

## BIOGRAPHICAL SKETCH

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NAME Thomas R. Kleyman, M.D.	POSITION TITLE Professor of Medicine		
eRA COMMONS USER NAME kleyman			
EDUCATION/TRAINING <i>(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)</i>			
INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	YEAR(s)	FIELD OF STUDY
Syracuse University, Syracuse, NY	B.S.	1973	Biochemistry
Washington University, St. Louis, MO	M.D.	1978	

### A. Personal Statement

My laboratory has a longstanding interest in epithelial transport physiology, particularly with regard to how structure relates to function. We are examining mechanisms by which external factors, including Na<sup>+</sup>, proteases, and shear stress, regulate the activity of epithelial Na<sup>+</sup> channels. We are examining conformation changes within the channel that modulate channel gating. We are particularly interested in defining the role of specific proteases in activating epithelial Na<sup>+</sup> channels in certain disorders, such as nephrotic syndrome, cystic fibrosis, and disorders associated with a decreased extracellular fluid volume or decreased effective arterial volume. We are examining mechanisms by which palmitoylation regulates epithelial Na<sup>+</sup> channels. We are also examining the regulation of large conductance, Ca<sup>2+</sup> activated K<sup>+</sup> channels by shear stress and by WNK kinases. I serve as the director of a T32 funded training grant (DK061296) entitled Renal and Epithelial Biology Training Program. I also serve as the director of a T35 short term medical student training grant (DK065521).

### B. Positions and Honors

#### Positions and Employment

1978-1981	Resident in Medicine, Presbyterian Hospital, New York
1981-1983	Fellow in Nephrology, Presbyterian Hospital, New York
1983-1984	Instructor in Medicine, Columbia University, New York, N.Y.
1984-1988	Assistant Professor of Medicine, Columbia University, New York, N.Y.
1987-1988	Visiting Assistant Professor, Institute of Biochemistry, University of Lausanne, Lausanne, Switzerland
1988-1997	Assistant Professor of Medicine, University of Pennsylvania, Philadelphia, PA
1991-1997	Assistant Professor of Physiology, University of Pennsylvania, Philadelphia, PA
1997-2000	Associate Professor of Medicine and of Physiology, with tenure University of Pennsylvania, Philadelphia, PA
1997-1999	Vice Chair, Department of Medicine, University of Pennsylvania, Philadelphia, PA
2000-	Chief, Renal-Electrolyte Division, Professor of Medicine and of Cell Biology and Physiology, with tenure, University of Pittsburgh, Pittsburgh, PA
2006-	Professor of Pharmacology, University of Pittsburgh, Pittsburgh, PA
2011-	Sheldon Adler Professor of Medicine, University of Pittsburgh, Pittsburgh, PA

#### Other Experiences and Memberships

1993-1994	Member, Fellowship Review Committee, National Kidney Foundation
1993-1997	Member, Cardiorenal Study Committee, American Heart Association
1993-1999	Member, Editorial Board, American Journal of Physiology: Cell Physiology
1994-1997	Member, Review Committee, American Heart Association, Southeastern Penn. Affiliate

1994-	Ad hoc reviewer, NIH
1995-2001	Member, Editorial Board, American Journal of Physiology: Renal Physiology
1998-2002	Co-Chair/Chair, Review Committee, Am. Heart Assoc., Mid-Atlantic Research Consortium
2001-2007	Associate Editor, American Journal of Physiology: Renal Physiology
2001-06;08-13	Member, Editorial Board, Journal of Biological Chemistry
2002-2012	Member, Editorial Board, Journal of Clinical Investigation
2002-2004	Chair, Res. Committee, Am. Heart Assoc., Pennsylvania-Delaware Affiliate
2003-2007	Member, Research Committee, Am. Heart Association, National Center
2004-2008	Member, Cellular and Molecular Biology of the Kidney Study Section, NIH
2007-2013	Editor-in-Chief, American Journal of Physiology: Renal Physiology
2012-	Deputy Editor-in-Chief, Physiological Reports

