BIOGRAPHICAL SKETCH

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NAME: McDonough Alicia Ann

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

POSITION TITLE: Professor, Integrative Anatomical Sciences

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 California, Berkeley, CA	AB	06/1972	Physiology
University of Hawaii, Honolulu, Hawaii	PhD	05/1977	Physiology
University of California , San Francisco,	Postdoctoral Fellow	07/1978	Molecular Physiol, CVRI
Columbia University, New York, New York	Postdoctoral Fellow	07/1980	Molecular Biology

Renal sodium transport is a key determinant of extracellular fluid volume and blood pressure, and renal potassium transport regulation is key to regulation of membrane potential. To address homeostatic mechanisms, my laboratory developed strategies to determine molecular mechanisms responsible for renal sodium and potassium transport regulation in *in vivo* whole animal models. We determined cellular mechanisms responsible for the pressure natriuresis response, for AngII and renal injury driven antinatriuresis, the natriuresis and diuresis that accompanies high salt diet, PTH, and ACE inhibitors, determined that AngII driven sodium transporter regulation alters potassium balance, and how altered extracellular potassium can signal sodium transporter regulation. Renal sodium transport can be regulated by changing the number of transporters in the plasma membrane or changing the activity/transporter by covalent modification. Our work provided the first *in vivo* evidence for acute regulation of sodium transporter (NHE3 and NCC) trafficking and regulation by transporter associated proteins including myosin motors, DPPIV. We accomplished our objectives by focusing on rodent models in which we can measure physiologically relevant variables (BP, GFR, clearance of lithium, and urine output). We accumulated extensive experience in both rats (normotensive and spontaneously hypertensive) and strains of genetically modified mice that have a blunted response to AngII hypertension. We interface multiple strategies including fractionation, microscopy and immuno-EM. We have recently reported sexual dimorphisms along the rat and mouse nephrons and their physiologic consequences. The APS EH Starling Lectureship (2009) reviewed what we know about how the proximal tubule simultaneously integrates anti-natriuretic (AngII, RSNA) and natriuretic (hypertension, high salt diet, ACEI) stimuli (PMID: 20106993). The Donald Seldin Lectureship from the AHA Council on Kidney and Cardiovascular Disease (2014) presented how the entire nephron can mount integrated responses to maintain effective circulating volume homeostasis driven by the error signal of hypertension (PMID:26101347). The 2017 Robert W. Schrier Endowed Lectureship from Am. Soc. Nephrology presented how inflammation drives hypertension, and the advantages of the female nephron. **The McDonough lab devotes significant effort to collaborations and consultation projects. Examples of groundbreaking *collaborations:***

1. Gonzalez-Villalobos RA, Janjoulia T, Fletcher NK, Giani JF, Nguyen MT, Riquier-Brison AD, Seth DM, Fuchs S, Eladari D, Picard N, Bachmann S, Delpire E, Peti-Peterdi J, Navar LG, Bernstein KE, **McDonough AA**. The absence of intrarenal ACE protects against hypertension. J Clin Invest. 2013 May;123(5):2011-23. PMID: 23619363.
2. Pei L, Solis G, Nguyen MT, Kamat N, Magenheimer L, Zhuo M, Li J, Curry J, **McDonough AA**, Fields TA, Welch WJ, Yu AS. Paracellular epithelial sodium transport maximizes energy efficiency in the kidney. J Clin Invest. 2016 Jul 1;126(7):2509-18. PMID: 27214555.
3. Zhang, J., Patel, M., Karlovich, N., Wu, M., Griffiths, R., Sparks, M., **McDonough, A.A.** and Crowley, S.

Interleukin-1 augments salt retention in angiotensin II-induced hypertension via nitric oxide-dependent regulation of the NKCC2 sodium co-transporter. Cell Metab. 2016 Feb 9;23(2):360-8. PMID: 26712462

4. Chu PL, Gigliotti JC, Cechova S, Bodonyi-Kovacs G, Chan F, Ralph DL, Howell N, Kalantari K, Klibanov AL, Carey RM, **McDonough AA,** Le TH. Renal Collectrin Protects against Salt-Sensitive Hypertension and Is Downregulated by Angiotensin II. J Am Soc Nephrol. 2017 Jun;28(6):1826-1837. PMID: 28062568.

