BIOGRAPHICAL SKETCH

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NAME: Bhalla, Vivek

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

POSITION TITLE: Assistant Professor of Medicine

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	B.S.	06/1994	Elec Eng Comp Sci-Bioelectronics
University of California, San Diego	M.D.	06/1998	Medicine

A. Personal Statement

My laboratory studies the role of the kidney at the intersection of two common diseases: diabetes and hypertension. I perform both basic and translational NIH-funded research, and as founder and director of the Stanford Hypertension Center, my clinical interests align with my long-term research goals. I have served on study sections at the NIH and AHA for my expertise in diabetes and hypertension, and have mentored predoctoral (7), and postdoctoral (8) trainees, of whom several have publications based on our work and four are now academic faculty. I am also a member and grant recipient of the NIH-funded Stanford Diabetes Research Center and have access to discounted fees for use of the Diabetes Genomics Analysis Core facility. The objective of the proposed research is to elucidate the mechanisms of insulin receptor-mediated regulation of sodium and glucose co-transport and its implications in health and disease. Specifically, we propose to use wild-type and inducible, renal tubular-specific insulin receptor knockout mice to perform whole animal physiology, and from primary culture of proximal tubules, molecular biology, mass spectrometry, and single cell RNAseq. This project is a competitive renewal for our current R01-funded project on the mechanisms of impaired sodium transport in the metabolic syndrome. We have discovered a role for insulin receptor signaling in the kidney to augment SGLT2 expression and glucose reabsorption and these data have been presented at national conferences and are currently under revision. Our R01-funded experiments established the physiologic relevance of the pathway for which we now propose to explore the mechanism in this renewal. We have also assembled a number of Consultants and cutting-edge techniques at Stanford Core facilities to assist with the execution of the proposed specific aims. Taken together, with my scientific background, motivation, and complementary collaborations, I am well qualified to lead the proposed project to a successful conclusion.

B. Positions and Honors

Research and Professional Experience

09/05-12/07	University of California, San Francisco	Adjunct Assistant Professor of Medicine
01/08-08/08	Stanford University	Acting Assistant Professor of Medicine
09/08-	Stanford University	Assistant Professor of Medicine, Tenure Track
09/12-	Stanford University	Director, Nephrology, Medical Student Curriculum
05/14-	Stanford University	Director, Stanford Hypertension Center

Board Certifications

2001-	American Board of Internal Medicine Specialty	Internal Medicine #205268
2003-	American Board of Internal Medicine Subspecialty	Nephrology #205268
2015-	American Society of Hypertension	Clinical Hypertension

Professional Activities

Manuscript Reviewer (Ad-Hoc)

08/04- European Molecular Biology Organization (EMBO) Journal
12/09- Proceedings of the National Academy of Sciences
09/11- Diabetes
10/12- Journal of the American Medical Association
04/14- American Journal of Physiology, Cellular Physiology
06/14- American Journal of Physiology, Endocrinology
12/14- Journal of the American Society of Nephrology
05/16 Circulation – Cardiovascular Genetics
07/16- American Heart Journal
11/17- Journal of Clinical Investigation
05/18- Endocrinology

Manuscript Reviewer (Editorial Board)
07/2007- American Journal of Physiology, Renal Physiology
05/2010- Frontiers in Physiology – Renal and Epithelial Physiology
04/2018- Physiologic Reviews

Manuscript Associate Editor
01/2013- European Journal of Clinical Investigation

Study Sections
07/08 National Institutes of Health, Adhoc Reviewer, ZHL1 CSR-D (O1) 1 - Grand Opportunities in Large Scale DNA Sequencing and Molecular Profiling of Well Phenotyped NHLBI Cohorts
04/11-10/11 American Heart Association, Molecular Signaling 4, Peer Review Committee
07/11, 07/15 NIH-Diabetes Complications Consortium, Reviewer, Pilot & Feasibility Grants
04/13-Current Child Health Research Institute, Stanford University
06/14 2014/10 ZDK1 GRB-G (O1) 1 - NIDDK-KUH-Fellowship Review
04/15-Current American Heart Association, Cardiorenal 3, Peer Review Committee
10/16 NIH, Ad hoc Reviewer, Molecular and Integrative Signal Transduction (MIST)
10/17 NIH, Ad hoc Reviewer, Kidney Molecular Biology and Genitourinary Organ Development (KMBD)

Advisory Committees
07/14-03/16 American Society of Nephrology -Biosciences Research Advisory Group
07/16-06/18 American Heart Association - Vice-Chair, Kidney and Cardiovascular Disease Council
06/18- American Heart Association - Chair, Kidney and Cardiovascular Disease Council
07/16-06/18 American Heart Association -Member, Council Operations Committee
2018 American Heart Association Hypertension Conference -Vice-Chair, Program Committee