### **Honors and Awards**

1974	Phi Beta Kappa, Syracuse University, Syracuse, NY
1978	Alpha Omega Alpha, Washington University, St. Louis, MO
1983-1988	American Heart Association, Clinician-Scientist Award
1987-1988	Zyma Foundation Fellowship
1991-1996	American Heart Association, Established Investigatorship Award
1996-	Member, American Society for Clinical Investigation
2004-	Member, Association of American Physicians
2006	MERIT Award, NIH
2008	Ussing Lecture, American Physiological Society
2008	Director's Bridge Award, NIH
2009	Schrier Lecture, American Society of Nephrology
2010	Seldin Lecture, American Heart Association

### **C. Peer-reviewed Publications**

Selected from 125 peer reviewed original publications

1. Bruns, J.B., M.D. Carattino, S. Sheng, A.B. Maarouf, O.A. Weisz, J.M. Pilewski, R.P. Hughey and T.R. Kleyman. Epithelial Na<sup>+</sup> channels are fully activated by furin- and prostaticin-dependent release of an inhibitory peptide from the gamma subunit. *J. Biol. Chem.* 282: 6153-6160, 2007. PMID: 17199078
2. Carattino, M.D., C.J. Passero, C.A. Steren, A.B. Maarouf, J.M. Pilewski, M.M. Myerburg, R.P. Hughey and T.R. Kleyman. Defining an inhibitory domain in the alpha subunit of the epithelial sodium channel. *Am. J. Physiol.* 294: F47-F52, 2008. PMID: 18032549
3. Carattino, M.D., R.P. Hughey and T.R. Kleyman, Proteolytic processing of the epithelial sodium channel gamma subunit has a dominant role in channel activation. *J. Biol. Chem.* 283: 25290-25295, 2008. PMC: 2533072
4. Passero, C.J., G.M. Mueller, H. Rondon-Berrios, R.P. Hughey and T.R. Kleyman. Plasmin activates epithelial Na<sup>+</sup> channels by cleaving the  $\gamma$  subunit. *J. Biol. Chem.* 283: 36586–36591, 2008 PMC: 2605981
5. Mueller G.M., A.B. Maarouf, C.L. Kinlough, N. Sheng, O.B. Kashlan, S. Okumura, S. Luthy, T.R. Kleyman\* and R.P. Hughey. Cys-palmitoylation of the beta subunit modulates gating of the epithelial sodium channel. *J. Biol. Chem.* 285:30453-30462, 2010. \*communicating author. PMC: 2945538
6. Kashlan, O.B., C.R. Boyd, C. Argyropoulos, S. Okumura, R.P. Hughey, M. Grabe and T.R. Kleyman. Allosteric Inhibition of the Epithelial Na<sup>+</sup> Channel through Peptide Binding at Peripheral Finger and Thumb Domains. *J. Biol. Chem.* 285: 35216-35223, 2010. PMC: 2966135
7. Kashlan, O.B., J.L. Adelman, S. Okumura, R.P. Hughey, T.R. Kleyman\* and M. Grabe. Constraint based, homology model of the extracellular domain of the epithelial Na<sup>+</sup> channel  $\alpha$  subunit reveals a mechanism of channel activation by proteases. *J. Biol. Chem.* 286: 649-660, 2011. \*communicating author. PMC: 3013024

