

**David Kennedy, Ph.D.**  
**Assistant Professor**  
**Medical University of Ohio, Ph.D., 2006**

The overall aim of my research is to develop a mechanistic understanding of the pathogenesis of accelerated cardiac and renal dysfunction during cardio-renal syndrome. Thus, we seek to identify novel mechanisms of cardiac and renal injury in order to aid and improve diagnostic, therapeutic, and preventive strategies in this high-risk population of patients. One of the primary scientific objectives of my laboratory is to understand the pathophysiology whereby endogenous counter-regulatory mechanisms become maladaptive and contribute to disease progression in patients with cardio-renal syndrome.

***\*\*\*See full length description below\*\*\****

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**Education**

B.S., Biology, John Carroll University, 1995  
M.S., Biological Sciences, Medical College of Ohio, 2001  
Ph.D., Biomedical Sciences, Medical University of Ohio, 2006

**Postgraduate Training**

- University of Toledo Health Science Center, Department of Medicine, Toledo, Ohio (Director: Professor Joseph I. Shapiro, Mercy Health Partners Endowed Chair of Medicine), 2006-2007
- David and Lindsay Morgenthaler Endowed Fellowship, Lerner Research Institute Cleveland Clinic Foundation, Department of Cell Biology, Cleveland, Ohio (Director: Professor Roy L. Silverstein, Vice Chair (Translational Research), Jan Bleeksma Endowed Chair in Vascular Biology Cleveland Clinic Lerner College of Medicine of Case Western Reserve University), 2007-2011

**Academic Appointments**

- Research Associate, Department of Cellular & Molecular Medicine, Lerner Research Institute, Cleveland Clinic, 2011-2013
- Secondary Appointment to Department of Nephrology and Hypertension, Glickman Urological & Kidney Institute, Cleveland Clinic, 2011-2015
- Project Scientist, Department of Cellular & Molecular Medicine, Lerner Research Institute, Cleveland Clinic, 2014-2015
- Assistant Professor of Medicine, Division of Cardiovascular Medicine, Department of Medicine, University of Toledo College of Medicine and Life Sciences, 2015-present

**Awards and Commendations**

- Liberato J.A. DiDio Award for Excellence in Graduate Research, 2001, 2003, 2004
- American Heart Association, Predoctoral Fellowship, 2003-2005
- Dr. Roberto Franco-Saenz Memorial Scholarship in Internal Medicine, 2004
- Cleveland Clinic Foundation/Lerner Research Institute, David and Lindsay Morgenthaler Endowed Fellowship, 2007-2010
- American Association for the Advancement of Science/Science Program for Excellence in Science, 2007
- American Heart Association, Postdoctoral Fellowship, 2008-2010
- American Society for Biochemistry and Molecular Biology Travel Award, 2009
- Manuscript of the Quarter, Department of Cell Biology, Lerner Research Institute,

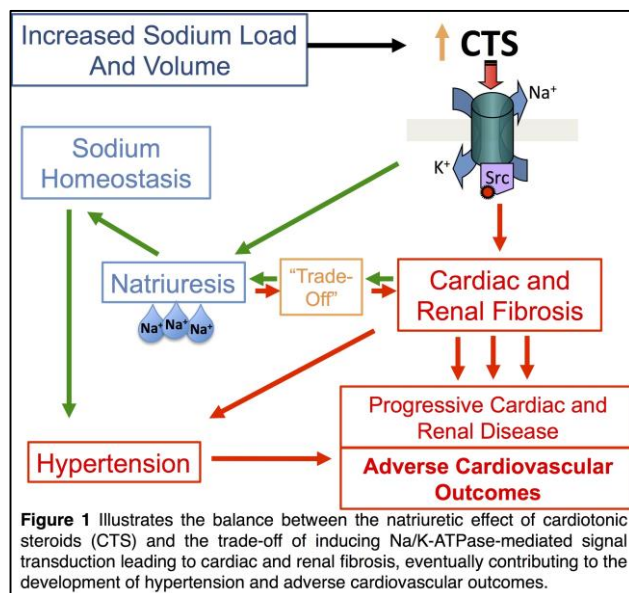
2009

- The William E. Lower Award for Basic Science Research, 2010
- The Chairman's Award for Art & Science, 2010
- The Department of Cell Biology Elsa Albrecht Fellow Award, 2010
- Fifth International Conference on Paraoxonases Young Scientist Travel Award, 2012
- American Society of Nephrology Advances in Research Travel Award, 2013

### Research Interest:

The devastating diseases of heart failure and renal failure are linked by maladaptation of the body's ability to handle sodium (salt) and volume (water) loads. Central to this process is an elegant regulatory system composed of effector steroid hormones – known as cardiotoxic steroids (CTS) – and their receptor complex, the sodium-potassium adenosine triphosphatase (Na/K ATPase). CTS are ligands of the Na/K-ATPase and production of these hormones are a compensatory mechanism for natriuresis (excretion of sodium in the urine via action on the Na/K-ATPase in the kidney and vascular tone in volume-expanded states such as salt-sensitive hypertension and chronic kidney disease, as well as edematous states like heart failure and pre-eclampsia.