Honors / Awards

1992-1994	UC Berkeley	Tau Beta Pi, Engineering Honors Society
1992-1994	UC Berkeley	Eta Kappa Nu, Elec Eng Honors Society
1994	UC Berkeley	Phi Beta Kappa
1994	UC Berkeley	Graduation with Honors
2000	UC Los Angeles	Solomon Scholars Resident Research Award
2003	NIH / NIDDK	Ruth L. Kirschstein National Research Service Award (F32)
2003	ASN	Fellow
2005	NIH / NIDDK	Mentored Clinical Scientist Award (K08)
2006	UC San Francisco	Excellence in Small Group Instruction, Nominee
2007	UC San Francisco	Teaching Awardee, Halie T. Debas Academy of Medical Educators
2008	NKF	Shaul G. Massry Young Investigator Grant Recipient
2010	ASN	Carl W. Gottschalk Career Development Award
2012	Stanford University	Kaiser Family Foundation Award for Excellence in Preclinical Teaching
2017	AHA	Fellow

2017 Stanford University School of Medicine Award for Outstanding Lecture / Presentation

C. Contributions to Science

***Understanding mechanisms of ENaC regulation*.** The aldosterone-dependent epithelial sodium channel, ENaC is associated with rare and more common forms of human hypertension. Thus, the signaling pathways that regulate ENaC are important for our understanding of mechanisms of hypertension. We have shown that aldosterone-induced serum-and-glucocorticoid kinase 1, SGK1, enhances ENaC surface expression and sodium transport via phosphorylation and inhibition of the ubiquitin ligase Nedd4-2 by inducing its interaction with 14-3-3 adaptor proteins. This inducible interaction requires two sites of Nedd4-2 phosphorylation, termed a major and a minor site. We showed that the interaction is dictated by aldosterone- and SGK1-mediated phosphorylation of the minor site. This data, in conjunction with earlier work by Snyder and colleagues, proposes that the minor sites of phosphorylation are a specific node for differential regulation of Nedd4-2 and ENaC by distinct hormonal pathways and upstream kinases (e.g. aldosterone-induced SGK1 vs. vasopressin-induced protein kinase A).

ENaC is expressed in several epithelia including lung, kidney, and colon, and in each of these tissues, the ubiquitin ligase Nedd4-2 is known to inhibit the channel. In collaboration with Kenneth Hallows, we showed that the energy sensor AMP-activated kinase inhibits ENaC via phosphorylation of Nedd4-2 by enhancement of the interaction between Nedd4-2 and ENaC. We next conducted an unbiased screen of phosphorylation of Nedd4-2 by mass spectrometry and demonstrated several novel sites of phosphorylation. We showed that three of these sites act as a substrate for a member of the c-Jun N-terminal kinase family. One of these sites located in the C-terminus of Nedd4-2 directly inhibited ubiquitin ligase activity and represents the first description of phosphorylation in the catalytic HECT domain of E3 ligases. This discovery was later corroborated by another group (Ding, et al, *Journal of Biological Chemistry*, 2013). These findings have implications for stress-induced pathways (e.g. inflammation) that can inhibit ENaC under select physiologic conditions.

1. **Bhalla V**, D Daidié D, Li H, Pao AC, LaGrange, LP, Wang J, Vandewalle A, Stockand JD, Staub O, Pearce D, “SGK1 regulates ubiquitin ligase Nedd4-2 by inducing interaction with 14-3-3”, *Molecular Endocrinology*, 2005 Dec;19(12): 3073-84. PMID: 16099816.

2. Chandran S, Li H, Dong W, Krasinska K, Adams C, Alexandrova L, Chien A, Hallows KR, **Bhalla V,** "Neural Precursor Cell-expressed Developmentally Down-regulated Protein 4-2 (Nedd4-2) Regulation by 14-3-3 Protein Binding at Canonical Serum and Glucocorticoid Kinase 1 (SGK1) Phosphorylation Sites,” *Journal of Biological Chemistry,* 2011 Oct 28; 286(43):37830-40. PMID: 21900244.

