BIOGRAPHICAL SKETCH

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NAME	POSITION TITLE
Brian D. Cain	Professor
eRA COMMONS USER NAME (credential, e.g., agency login) bdcain	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
University of Colorado Boulder, CO	BA	05/77	Mol. Cell. Devel. Biology
University of Illinois Champaign-Urbana, IL	PhD	08/83	Cell Biology
Stanford University Stanford, CA	Postdoctoral Fellow	08/88	Biol. Sciences

A. Personal Statement

My laboratory has been actively engaged in research on ion transport in the renal distal collecting duct for over 20 years. This research has been conducted in direct collaboration with Dr. Charles Wingo (Dept. of Medicine, UF) and later Dr. Michelle Gumz (Dept. of Medicine, UF). The earliest work resulted in the molecular identification of the H^+,K^+-ATPase subunits expressed in the rabbit kidney. The HKα1, HKβ, HKα2, and the HKα2c that is apparently unique to the rabbit were found. The rabbit HKα2 gene was cloned and the promoter characterized in detail. The source of the HKα2c subunit turned out to be alternative transcription start site resulting in an altered structure for the first exon.

The direction of the research changed dramatically with an experiment designed to identify aldosterone-responsive genes in the kidney. Surprisingly, the *EDN1* gene encoding endothelin-1 was among the most highly induced aldosterone genes. We have shown that aldosterone treatment of cells results in direct binding of both the mineralocorticoid receptor and the glucocorticoid receptor to the 5' regulatory region of the *Edn1* gene in a murine collecting duct cell line (mIMCD-3). Dexamethasone stimulates transcription by activating the glucocorticoid receptor alone. Both receptors bind to the same hormone response element. To extend our understanding of the regulatory mechanisms governing ET-1 expression in collecting duct cells, we determined the miRNA content of mIMCD-3 cells by microarray analysis. The results were validated by real-time PCR and direct binding of the RNA induced silencing complex to *Edn1* mRNA was demonstrated. Clearly, miRNAs regulate expression of endothelin-1 levels. Most recently, we discovered an antisense RNA called *EDN1*-AS transcribed from within the human *EDN1* gene locus. The transcript apparently spans across the entire transcription unit of *EDN1.*

In a completely independent line of research, my laboratory has made major contributions to understanding F_1F_0-ATP synthase. In the past, the research focused on the *Escherichia coli* enzyme. Our particular interest is on the stator subunits in the membrane embedded F_0 sector. Important discoveries include identification of many of the *a* subunit amino acids that participate in H^+ translocation through F_0, modeling of human mitochondrial disease associated mutations in the bacterial enzyme, and characterization of plasticity in the peripheral stalk *b* subunits. In our most recent work, the peripheral stalk studies have been extended to include the *Saccharomyces cerevisiae* F_1F_0 ATP synthase.

B. Positions and Honors

Professional positions:

Assistant Professor. Department of Biochemistry and Molecular Biology, University of Florida.1988 - 1994
Associate Professor, Department of Biochemistry and Molecular Biology, University of Florida. 1994 - 2000
Professor, Department of Biochemistry and Molecular Biology, University of Florida. 2000-present

Other professional experience and memberships:
American Society for the Advancement of Science, Member 1988-present
American Society for Biochemistry and Molecular Biology, Member 1992-present
American Cancer Society (Florida Chapter) Review Subcommittee, Member 1991-2002; Chair 2001-2002
NIH Physical Biochemistry Study Section, Ad Hoc Member 1996, Member 1997-2001; Chair 1999-2001
NIH Physiological Chemistry Study Section, Ad Hoc Member 2002
NIGMS Special Emphasis Panel, Specialized Centers for the Protein Structure Initiative, Member 2005
NIH George W. O'Brien Kidney Research Center Grant Study Section, Member 2002, 2007, 2012
American Heart Association, Molecular Signaling BSc3 Peer Review Committee, 2013
Editorial Advisory Board, *Life Science* Special Issues, Member 2012, 2014
Editorial Board, *The Journal of Biological Chemistry*, Member 2000-2005, 2012-present

