutions prevent post-subarachnoid hemorrhage-induced vasospasm in primates (*JAMA* 2005) and prevent hepatic and cardiac ischemia-reperfusion injury and infarction in mice (*JCI* 2005). (3) The characterization of a novel mechanism of disease, hemolysis-associated endothelial dysfunction (*Nature Medicine* 2002; *JAMA* 2005; *JCI* 2005). This work has described a state of resistance to NO in patients with sickle cell disease caused by scavenging of nitric oxide by hemoglobin that is released into plasma during hemolysis. (4) The mechanistic, clinical, and epidemiological description of a human disease syndrome, hemolysis-associated pulmonary hypertension, which occurs in 10% of patients with sickle cell disease and is a major cause of mortality in this population (*NEJM* 2004, *JAMA* 2012).

B. Positions and Honors

Positions

1991-1995 Internship, Residency, Chief Residency, Department of Internal Medicine, Oregon Health Sciences University (OHSU), Portland, OR
1995-1996 Critical Care Fellow, Critical Care Medicine Department, NIH
1996-1998 Pulmonary-Critical Care Fellow, Pulmonary Division, University of Washington. Seattle, WA
1998-2000 Senior Research Fellow, Critical Care Medicine Department, NIH
1995-2000 Commander, US Public Health Service (0-5)
2000-2004 Section Head, Sickle Cell/Nitric Oxide Therapeutics Section, Critical Care Medicine Department, Clinical Center, Cardiovascular Branch, NHLBI, NIH, Bethesda, MD

2004-2005 Section Head, Vascular Therapeutics Section, Cardiovascular Branch, NHLBI, NIH
2005-2008 Chief, Pulmonary and Vascular Medicine Branch, NHLBI, NIH
2008-Present Chief, Pulmonary, Allergy and Critical Care Medicine Department, University of Pittsburgh
2013-Present Director, Pittsburgh Heart, Lung, Blood and Vascular Medicine Institute
Co-Director, Heart and Vascular Institute, UPMC

Honors

1985-1986 Henry K. Stanford Merit Scholarship, Florida Honors Merit Scholarship, Florida Academic Merit Scholarship, University of Miami
1991 Honors Program in Medical Education, University of Miami, Florida, 1991
1994 Alpha Omega Alpha
1999 Achievement Medal, US Public Health Service, NIH
2002 Clinical Center Director's Award (category of Science)
2006 American Society of Clinical Investigations (ASCI)
2006 The NIH Director's Award for Mentoring in making contributions to understanding the role of nitric oxide in sickle cell anemia patients
2006 The NIH Merit Award in recognition for accomplishments in both basic and clinical sciences in the use of nitrite and NO in clinical applications
2007 Presented at the Nobel Form, Karolinska Institutet as part of the series "Frontiers I Biomedical Research", Stockholm, Sweden
2008 Inducted to the American Association of Physicians (AAP)
2009 Elected to American Society of Clinical Investigations (ASCI) Council
2012 Robert F. Johnston, M.D., Memorial Lecturer at Drexel University College of Medicine
2012 Howard P. Lewis Visiting Professor of Medicine and Speaker, OHSU
2012 American Heart Association 3PCR Dickinson W. Richards Lecture
2013 Recognition Award for Scientific Accomplishments from the American Thoracic Society

C. Selected Peer-reviewed Publications (Selected from more than 260 peer-reviewed publications)

1. **Gladwin MT**, Shelhamer JH, Schechter AN, Pease-Fye ME, Waclawiw MA, Panza JA, Ognibene FP, Cannon III RO. Role of circulating nitrite and S-nitrosohemoglobin in regulation of regional blood flow in humans. Proc Natl Acad Sci 2000; 97:11482-11487. PMID: 11027349. PMC17226

2. Reiter CD, Wang X, Tanos-Santos J, Hogg N, Cannon RO,Schechter AN, and **Gladwin MT.** Cell free hemoglobin limits NO bioavailability in sickle cell disease. Nature Medicine 2002; 8:1383-1389.

3. Cosby K, Partovi KS, Crawford JH, Patel RP, Reiter C, Martyr S, Yang BK, Waclawiw MA, Zalos G, Xu X, Huang KT, Shields H, Kim-Shapiro DB, Schechter A, Cannon RO, **Gladwin MT**. Nitrite reduction to nitric oxide by deoxyhemoglobin vasodilates the human circulation. Nat Med 2003; 9:1498-1505. PMID: 14595407

4. Hunter CJ, Dejam A, Blood AB, Shields H, Kim-Shapiro DB, Machado RF, Tarekegn S, Mulla N, Hooper AO, Schechter AN, Power GG, **Gladwin MT**. Inhaled nebulized nitrite is a hypoxia-sensitive NO-dependent selective pulmonary vasodilator. Nat Med 2004; 10:1122-1127. PMID: 15361865

5. **Gladwin MT,** Sachdev V, Jison M, Plehn JF, Minter K, Brown B, Coles WA, Nichols JS, Ernst I, Hunter LA, Blackwelder W, Schechter AN, Rodgers GP, Castro O, and Ognibene FP. Pulmonary Hypertension as a Risk Factor for Death in Patients with Sickle Cell Disease. New England Journal of Medicine 2004; 350:886-895.