3. **Bhalla V*^**, Hallows KR*, Oyster NM, Wijngaarden MA, Lee JK, Li H, Xia X, Huang Z, Chalkley RJ, Burlingame AL, Pearce D, “Phosphopeptide Screen Uncovers JNK1 as a Potentiator of Nedd4-2-Mediated Epithelial Na+ Channel Inhibition”, *Journal of Biological Chemistry*, 2010, Jul 9; 285(28): 21671-8. PMID: 20466724.
*- co-first author; ^- corresponding author

***Understanding mechanisms of insulin-regulated tubular transport in obesity and insulin resistance*.** We have published a mouse model of sodium-sensitive hypertension in obesity and insulin resistance and contrary to *in vitro* experiments and expression studies, ENaC activity is not altered in this setting. We have subsequently demonstrated that renal tubular insulin receptor signaling plays only a minor role in hypertension but a major role in glucose reabsorption and SGLT2 abundance. This is the first report of insulin receptor activity in the setting of peripheral insulin resistance and have implications for understanding mechanisms of hypertension, mechanisms of SGLT2 regulation, insulin resistance in different tissues, and insulin signaling in kidney disease.

1. Nizar JM, Dong W, McClellan RB, Labarca M, Zhou Y, Wong J, Goens DG, Zhao M, Velarde N, Bernstein D, Pellizzon M, Satlin LM, **Bhalla V**, “Sodium-Sensitive Elevation in Blood Pressure is ENaC Independent in Diet-Induced Obesity and Insulin Resistance”, American Journal of Physiology- Renal Physiology, 2016 May 1;310(9):F812-20, PMID: 26841823.
* subject of editorial (Ecelbarger CA, et al, in the same issue)

2. Nizar JM, **Bhalla V**, “Molecular Mechanisms of Sodium-Sensitive Hypertension in the Metabolic Syndrome”, *Current Hypertension Reports*, 2017 Aug; 19(8):60, PMID: 28676941.

3. Nizar JM, Shepard BD, Vo VT, **Bhalla V**, “Renal tubule insulin receptor modestly promotes elevated blood pressure, and markedly stimulates glucose reabsorption”, *Journal of Clinical Investigation Insight*, 2018, Aug. 23, electronic publication.

***Development of novel tools for renal physiology*.** To extend our work to *in vivo* models of disease we have focused on the metabolic syndrome. The metabolic syndrome is associated with impaired natriuresis and sodium-sensitive hypertension, and is the most common cause for hypertension. However, the mechanisms and specific nephron segments that mediate these effects in the kidney are unknown. Therefore, we sought to develop tools to study the role of distal nephron ion transport in the metabolic syndrome because no cell line could reliably recapitulate the effects of obesity and insulin resistance on distal nephron function. To this end we have recently characterized a method for isolation and primary culture of the aldosterone-sensitive distal nephron from mice. This widely portable technique provides for use of distal nephron preparations for studies of gene expression, biochemistry, and electrophysiology. This study was deemed an Innovative Methodology by the *American Journal of Physiology / Renal Physiology*, and has been adopted by others (Edinger RS, et al, *JASN*, 2014). We have also optimized the study of renal physiology and ion transport in mice and have published our findings as an Innovative Methodology.

1. Edinger RS, Coronnello C, Bodnar AJ, Labarca M, **Bhalla V**, LaFramboise WA, Benos PV, Ho J, Johnson JP, Butterworth MB, “Aldosterone regulates microRNAs in the cortical collecting duct to alter sodium transport”, Journal of the American Society of Nephrology, 2014; 25(11):2445-57. PMID: 24744440

2. Labarca M, Nizar JM, Walczak EM, Dong W, Pao AC, **Bhalla V**, “Harvest and Primary Culture of the Murine Aldosterone-Sensitive Distal Nephron”, *American Journal of Physiology- Renal Physiology*, 2015, Jun 1; 308(11): F1306-15. PMID: 25810438. * published as *Innovative Methodology*

3. Nizar JM, Bouby, N, Bankir L, **Bhalla V**, “Improved protocols for the study of urinary electrolyte excretion and blood pressure in rodents: use of gel food and stepwise changes in diet composition”, American Journal of Physiology- Renal Physiology, 2018 Jun 1; 314(6):F1129-F1137. PMID: 29357416. * published as *Innovative Methodology*

***Understanding the pathogenesis of diabetic kidney disease*.** Diabetes and pre-diabetes influence ion transport and blood pressure regulation, but also contributes to glomerular disease. DKD represents the most common cause of end-stage kidney failure in the world, is the most morbid complication of diabetes, is not yet curable, and there have been no major therapeutic advances in the past 14 years. However, it is well known that only a minority of patients will advance to end-stage kidney disease due to diabetes, and understanding what makes certain individuals susceptible to DKD has been a focus of the laboratory. To this end, I have received NIH grant funding to explore novel immune modulators of susceptibility to DKD and to develop novel autoantibody biomarkers for this disease in humans. I also have authored perspectives on the pathogenesis of DKD and studies of clinical markers of susceptibility to DKD, e.g. race/ethnicity. In our most recently published work we have identified a glomerular-enriched factor, Esm-1, in DKD-susceptible mice that influences leukocyte infiltration. The current proposal explores the mechanisms of Esm-1 function *in vivo* and *in vitro*.