Honors and Awards:
NRSA Postdoctoral Fellowship, Stanford University, 1984-1986
University of Florida, College of Medicine Exemplary Teaching Award, 2007-2014
University of Florida, College of Medicine Doctoral Mentoring Award, 2009, 2014
Bioenergetics Gordon Research Conference, Vice-Chair 2009, Chair 2011
13th International Conference on Endothelin, Scientific Advisory Board, 2013
University of Florida Sigma Xi Senior Faculty Research Award, 2014

C. Selected Peer-Reviewed Publications

Five Most relevant publications to the current application

1. Stow, LR, ML Gumz, IJ Lynch, MM Greenlee, **BD Cain**, CS Wingo (2009) Aldosterone modulates steroid receptor binding to the endothelin-1 gene (e*dn1*). *J. Biol. Chem.* 284, 30087-30096. PMID 19638349.
2. Stow, LR, ME Jacobs, CS Wingo, **BD Cain** (2011) Endothelin-1 gene regulation. *FASEB J.* 25, 16-28. PMID 20837776.
3. Stow, LR, GE Voren, ML Gumz, CS Wingo, **BD Cain** (2012) Dexamethasone stimulates endothelin-1 gene expression in renal collecting duct cells. *Steroids* 77, 360-366. PMID 22209709.
4. Welch, AK, ME Jacobs, CS Wingo, **BD Cain** (2013) Early progress in epigenetic regulation of the endothelin pathway genes. *Br. J. Pharmacol.* 168,327-334. PMID 22220553.
5. Jacobs, ME, LA Jeffers, AK Welch, CS Wingo, **BD Cain** (2014) microRNA regulation of endothelin-1 mRNA in renal collecting duct cells. *Life Sci.* [Epub ahead of print]

Additional recent publications of importance to this application

1. Welch, AK, SB Claggett, **BD Cain** (2008) The b_{arg36} contributes to efficient coupling in F_1F_O ATP synthase in *Escherichia coli. J. Biomembr. Bioenerg.* 40,1-8. PMID PMID 18204891.
2. Lynch, IJ, A Rudin, SL Xia, LR Stow, GE Shull, ID Weiner, **BD Cain,** CS Wingo (2008) Impaired acid secretion in cortical collecting duct intercalated cells from H-K-ATPase-deficient mice: role of HKalpha isoforms. *Am. J. Physiol.Renal Physiol.* 294, F621-627. PMID 18057185.
3. Gumz, ML, LR Stow, IJ Lynch, MM Greenlee, A Rudin, **BD Cain**, CS Wingo (2009). The circadian clock protein Period 1 regulates expression of the renal epithelial sodium channel in mice. *J. Clin Invest.* 119**,** 2423-2434. PMID 19587447.
4. Gumz, ML, K. Cheng, IJ Lynch, LR Stow, MM Greenlee, **BD Cain**, CS Wingo (2010) Regulation of ENaC expression by the circadian clock protein Period-1 in mpkCCD(c14) Cells. *Biochim. Biophys. Acta* 1799, 622-629. PMID 20868778.
5. Kim, HY, JW Verlander, JM Bishop, **BD Cain,** KH Han, P Igarashi, HW Lee, ME Handlogten, ID Weiner, (2009) Basolateral expression of the ammonia transporter family member Rh C glycoprotein in the mouse kidney. *Am. J. Physiol. Renal Physiol.* 296, F543-555. PMID 19129254.
6. Claggett, SB, MO Plancher, SD Dunn, **BD Cain** (2009) The *b* Subunits in the peripheral stalk of F_1F_0 ATP synthase preferentially adopt an offset relationship. *J. Biol. Chem.* 284, 16531-16540. PMID 19369253.
7. Greenlee, MM, IJ Lynch, ML Gumz, **BD Cain,** CS Wingo (2010) The renal H,K-ATPases. *Curr. Opin. Nephrol. Hypertens.* 19, 478-482. PMID 20594946.