B. Positions and Honors

1. Positions and Employment

1977 - 1978	NIH-NRSA Postdoctoral fellow, CVRI, UCSF, San Francisco, CA
1978 - 1981	NIH-NRSA Postdoctoral Fellow, Biochemistry, Columbia University, New York, NY
1981 - 2008	Assistant Prof. → Professor of Physiology, Keck School of Medicine, USC, Los Angeles, CA
2008 -	Professor of Integrative Anatomical Sciences, Keck School of Medicine (department name changed from Cell Biology to Integrative Anatomical Sciences in 2017)

2. Other Experience and Professional Memberships

1988 - present	Editorial Board, American Journal of Physiology: Cell Physiology, Associate Editor 2008-2014
2013 -	Editorial Board, Physiological Reports
2017 - 2018	Editorial Board, FASEB Journal , 2018- FASEB publications committee
1997 –01, 2018-	Editorial Board, Journal of the American Society of Nephrology
1995 - 1998	Editorial Board, Hypertension
2008 - 2014	Study Section Regular Member, American Society of Nephrology
2010 - present	Review Panel Member, Swiss National Science Foundation NCCR in Kidney.CH
2013 – 2017	Study Section Regular Member, American Heart Association - Cell Transport
94-99,06-08,18-	Study Section Regular Member, NIH: GMB, CMBK, KMBD (current)
2014 - 2016	Publication Committee, American Physiological Society
2012 - 2016	Basic Research Advisory Group, American Society of Nephrology
2015 - 2017	AHA Kidney in Cardiovascular Disease Membership and Communications Chair

3. Honors

1984	Established Investigator Award, American Heart Association
2007, ’12, ‘18	Faculty Teaching Awards - Year II , Keck School of Medicine of USC; Master Teacher
2009	Ernest H. Starling Distinguished Lectureship, American Physiological Society
2010	Suk Ki Hong Memorial Lecturer, SUNY Buffalo, NY
2014	Donald Seldin Lecture, AHA. Council on Kidney in Cardiovascular Disease
2015	Clarenberg Distinguished Lecture, Kansas State University College of Veterinary Medicine
2016	J.J. Smith Endowed Lecture, Medical College of Wisconsin
2017	Robert W. Schrier Endowed Lectureship – Am. Soc. Nephrology Kidney Week
2018	Steve Hebert Lectureship, American Physiological Society Epithelial Transport Group
2018	Phi Kappa Phi, USC Chapter, Faculty Recognition Award
2019	Hopfer Lecture, Case Western Reserve University School of Medicine’s

C. Contribution to Science

1. Regulation of proximal tubule sodium transporters by blood pressure, AngII, RSNA and dietary salt and sex. 20 years ago we initiated studies to determine the renal molecular mechanisms responsible for integrated regulation of effective circulating volume (ECV). We provided the *in vivo* evidence for transporter trafficking in the kidney and discovered that natriuretic stimuli (elevated perfusion pressure, high-salt diet, inhibition of AngII production or PTH) provoke dynamic redistribution of proximal tubule (PT) Na^+/H^+ exchanger isoform 3 (NHE3) and Na^+-phosphate cotransporter (NaPi2) along with their regulators, and molecular motors to the base of the microvilli. These findings establish that acute ECV and BP homeostasis are facilitated by redistribution of transporter complexes up and down the PT microvilli. Recently, we defined sexual dimorphic phenotypes along the nephron which suggest that lower proximal reabsorption in female rats expedites

excretion of a saline load and enhances distal sodium reabsorption (via NCC and ENaC activation), which facilitate K^+ secretion and sets plasma K^+ at a lower level, explaining, in part, the "female advantage" in CVD.

- **a.** Yang LE, Maunsbach AB, Leong PK, McDonough AA. Differential traffic of proximal tubule Na+ transporters during hypertension or PTH: NHE3 to base of microvilli vs. NaPi2 to endosomes. Am J Physiol Renal Physiol. 2004 Nov;287(5):F896-906. PMID: 15265767.
- **b.** Yang LE, Leong PK, McDonough AA. Reducing blood pressure in SHR with enalapril provokes redistribution of NHE3, NaPi2, and NCC and decreases NaPi2 and ACE abundance. Am J Physiol Renal Physiol. 2007;293(4):F1197-208. PMID: 17652375.
- **c.** Brasen JC, Burford JL, McDonough AA, Holstein-Rathlou NH, Peti-Peterdi J. Local pH domains regulate NHE3-mediated Na^+ reabsorption in the renal proximal tubule. Am J Physiol Renal Physiol. 2014 Dec 1;307(11):F1249-62. PMID: 25298526.
- **d.** Veiras LC, Girardi AC, Curry J, Pei L, Ralph DL, Tran A, Castelo-Branco, RC, Pastor-Soler N, Arranz CT, Yu ASL, and McDonough AA. Sexual Dimorphic Pattern of Renal Transporters and Electrolyte Homeostasis. J Am Soc Nephrol 28: 3504–3517, 2017. PMID: https://www.ncbi.nlm.nih.gov/pubmed/28774999