However, CTS also exert “off-target” signal transduction effects beyond their direct effects on the Na/K-ATPase. Hence, chronic stimulation of Na/K-ATPase signaling by CTS has important implications for not only for the natriuretic response to increased salt and water load but also in a “trade-off” pathological adaptation to volume expansion including hypertension, hypertrophy, and fibrosis. One of our laboratory's major contributions to this field is the clinical and experimental evidence demonstrating the pro-inflammatory and pro-fibrotic pathways initiated by these steroid hormones in both cardiac and renal tissue which make them attractive therapeutic targets for intervention in cardiac and renal disease (Figure 1).



Patients with heart failure and chronic kidney disease often experience progressive cardiac and renal compromise (referred to as “cardio-renal syndrome”) leading to recurrent hospitalizations and clinical deterioration which contemporary therapies of neurohormonal blockade fail to adequately address. As the synthesis and regulation of CTS in volume-expanded states such as heart failure and chronic kidney disease is unknown, developing a fundamental, integrated, and mechanistic understanding of the CTS-Na/K ATPase effector/receptor complex is of critical importance. Thus, the vision and approach of our laboratory's ongoing and planned research program is to address this critical unmet need as it relates to the synthesis, regulation, translational significance, and therapeutic targets of the CTS-Na/K ATPase axis using a variety of innovative molecular, biochemical, and bioinformatic approaches including systems genetics, targeted genetic and immunologic manipulation of in vitro and in vivo model

systems, high performance liquid chromatography and mass spectrometry, as well as advanced, high-content cellular, molecular and physiologic phenotyping.

## Publications

<http://www.ncbi.nlm.nih.gov/myncbi/browse/collection/47546090/?sort=date&direction=descending>

Drummond CA, Hill MC, Shi H, Fan X, Xie JX, Haller ST, **Kennedy DJ**, Liu J, Garrett MR, Xie Z, Cooper CJ, Shapiro JI, Tian J. Na/K-ATPase Signaling Regulates Collagen Synthesis Through microRNA-29b-3p in Cardiac Fibroblasts. *Physiol Genomics*. 2016; *In Press*.

**Kennedy DJ**, Shrestha K, Sheehey B, Li XS, Guggilam A, et al. Elevated Plasma Marinobufagenin, An Endogenous Cardiotoxic Steroid, Is Associated With Right Ventricular Dysfunction and Nitrate Stress in Heart Failure. *Circ Heart Fail*. 2015 Nov;8(6):1068-76.

Chen Y, **Kennedy DJ**, Ramakrishnan DP, Yang M, Huang W, et al. Oxidized LDL-bound CD36 recruits an Na<sup>+</sup>/K<sup>+</sup>-ATPase-Lyn complex in macrophages that promotes atherosclerosis. *Sci Signal*. 2015 Sep 8;8(393):ra91.

Tang WH, Wang Z, **Kennedy DJ**, Wu Y, Buffa JA, et al. Gut microbiota-dependent trimethylamine N-oxide (TMAO) pathway contributes to both development of renal insufficiency and mortality risk in chronic kidney disease. *Circ Res*. 2015 Jan 30;116(3):448-55.

Brown PM, **Kennedy DJ**, Morton RE, Febbraio M. CD36/SR-B2-TLR2 Dependent Pathways Enhance Porphyromonas gingivalis Mediated Atherosclerosis in the Ldlr KO Mouse Model. *PLoS One*. 2015;10(5):e0125126.

**Kennedy DJ**, Fan Y, Wu Y, Pepoy M, Hazen SL, et al. Plasma ceruloplasmin, a regulator of nitric oxide activity, and incident cardiovascular risk in patients with CKD. *Clin J Am Soc Nephrol*. 2014 Mar;9(3):462-7

Fedorova LV, Tamirisa A, **Kennedy DJ**, Haller ST, Budnyy G, et al. Mitochondrial impairment in the five-sixth nephrectomy model of chronic renal failure: proteomic approach. *BMC Nephrol*. 2013 Oct 4;14:209.

Shao Z, Shrestha K, Borowski AG, **Kennedy DJ**, Epelman S, et al. Increasing serum soluble angiotensin-converting enzyme 2 activity after intensive medical therapy is associated with better prognosis in acute decompensated heart failure. *J Card Fail*. 2013 Sep;19(9):605-10.

**Kennedy DJ**, Tang WH, Fan Y, Wu Y, Mann S, et al. Diminished antioxidant activity of high-density lipoprotein-associated proteins in chronic kidney disease. *J Am Heart Assoc*. 2013 Apr 4;2(2):e000104

**Kennedy DJ**, Chen Y, Huang W, Viterna J, Liu J, et al. CD36 and Na/K-ATPase- $\alpha$ 1 form a proinflammatory signaling loop in kidney. *Hypertension*. 2013 Jan;61(1):216-24.