8. Shi, S., B.M. Blobner, O.B. Kashlan and T.R. Kleyman. Extracellular Finger Domain Modulates the Response of the Epithelial Sodium Channel to Shear Stress. *J. Biol. Chem.* 287:15439-15444, 2012. PMC: 3346134
9. Kashlan, O.B., B. M. Blobner, Z. Zuzek, M.D. Carattino and T.R. Kleyman. Inhibitory Tract Traps the Epithelial Na<sup>+</sup> Channel in a Low Activity Conformation. *J. Biol. Chem.* 287:20720-6, 2012. PMC: 3370254
10. Shi, S., M.D. Carattino and T.R. Kleyman. Role of the wrist domain in the response of the epithelial sodium channel to external stimuli. *J. Biol. Chem.* 287: 44027-35, 2012. PMC:3531719
11. Chen, J., T.R. Kleyman\* and S. Sheng. Gain-of-function variant of the human epithelial sodium channel. *Am. J. Physiol.* 304:F207-13, 2013. \*communicating author. PMC: 3543625
12. Wang, Z., A.R. Subramanya, L.M. Satlin, N.M. Pastor-Soler, M.D. Carattino, and T.R. Kleyman. Regulation of large conductance Ca<sup>2+</sup>- activated K<sup>+</sup> channels by WNK4 kinase. *Am J. Physiol.* 305:C846-53, 2013 PMC: 3798677
13. Shi, S. and T.R. Kleyman. Gamma subunit second transmembrane domain contributes to epithelial sodium channel gating and amiloride block. *Am J. Physiol.* 305: F1585-F1592, 2013. PMC: 3882368
14. Chen, J., T.R. Kleyman\* and S. Sheng. Deletion of  $\alpha$ -subunit exon eleven of the epithelial Na<sup>+</sup> channel reveals a regulatory module. *Am J. Physiol.* 306:F561-F567, 2014. \*communicating author. PMC: 3949035
15. Mukherjee, A., G.M. Mueller, C.L. Kinlough, N. Sheng, Z. Wang, S.A. Mustafa, O.B. Kashlan, T.R. Kleyman\* and R.P. Hughey. Cys-palmitoylation of the gamma subunit has a dominant role in modulating activity of the epithelial sodium channel. *J. Biol. Chem.* In press. \*communicating author. PMC: In Process

**D. Research Support**  
**Ongoing Research Support**

R37 DK051391

09/05/11 - 08/31/16

NIH/NIDDK

Biomechanical Regulation of Renal Ion Transporters

The major goals of this project are (1) to define mechanisms by which variations in tubular fluid flow rate regulate ENaC-mediated Na transport in the cortical collecting duct (CCD) and (2) to define mechanisms by which variations in tubular fluid flow rate regulate intercalated cell-mediated acid-base transport in the CCD.

Role: PI

R01 DK065161

07/01/09 - 06/30/14

NIH/NIDDK

Sodium Channel Biogenesis

The major goals of this project are (1) to define quality control mechanisms within the ER that target ENaC for degradation, and (2) to define the mechanisms by which channels are activated by proteases, and (3) to define the role of palmitoylation in the processing of ENaC subunits and regulation of channel activity.

Role: PI (multiple PI)

R01 DK038470

07/15/10 – 06/30/14

NIH/NIDDK

Maturation of K Transport in the Distal Nephron

The major goals of this project are to: (1) to characterize the role of NKCC1 in flow-induced K<sup>+</sup> secretion in the distal nephron, and (2) to characterize the unique cell-specific BK $\alpha$  variants and  $\beta$  isoforms in PC and IC responsible for differential regulation by mechano-activated signaling pathways.

Role: Co-I

R01 DK098201

02/10/14 – 01/31/19

NIH/NIDDK

Allosteric ENaC Regulation

The major goals of this project are (1) to determine the mechanism of ENaC inhibition by extracellular Na<sup>+</sup> and (2) to build and refine structural models of ENaC subunits.

Role: Co-I

P30 DK079307

09/16/13 - 07/31/18

NIH/NIDDK

Pittsburgh Center for Kidney Research

The objective of the Center is to both reinforce and expand interactions among investigators at the University of Pittsburgh and colleagues at Mount Sinai School of Medicine, to develop new directions of investigation using electrophysiological, cell biological, molecular, and genetic tools, and to attract new investigators to renal-related research. The Center will be focused on four main cores, which will support the work of investigators at the University of Pittsburgh and Mount Sinai School of Medicine. Core A is a cellular physiology core. Core B is a single nephron and organ physiology core. Core C is a urinary tract epithelial imaging core. Core D will focus on the use of model organisms to elucidate novel aspects of kidney function. The Center will support three pilot and feasibility projects.

Role: PI