6. Huang Z, Shiva S, Kim-Shapiro DB, Patel RP, Ringwood LA, Irby CE, Huang KT, Ho C, Schechter AN, Hogg N, **Gladwin MT**. Enzymatic function of hemoglobin as a nitrite reductase that produces NO under allosteric control. J Clin Invest. 2005 Aug;115(8):2099-107. PMC1177999

7. Shiva S, Wang X, Ringwood LA, Xu X, Yuditskaya S, Annavajjhala V, Miyajima H, Hoog N, Harris ZL, Gladwin MT. Ceruloplasmin is a NO oxidase and nitrite synthase that determines endocrine NO hemostasis. Nat Chem Biol 2006; 2(9):486-483. PMID: 16906150

8. Rother RP, Bell L, Hillmen P, and **Gladwin MT**. The clinical sequelae of intravascular hemolysis and estracellular plasma hemoglobin. Journal of the American Medical Association 2005; 293:1653-1662.

9. Shiva S, Huang Z, Grubina R, Sun J, Ringwood LA, MacArthur PH, Xu X, Murphy E, Darley-Usmar VM, **Gladwin MT**. Deoxymyoglobin is a nitrite reductase that generates nitric oxide and regulates mitochondrial respiration. Circ Res. 2007 Mar 16;100(5):654-61

10. Shiva S, Sack MN, Greer JJ, Duranski M, Ringwood LA, Burwell L, Wang X, Macarthur PH, Shoja A, Raghavachari N, Calvert JW, Brookes PS, Lefer DJ, **Gladwin MT**. Nitrite augments tolerance to ischemia/ reperfusion injury via the modulation of mitochondrial electron transfer. J Exp Med 2007; 204:2089-2102. PMC2118713

11. Lundberg JO, Weitzberg E, and **Gladwin MT**. The nitrate-nitrite-nitric oxide pathway in physiology and therapeutics. Nature Reviews Drug Discovery 2008; 7:156-167.

12. **Gladwin MT**, Vichinsky E. Pulmonary complications of sickle cell disease. N Engl J Med. 2008 Nov 20;359(21):2254-65.

13. Lee JS, **Gladwin MT**. Bad blood: the risks of red cell storage. Nat Med. 2010 Apr;16(4): 381-2.

14. Rees DC, Williams TN, **Gladwin MT**. Sickle-cell disease. Lancet. 2010 Dec 11;376(9757):2018-31.

15. Sachdev V, Kato GJ, Gibbs JS, Barst RJ, Machado RF, Nouraie M, Hassell KL, Little JA, Schraufnagel DE, Krishnamurti L, Novelli EM, Gigris RE, Morris CR, Rosenzweig EB, Badesch DB, Lanzkron S, Castro OL, Taylor JG 6th, Hannoush H, Goldsmith JC, **Gladwin MT**, Gordeuk VR, Walk-PHASST Investigators. Echocardiographic markers of elevated pulmonary pressure and left ventricular diastolic dysfunction are associated with exercise intolerance in adults and adolescents with homozygous sickle cell anemia in the United States and United Kingdom. Circulation. 2011 Sep 27; 124 (13): 1452-60. PMCID: PMC3183314

16. **Gladwin MT**, Tejero J. Nitrite-NO bailout for a NOS complex too big to fail. Nat Med. 2011 Dec 6;17(12):1556-7.

17. Donadee C, Raat NJ, Kanias T, Tejero J, Lee JS, Kelley EE, Zhao X, Liu C, Reynolds H, Azarov I, Frizzell S, Meyer EM, Donnenberg AD, Qu L, Triulzi D, Kim-Shapiro DB, **Gladwin MT**. (2011). Nitric oxide scavenging by red blood cell microparticles and cell-free hemoglobin as a mechanism for the red cell storage lesion. Circulation. 124(4):465-76. PMID: 21747051. PMC Journal – In Process. NIHMSID: NIHMS307708.

18. **Gladwin MT**. Adenosine receptor crossroads in sickle cell disease. Nat Med. 2011 Jan;17(1):38-40.