Baines RJ, Chana RS, Hall M, Febbraio M, **Kennedy D**, et al. CD36 mediates proximal tubular binding and uptake of albumin and is upregulated in proteinuric nephropathies. *Am J Physiol Renal Physiol*. 2012 Oct;303(7):F1006-14

Haller ST, **Kennedy DJ**, Shidyak A, Budny GV, Malhotra D, et al. Monoclonal antibody against marinobufagenin reverses cardiac fibrosis in rats with chronic renal failure. *Am J Hypertens*. 2012 Jun;25(6):690-6.

Liu J, **Kennedy DJ**, Yan Y, Shapiro JI. Reactive Oxygen Species Modulation of Na/K-ATPase Regulates Fibrosis and Renal Proximal Tubular Sodium Handling. *Int J Nephrol*. 2012;2012:381320.

Haller S, Adlakha S, Reed G, Brewster P, **Kennedy D**, et al. Platelet activation in patients with atherosclerotic renal artery stenosis undergoing stent revascularization. *Clin J Am Soc Nephrol*. 2011 Sep;6(9):2185-91.

Kolmakova EV, Haller ST, **Kennedy DJ**, Isachkina AN, Budny GV, et al. Endogenous cardiotonic steroids in chronic renal failure. *Nephrol Dial Transplant*. 2011 Sep;26(9):2912-9.

**Kennedy DJ**, Kashyap SR. Pathogenic role of scavenger receptor CD36 in the metabolic syndrome and diabetes. *Metab Syndr Relat Disord*. 2011 Aug;9(4):239-45.

Nicholls HT, Kowalski G, **Kennedy DJ**, Risis S, Zaffino LA, et al. Hematopoietic cell-restricted deletion of CD36 reduces high-fat diet-induced macrophage infiltration and improves insulin signaling in adipose tissue. *Diabetes*. 2011 Apr;60(4):1100-10.

**Kennedy DJ**, Kuchibhotla S, Westfall KM, Silverstein RL, Morton RE, et al. A CD36-dependent pathway enhances macrophage and adipose tissue inflammation and impairs insulin signalling. *Cardiovasc Res*. 2011 Feb 15;89(3):604-13.

**Kennedy DJ**, Kuchibhotla SD, Guy E, Park YM, Nimako G, et al. Dietary cholesterol plays a role in CD36-mediated atherogenesis in LDLR-knockout mice. *Arterioscler Thromb Vasc Biol*. 2009 Oct;29(10):1481-7.

Fedorova LV, Raju V, El-Okdi N, Shidyak A, **Kennedy DJ**, et al. The cardiotonic steroid hormone marinobufagenin induces renal fibrosis: implication of epithelial-to-mesenchymal transition. *Am J Physiol Renal Physiol*. 2009 Apr;296(4):F922-34.

Cooper CJ, Haller ST, Colyer W, Steffes M, Burket MW, Thomas WJ, Safian R, Reddy B, Brewster P, Ankenbrandt MA, Virmani R, Dippel E, Rocha-Singh K, Murphy TP, **Kennedy DJ**, Shapiro JI, D'Agostino RD, Pencina MJ, Khuder S. Embolic protection and platelet inhibition during renal artery stenting. *Circulation*. 2008 May 27;117(21):2752-60.

Kuchibhotla S, Vanegas D, **Kennedy DJ**, Guy E, Nimako G, et al. Absence of CD36 protects against atherosclerosis in ApoE knock-out mice with no additional protection provided by absence of scavenger receptor A I/II. *Cardiovasc Res*. 2008 Apr 1;78(1):185-96.

**Kennedy DJ**, Elkareh J, Shidyak A, Shapiro AP, Smaili S, et al. Partial nephrectomy as a model for uremic cardiomyopathy in the mouse. *Am J Physiol Renal Physiol*. 2008 Feb;294(2):F450-4.

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**Kennedy DJ**, Malhotra D, Shapiro JI. Molecular insights into uremic cardiomyopathy: cardiotonic steroids and Na/K ATPase signaling. *Cell Mol Biol (Noisy-le-grand)*. 2006 Dec 30;52(8):3-14.

Shapiro JI, **Kennedy DJ**, Malhotra D, Xie M, Vetteth S. Hypokalemia potentiates ouabain's effect on calcium cycling and cardiac growth. *Cell Mol Biol (Noisy-le-grand)*. 2006 Dec 30;52(8):87-91.

**Kennedy DJ**, Vetteth S, Xie M, Periyasamy SM, Xie Z, et al. Ouabain decreases sarco(endo)plasmic reticulum calcium ATPase activity in rat hearts by a process involving protein oxidation. *Am J Physiol Heart Circ Physiol*. 2006 Dec;291(6):H3003-11.

**Kennedy DJ**, Burket MW, Khuder SA, Shapiro JI, Topp RV, et al. Quality of life improves after renal artery stenting. *Biol Res Nurs*. 2006 Oct;8(2):129-37.

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Burket MW, Cooper CJ, **Kennedy DJ**, Brewster PS, Ansel GM, et al. Renal artery angioplasty and stent placement: predictors of a favorable outcome. *Am Heart J*. 2000 Jan;139(1 Pt 1):64-71.