2. Regulation of distal tubule sodium transporters by blood pressure, AngII, and dietary salts. Evidence suggests that DCT Na-Cl cotransporter (NCC) activity significantly influences the BP set point. In collaboration with Maunsbach (Aarhus, DK), we reported the first *in vivo* evidence for regulation of DCT NCC trafficking between sub-apical vesicles (SCV) and apical plasma membranes (APM) in response to AngII (awarded AJP Renal "Paper of the Year") and from APM to SCV in response to high salt diet, ACEi or hypertension. Subsequently, we determined that phosphorylated NCC is restricted to the APM and is organized in multimeric proteins that include γadducin. Recently, we determined that NCC regulation during AngII hypertension is secondary to altered K^+ status, explaining, in part, the beneficial effects of raising diet K^+.

- **a.** Sandberg MB, Maunsbach AB, McDonough AA. Redistribution of distal tubule Na+-Cl- cotransporter (NCC) in response to a high-salt diet. Am J Physiol Renal Physiol. 2006 Aug;291(2):F503-8. PMID: 16554416.
- **b.** Sandberg MB, Riquier AD, Pihakaski-Maunsbach K, McDonough AA, Maunsbach AB. ANG II provokes acute trafficking of distal tubule Na+-Cl(-) cotransporter to apical membrane. Am J Physiol Renal Physiol. 2007 Sep;293(3):F662-9. PMID: 17507603.
- **c.** Veiras, LC, Han J, Ralph DL, McDonough AA. Potassium Supplementation Prevents Sodium Chloride Cotransporter Stimulation during Angiotensin II. Hypertension. .2016 Oct;68(4):904-912. PMID: 27600183

3. Integrated regulation of salt transporters along the nephron during hypertension. During chronic AngII infusion -dependent hypertension, AngII stimulates, while hypertension inhibits, Na^+ transporter activity in order to balance Na^+ output to input. We discovered that AngII infusion activates Na^+ transporters and channels from the cTAL to the CD and inhibits PT and medullary TAL transporters, secondary to elevated BP, in order to maintain Na^+ and volume homeostasis (at the expense of elevated blood pressure). In collaborative studies, we addressed the molecular mechanisms responsible for blunted AngII dependent hypertension in mouse models with: negligible intrarenal ACE activity, knockouts of AT1R, IFN-gamma or IL-17. Our findings, presented as the Donald Seldin Lecture at the AHA Council on Hypertension, demonstrate that factors that stimulate PT and TAL transporters (AngII and cytokines), "put the brakes" on the pressure natriuresis responses that depress transporters and drive higher blood pressures necessary to match Na output to input.

- a. Gonzalez-Villalobos RA, Janjoulia T, Fletcher NK, Giani JF, Nguyen MT, Riquier-Brison AD, Seth DM, Fuchs S, Eladari D, Picard N, Bachmann S, Delpire E, Peti-Peterdi J, Navar LG, Bernstein KE, McDonough AA. The absence of intrarenal ACE protects against hypertension. J Clin Invest. 2013 May;123(5):2011-23. PMID: 23619363.
- b. Nguyen MT, Lee DH, Delpire E, McDonough AA. Differential regulation of Na+ transporters along nephron during ANG II-dependent hypertension: distal stimulation counteracted by proximal inhibition. Am J Physiol Renal Physiol. 2013 Aug 15;305(4):F510-9. PMID: 23720346.
- c. Kamat NV, Thabet SR, Xiao L, Saleh MA, Kirabo A, **Madhur MS**, Delpire E, Harrison DG, **McDonough AA.** Renal transporter activation during angiotensin-II hypertension is blunted in interferon-γ-/- and interleukin-17A-/- mice. Hypertension. 2015 Mar;65(3):569-76. PMID: 25601932.