19. Machado RF, Barst RJ, Yovetich NA, Hassell KL, Kato GJ, Gordeuk VR, Gibbs JS, Little JA, Schraufnagel DE, Krishnamurti L, Girgis RE, Morris CR, Rosenzweig EB, Badesch DB, Lanzkron S, Onyekwere O, Castro OL, Sachdev V, Waclawiw MA, Woolson R, Goldsmith JC, **Gladwin MT**; on behalf of the walk-PHaSST Investigators and Patients. Hospitalization for pain in patients with sickle cell disease treated with sildenafil for elevated TRV and low exercise capacity. Blood. 2011 Jul 28;118(4):855-864. PMC3148167

20. Tiso M, Tejero J, Basu S, Azarov I, Wang X, Simplaceanu V, Frizzll S, Jayaraman T, Geary L, Shapiro C, Ho C, Shiva S, Kim-Shapiro DB, **Gladwin MT**. Human neuroglobin functions as a redox regulated nitrite reductase. J Biol Chem. 2011 Feb 4. [Epub ahead of print] PMC3093900

21. Mehari A, **Gladwin MT**, Tian X, Machado RF, Kato GJ. Mortality in adults with sickle cell disease and pulmonary hypertension. JAMA. 2012 Mar 28;307(12):1254-6. PMC3511048

22. **Gladwin MT**, Kanias T, Kim-Shapiro DB. Hemolysis and cell-free hemoglobin drive an intrinsic mechanism for human disease. J Clin Invest. 2012 Mar 26:1-4. doi: 10.1172/JCI62972. PMID: 22446184. PMC3314481

23. **Gladwin MT**, Kim-Shapiro DB. Vascular biology: Nitric oxide caught in traffic. Nature. 2012 Nov 15;491(7424):344-5.

24. Yazji I, Sodhi CP, Lee EK, Good M, Egan CE, Afrazi A, Neal MD, Jia H, Lin J, Ma C, Branca MF, Prindle T, Richardson WM, Ozolek J, Billiar TR, Binion DG, **Gladwin MT**, Hackam DJ. Endothelial TLR4 activation impairs intestinal microcirculatory perfusion in necrotizing enterocolitis via eNOS-NO-nitrite signaling. Proc Natl Acad Sci U S A. 2013 Jun 4;110(23):9451-6. PMCID: PMC3677476

25. Wood KC, Cortese-Krott MM, Kovacic JC, Noguchi A, Liu VB, Wang X, Raghavachari N, Boehm M, Kato GJ, Kelm M, **Gladwin MT**. Circulating Blood Endothelial Nitric Oxide Synthase Contributes to the Regulation of Systemic Blood Pressure and Nitrite Homeostasis. Arterioscler Thromb Vasc Biol. 2013 Aug;33(8):1861-1871. PMCID in process.

D. NIH Research Support (support from ITxM, HCWP, UPMC, pharmaceutical, and DOD, not listed)

Ongoing Research Support

1T32HL110849-01A1 NIH Gladwin (PI) 04/01/2012-04/01/2018
Translational Pulmonary Vascular Biology

2T32HL007563-26 NIH Gladwin (PI) 07/01/2013-04/01/2019
Translational Training Program in Pulmonary Biology and

PO1HL103455 NIH Gladwin (PI) 04/01/2011-03/31/2016
Vascular Subphenotypes of Lung Disease

2 R01HL098032 NIH Gladwin (PI) 07/31/13 - 07/31/19
Storage Lesion in Banked Blood Due to Disruption of Nitric Oxide Hemostasis

RO1HL096973-01A1 NIH Gladwin (PI) 04/15/10 - 03/15/14
Myoglobin as a nitrite reductase that regulates hypoxic cardiac NO signaling

R37 HL058091-16 NHLBI Gladwin (PI) 05/01/12-04/30/17
Effects of Nitric Oxide in Sickle Cell Blood

R01 HL103927-03 NHLBI Co-I (Shiva PI) 02/01/11-11/30/13
Phase II Clinical Trial to Evaluate the Benefits of Postconditioning in STEMI

R34 HL117344-01 NHLBI Co-I (Morris PI) 09/26/12-06/30/14
Statins for Pulmonary and Cardiac Complications of Chronic HIV

DOD PI (Gladwin) 12/28/10-01/27/14
Small Molecule, Gas Based Therapies to Prevent Organ Injury from Trauma/Hemorrhage

Completed Research Support

Intramural Funding (Gladwin PI of Section and Branch) 2000-2008

RC1DK085852 NIH Gladwin (PI) 09/30/09 - 09/29/11
Dietary Nitrite Activation of PPARgamma Improves Insulin Sensitivity

1 RC2 HL101212-01 NHLBI Steinberg (PI) 09/30/09 - 08/31/11
Genetic Diversity of Sickle Cell Anemia

P30AR058910 NIH Gladwin (PI) 09/30/09 - 09/29/11
Center for Translational Vascular Biology in Autoimmune Diseases

RO1HL095973 Loma Linda University Blood (PI) 08/15/09 - 05/31/13
Role of Nitrate and Hemoglobin in Vascular NO Homeostasis in the Fetus and Adult
Role: Co-investigator