1. **Bhalla V**, Velez MG, Chertow GM, “A Transcriptional Blueprint for Human and Murine Diabetic Kidney Disease”, *Diabetes*, 2013 Jan; 62(1):31-3. PMID: 23258910.

2. **Vivek Bhalla**, Beinan Zhao, Kristen M.J. Azar, Elsie J. Wang, Sarah Choi, Eric C. Wong, Stephen P. Fortmann, Latha P. Palaniappan, “Racial/Ethnic Differences in the Prevalence of Proteinuric and Non-proteinuric Diabetic Kidney Disease”, *Diabetes Care*, 2013, May; 36(5): 1215-21. PMID: 23238659.

3. Zheng X, **Bhalla V**, “The Missing Link- Studying the alternative TGF-β pathway provides a unifying theory for different components of diabetic nephropathy”, *Diabetes*, 2015, Jun; 64(6):1898-900. PMID: 25999532.

4. Zheng X, Soroush F, Long J, Hall ET, Adishesha PK, Bhattacharya S, Kiani MF, **Bhalla V**. Murine glomerular transcriptome links endothelial cell-specific molecule-1 deficiency with susceptibility to diabetic nephropathy. *PLoS One* 2017 Sep 21; 12(9):e0185250. PMID: 28934365.

Complete List of Published Work in MyBibliography
https://www.ncbi.nlm.nih.gov/sites/myncbi/1Rgp10wCrIeA4/bibliography/47784616/public/?sort=date&direction=ascending

D. Research Support

Pending

Bhalla (co-PI)
Stanford Medicine Translational and Clinical Innovation Fund 07/01/17-6/30/19
Exploiting Sugars to Elude a Genetic Defect- Precision Therapy for Precision Medicine
Goal: The co-PIs will use mass-spectrometry of isolated, wild-type and glycosylation-deficient mutant CLC-Kb to determine the glycopeptide composition of this channel and will perform rescue experiments using direct sugar substitution in culture.

Bhalla (PI) 09/01/18 – 08/31/23
NIH NIDDK R01 DK110385-01A1 Percentile Score: 11%
Mechanisms and Consequences of Defective Flow-induced Potassium Secretion in the Metabolic Syndrome
Goal: The PI will test the hypothesis that insulin resistance in the distal nephron is a phenocopy for BK channel deficiency with decreased insulin signaling leading to disrupted calcium (Ca^{2+})-activated BK channel activity, and thus, defective FIKS and K adaptation, with consequent hyperkalemia.

Bhalla (co-PI)
US-Israel Binational Science Foundation 07/01/18-6/29/22
The Role of Ferritin as a Ferric Iron Exporter in Kidney Iron Homeostasis
Goal: The co-PIs will study the role of ferritin trafficking in kidney iron homeostasis we will elucidate mechanisms and regulation of ferritin secretion using primary cultures of: 1) glomeruli, 2) proximal and distal tubular epithelium and 3) renal mononuclear phagocytes.

Past (select, last 3 years)

Bhalla (co-PI)
Stanford Diabetes Research Center Pilot Grant 12/01/16-11/30/17
Validation of cell free RNA associated with human diabetic kidney disease
Goal: This grant allowed us to validate candidate cell-free RNAs for their association with kidney disease (albuminuria) in patients with Type 2 diabetes mellitus. Manuscript in preparation.

Bhalla (PI)
NIH / NIDDK, Parent Grant Program (R01) 09/01/11-08/31/16
ENaC Transport in Insulin Resistance: Role of Insulin & IGF-I Receptors
Goal: This project addressed the mechanisms that lead to salt-sensitive hypertension in the insulin resistance syndrome using renal tubular epithelial cell-specific knockout mice.

Bhalla (PI)
France-Stanford Center for Interdisciplinary Studies 09/01/14-06/30/16
Role of Insulin in Sodium and Potassium Homeostasis: Implications for Obesity-Associated Hypertension
Goal: This project initiated a joint collaboration between Dr. Lise Bankir (INSERM) and my laboratory to better understand the mechanisms ion transport in the setting of obesity and the metabolic syndrome.

Bhalla (PI)
Cardiovascular Institute Seed Grant 10/01/14-09/30/15
Validation of Novel Antibody Biomarkers for Human Diabetic Kidney Disease
Goal: This grant will allow us to validate candidate autoantibodies for their association with kidney disease (albuminuria) in patients with Type 2 diabetes mellitus.