4. Integrative control of potassium homeostasis. We defined sodium pump isoform expression in muscle types and provided evidence that the alpha 2 isoform regulates K^+ uptake and clearance from the ECF into the

body's main buffer pool: muscle ICF. We innovated a novel "K clamp" that allows us to define how high fat diet, AMPK and dexamethasone affect cellular K uptake; e.g., we defined insulin resistance to K^+ uptake during K^+ deficient diets. We determined that signaling is mediated both through the gut and directly via changes in plasma [K^+]. These lines of investigation support the consideration of dietary K^+ in fighting CVD.

a. Thompson CB, McDonough AA. Skeletal muscle Na,K-ATPase alpha and beta subunit protein levels respond to hypokalemic challenge with isoform and muscle type specificity. J Biol Chem. 1996 Dec 20;271(51):32653-8. PMID: 8955095.
b. Chen P, Guzman JP, Leong PK, Yang LE, Perianayagam A, Babilonia E, Ho JS, Youn JH, Wang WH, McDonough AA. Modest dietary K^+ restriction provokes insulin resistance of cellular K^+ uptake and phosphorylation of renal outer medulla K^+ channel without fall in plasma K^+ concentration. Am J Physiol Cell Physiol. 2006 May;290(5):C1355-63. PMID: 16354756.
c. Rengarajan S, Lee DH, Oh YT, Delpire E, Youn JH, McDonough AA. Increasing plasma [K^+] by intravenous potassium infusion reduces NCC phosphorylation and drives kaliuresis and natriuresis. Am J Physiol Renal Physiol. 2014 May 1;306(9):F1059-68. PMID: 24598799.

5. Cardiac sodium pump isoform regulation and relevance to heart failure.
The heart becomes more sensitive to cardiac glycosides (CG) with age, thyroid hormone treatment and altered K status, and as it fails. We provided molecular mechanisms by determining the sodium pump (NKA) and Na-Ca exchanger (NCE) expression patterns in regions of the heart. In rodent models, we determined that low thyroid hormone, hypokalemia and amiodarone all reduce the sodium pump alpha 2 abundance which renders the heart more sensitive to CG. In human hearts, we determined region specific expression patterns of NKA and NCE at baseline. Our high impact findings revealed that heart failure itself leads to depressed abundance of NKA which, like CG treatment, increases contractility.

a. Azuma KK, Hensley CB, Putnam DS, McDonough AA. Hypokalemia decreases Na(+)-K(+)-ATPase alpha 2- but not alpha 1-isoform abundance in heart, muscle, and brain. Am J Physiol. 1991 May;260(5 Pt 1):C958-64. PMID: 1852110.
b. Wang J, Schwinger RH, Frank K, Müller-Ehmsen J, Martin-Vasallo P, Pressley TA, Xiang A, Erdmann E, McDonough AA. Regional expression of sodium pump subunits isoforms and Na+-Ca++ exchanger in the human heart. J Clin Invest. 1996 Oct 1;98(7):1650-8. PMID: 8833915.
c. Schwinger RH, Wang J, Frank K, Müller-Ehmsen J, Brixius K, McDonough AA, Erdmann E. Reduced sodium pump alpha1, alpha3, and beta1-isoform protein levels and Na+,K+-ATPase activity but unchanged Na+-Ca2+ exchanger protein levels in human heart failure. Circulation. 1999 Apr 27;99(16):2105-12. PMID: 10217649.

Complete List of Published Work in My Bibliography:
in Pub Med: http://www.ncbi.nlm.nih.gov/pubmed/?term=McDonough+AA+not+WNS

D. Research Support

4. Ongoing Research Support

NIH NIDDK 5U24DK115255-02 subaward 3230722
PI: AA McDonough
Title: ***Impact of diabetes on renal transporters in females and males***
Agency: National Institute of Diabetes, Digestive and Kidney Diseases
Project period – 01/01/2019 – 12/31/2020
Total Costs: $100,000 direct: $62,500.

NIH NHLBI 2R01DK083785-06.
PI: AA McDonough
Title: ***Sodium transporter regulation during hypertension***
Agency: National Institute of Diabetes, Digestive and Kidney Diseases
Project period – 04/01/2016 – 03/31/2020

NIH NHLBI 1 R01 DK098382-01A1
PI: SB Gurley 0.6 Calendar
Title: ***Actions of Angiotensin II along the Nephron to Regulate Blood Pressure***
Sub-contract with Duke University

Project Period - 4/01/2013 – 3/31/2019

Recently Completed Research Support

AHA 15GRNT23160003

PI: AA McDonough

Title: ***Inflammation, sodium transporter activation and hypertension***

Agency: American Heart Association Western States Affiliate 01/01/2015 – 12/31/2017

USC Dean's Pilot Project

PIs: McDonough and Pastor Soler

Title*:* ***Addressing the consequences of uninephrectomy after kidney donation***

Agency: Keck School of Medicine Project Period: 01/01/2017 to 12/31/2018