

**BIOGRAPHICAL SKETCH**

Provide the following information for the Senior/key personnel and other significant contributors.  
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Bhalla, Vivek

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

POSITION TITLE: Associate 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**

A primary goal of our research is to study susceptibility and resistance mechanisms for glomerular disease. For this work we have focused on the contribution of systemic Esm-1 to diabetic nephropathy and now propose to expand this work to study the broader role of glomerular-derived Esm-1, mechanisms of Esm-1 action, and genetic regulation of systemic Esm-1. This work has fundamental implications for the role of endothelial cells in glomerular disease as well as the role of Esm-1 in the immune system. I direct a basic science research program on kidney complications of diabetes, including nephropathy and salt-sensitive hypertension using *in vivo* and *in vitro* approaches. I have had NIH funded grants in my laboratory at Stanford University for the mechanisms of hypertension and previously for the role of Esm-1 in DN. I also have been funded through NIDDK as co-PI for the Renal Science Core of the U01 CURE Consortium and as PI of an R25 mentoring program geared toward training the next generation of pre-doctoral kidney and urology researchers. As a physician-scientist and a practicing nephrologist, I have published on DN in basic research, diabetic kidney disease (DKD) in the clinical research arena, and have served on NIH and AHA study sections regarding DKD basic and translational research projects. I was a site-PI on the BEACON Phase 3 clinical trial for progression of Stage 4 CKD in patients with diabetes, participated in clinical research on DKD as a consulting investigator for the Palo Alto Medical Center Research Institute, and give lectures and provide consultation for expertise in DKD. For the current proposal, with my ongoing collaborations with Drs. Avi Rosenberg from Johns Hopkins University, Wang and Liu from the University of South Florida, Moshe Levi from Georgetown University, Samir Parikh from UT Southwestern, and Adriana Hung from Vanderbilt University, we are well positioned to study the mechanisms of Esm-1-mediated inhibition of albuminuria and its implications for DKD. Taken together, with my scientific background, motivation, and complementary collaborations, I am well qualified to lead the proposed project to a successful conclusion.

Ongoing and recently completed projects that I would like to highlight include:

NIH NIDDK 1U01DK130060-01

Bhalla/Freidman/Waikar (Multi-PI)

09/01/21- 08/31/26

Chronic Kidney Diseases of Uncertain Etiology (CKDu) in Agricultural Communities (CURE) research Consortium Renal Science Core

Goal: To bring the best investigative methods and scientific technology to the problem of CKDu.

NIH NIDDK KUH R25

Bhalla (PI) Role: Program Director

09/15/20 – 07/31/25

The Stanford Pre-Renal Initiative: Undergraduate Training in Kidney Health

Goal: To establish a new initiative to foster interest and training in Nephrology, Urology, and Hematology that aligns with the mission of KUH.

Bhalla (Co-I)

NIH NIDDK R01DK127138 (Anand)

09/01/20 – 08/31/25

Chronic disease of unknown etiology (CKDu): applying a multidisciplinary approach to investigate the world's most common tubulointerstitial kidney disease

Goal: We will launch a multidisciplinary prospective study on CKDu in agricultural communities throughout the world. We will apply parallel epidemiologic, clinical, and molecular tools to investigate various etiologies.

Bhalla (Project co-I)(Center PI: Turakhia, Project PI: Wang)

American Heart Association – Strategic Focused Research Network: Health Technology 07/01/20 – 03/31/24

Heart Health Technology Center: Innovation to Implementation

Goal: We will use technology on unmet-needs in healthcare to iteratively develop, test, and implement at scale. We will also train future leaders in digital health technology for cardiovascular disease.

Stanford Medicine Translational and Clinical Innovation Fund

Bhalla (PI). Role: co-investigator

04/01/20-06/30/24

Exploiting Sugars to Elude a Genetic Defect- Precision Therapy for Precision Medicine

Goal: The co-PIs will determine the glycopeptide composition of isolated, wild-type and glycosylation-deficient mutant CLC-Kb and perform rescue experiments by sugar substitution of mutant channels.

The four most relevant publications for this work are included below. I have included a link to my bibliography for the complete list of publications.

1. Zheng X, **Bhalla V**, “The Missing Link- Studying the alternative TGF- $\beta$  pathway provides a unifying theory for different components of diabetic nephropathy”, *Diabetes*, 2015, Jun; 64(6):1898-900. PMCID: PMC4439567.
2. 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. PMCID: PMC5608371.
3. Zheng X, Higdon LE, Gaudet A, Shah M, Balistieri A, Li C, Nadai P, Palaniappan L, Yang X, Santo B, Ginley B, Wang X, Myakala K, Nallagatla P, Levi M, Sarder P, Rosenberg A, Maltzman J, de Freitas Caires N, **Bhalla V**. Endothelial Cell-Specific Molecule-1 Inhibits Albuminuria in Diabetic Mice. *Kidney360*. 2022 Jul 19;3(12):2059-2076. doi: 10.34067/KID.0001712022. eCollection 2022 Dec 29. PMID: 36591362.
4. Gaudet A, Zheng X, Kambham N, **Bhalla V**, Glomerular Esm1 mediates transcriptional polarization associated with diabetic kidney disease, manuscript accepted for publication, *Am J Physiol Renal Physiol*. 2024 Apr 4; 2023.03.01.530562. doi: 10.1101/2023.03.01.530562. PMID: 36993439. PMCID: PMC10054923