8. Shao, J, ML Gumz, **BD Cain**, SL Xia, GE Shull, IR van Driel, CS Wingo (2010) Pharmacological profiles of the gastric and colonic H,K-ATPases. *Biochim. Biophys. Acta* 1800, 906-911. PMID 20594946.
9. Gumz, ML, IJ Lynch, MM Greenlee, **BD Cain**, CS Wingo (2010) The renal H^+, K^+ ATPases: physiology, regulation, and structure. *Am. J. Physiol. Renal Physiol.* 298, F12-21. PMID 19640897.
10. Greenlee, MM, IJ Lynch, ML Gumz, **BD Cain**, CS Wingo (2011) Mineralocorticoids stimulate the activity and expression of renal H^+,K^+-ATPases. *J. Am. Soc. Nephrol.* 22, 49-58. PMID 21164026.
11. Wachter, A, Y Bi, SD Dunn, **BD Cain**, H Sieleff, H Wintermann, S Engelbrecht, W Junge (2011) Two rotary motors in F-ATP synthase are elastically coupled by a flexible rotor and a stiff stator stalk. *Proc. Natl. Acad. Sci.* 108, 3924-3929. PMID 21368147.
12. Hamazaki T, WY leung, **BD Cain,** DA Ostrov, PE Thorsness, N Terada (2011) Functional expression of human adenine nucleotide translocase 4 in *Saccharomyces cerevisiae. PLoS One* 6,e19250. PMID 21532989.
13. Welch, AK, CJ Bostwick, **BD Cain** (2011) Manipulations in the peripheral stalk of the *Saccharomyces cerevisiae* F_1F_0 ATP Synthase. *J. Biol. Chem.* 286, 10155-10162. PMID 21257750.
14. Stow, LR, J Richards, KY Cheng, IJ Lynch, LA Jeffers, MM Greenlee, **BD Cain**, CS Wingo, ML Gumz (2012) The circadian clock protein Period-1 contributes to blood pressure control and coordinately regulates renal sodium transport genes. *Hypertension* 59,1151-1156. PMID 22526258.
15. Lynch, IJ, AK Welch, DE Kohan, **BD Cain,** CS Wingo (2013) Endothelin-1 inhibits sodium reabsorption by ETA and ETB receptors in the mouse cortical collecting duct. *Am. J. Physiol.* 305, F568-F573. PMID 23698114.
16. Jacobs, ME, CS Wingo, **BD Cain** (2013) An emerging role for microRNA in the regulation of endothelin-1. *Front. Physiol.* 4, 22, 1-6. PMID 23424003.
17. Richards, J, AK Welch, SJ Barilovits, S All, KY Cheng, CS Wingo, **BD Cain**, ML Gumz (2014) Tissue-specific and time-dependent regulation of the endothelin axis by the circadian clock protein Per1. *Life Sci.* [Epub ahead of print]

D. Research Support

Current Research Support

R01 DK82680 Wingo and Cain (co-PIs) one-year no cost extension to 8/31/15
NIH/NIDDK
An Aldosterone-Endothelin Feedback Mechanism on Sodium Transport
The major goals of this project are to: 1) study aldosterone-mediated edn1 gene induction in vivo; 2) study the physiological effects of edn1 induction in the collecting duct; 3) investigate the molecular mechanism of edn1 induction by aldosterone.

Completed Research Support During Past 3 Years

Toray 3D-Gene Award Cain (PI) 1/01/12-12/31/12
Aldosterone dependent changes in the miRNA landscape in murine inner medullary collecting duct cells
The major goal of this project is to: 1) identify changes in global miRNA expression resulting from aldosterone treatment of mIMCD-3 cells.

U01 HD60474 Terada (PI), Cain (collaborator) 2/01/09-1/31/14
NIH/NIHD
Developing Male Contraceptives by Targeting Ant4
The major goals of this project are to: 1) identify lead compounds to inhibit Ant4; 2) test the effects of lead compounds on sperm motility; 3) test inhibition of the ATP/ADP exchanger; 4) test the compounds on male meiosis and fertility in vivo; 5) conduct optimization studies.