## B. Positions, Scientific Appointments and Honors

06/2020 – Present	Associate Professor of Medicine, Tenure Track, Stanford University
05/2014 – Present	Founder, Director, Stanford Hypertension Center, Stanford University
09/2012 – 10/2022	Director, Nephrology, Medical Student Curriculum, Stanford University
09/2008 – 05/2020	Assistant Professor of Medicine, Tenure Track, Stanford University
09/2005 – 12/2007	Adjunct Assistant Professor of Medicine, University of California, San Francisco

## Manuscript Peer Review

2018 – Present	Editorial Board, Physiologic Reviews
2018 – 2020	Guest Editor, Current Opinion in Nephrology and Hypertension
2013 – 2019	Associate Editor, European Journal of Investigation
2010 – Present	Editorial Board, Frontiers in Physiology – Renal and Epithelial Physiology
2007 – Present	Editorial Board, American Journal of Physiology, Renal Physiology

### Study Section Peer Review

2023	NIH, Ad hoc Reviewer, George M. O'Brien Kidney Consortium Review
2019 – Present	NIH, Standing Member, DDK-D KUH Fellowship Application Review Committee
2017	NIH, Ad hoc Reviewer, Kidney Molecular Biology & Genitourinary Organ Development (KMBD)
2016	NIH, Ad hoc Reviewer, Molecular and Integrative Signal Transduction (MIST)
2015 – 2018	American Heart Association, Cardiorenal 3, Peer Review Committee
2011, 2015	NIH, Ad hoc Reviewer, NIH-Diabetes Complications Consortium, Pilot & Feasibility Grants
2011	American Heart Association, Molecular Signaling 4, Peer Review Committee
2008	NIH, Ad hoc Reviewer, ZHL1 CSR-D (O1) 1

### National Service

2022 – Present	Member, Program Committee, AHA Scientific Sessions
2020 – Present	Member, Validated Device Listing Advisory Group, American Medical Association
2020 – 2022	Immediate Past-Chair, Council on Kidney and Cardiovascular Disease, AHA
2019 – 2021	Member, Kidney Week Program Committee, American Society of Nephrology
2018 – 2022	Executive Program Committee, AHA Hypertension Conference
2018 – 2020	Chair, Council on Kidney and Cardiovascular Disease, American Heart Association
2016 – 2018	Vice-Chair, Council on Kidney and Cardiovascular Disease, American Heart Association
2014 – 2016	Biosciences Research Advisory Group, American Society of Nephrology

### Honors

2022	Member, American Society of Clinical Investigation
2017	Fellow, American Heart Association
2017	Stanford School of Medicine Awardee, Outstanding Lecture / Presentation
2012	Kaiser Family Foundation Awardee for Excellence in Preclinical Teaching
2010	Carl W. Gottschalk Career Development Awardee, American Society of Nephrology
2008	Shaul G. Massry Young Investigator Grant Recipient, National Kidney Foundation
2007	Teaching Awardee, Halie T. Debas Academy of Medical Educators
2006	Nominee, Excellence in Small Group Instruction, UC San Francisco
2005	Mentored Clinical Scientist Awardee (K08), NIH / NIDDK
2003	Fellow, American Society of Nephrology

### C. Contributions to Science

**1. 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*.

- a. 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: 28981371. PMCID: PMC5608371.
- b. Zheng X, Higdon LE, Gaudet A, Shah M, Balistieri A, Li C, Nadai P, Palaniappan L, Yang X, Santo B, Ginley B, Wang X, Myakala K, Nallagatla P, Levi M, Sarder P, Rosenberg A, Maltzman J, de Freitas Caires N, **Bhalla V**. Endothelial Cell-Specific Molecule-1 Inhibits Albuminuria in Diabetic Mice. *Kidney360*. 2022 Jul 19;3(12):2059-2076. PMID: 36591362
- c. Gaudet A, Zheng X, Kambham N, **Bhalla V**, Glomerular Esm1 mediates transcriptional polarization associated with diabetic kidney disease, manuscript accepted for publication, *Am J Physiol Renal*

**2. 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.

- a. **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.
- b. 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. PMCID: PMC3199524.
- c. **Bhalla V**<sup>\*</sup>, Hallows KR<sup>\*</sup>, 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<sup>+</sup> Channel Inhibition", *Journal of Biological Chemistry*, 2010, Jul 9; 285(28): 21671-8. PMCID: PMC2898378.

\*- co-first author; ^- corresponding author

**3. 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.

- a. 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. PMCID: PMC4867314. \* subject of editorial (Ecelbarger CA, et al, in the same issue)
- b. Nizar JM, **Bhalla V**, "Molecular Mechanisms of Sodium-Sensitive Hypertension in the Metabolic Syndrome", *Current Hypertension Reports*, 2017 Aug; 19(8):60, PMCID: PMC4867314.
- c. 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; 3(16). pii: 95107. doi: 10.1172/jci.insight.95107. PMCID: PMC6141164.

**4. 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.

- a. Edinger RS, Coronello 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: PMC4214524.
- b. 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: PMC4451330. \* published as *Innovative Methodology*
- c. 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: PMC6032076. \* published as *Innovative Methodology*

**5. Role of the renin-angiotensin-aldosterone system in hypertension.** Approximately 10% of patients have a secondary cause of hypertension, and in this cohort, primary and secondary forms of hyperaldosteronism are the most common etiologies. Despite guideline recommendations for all patients with hypertension and for patients with resistant hypertension, screening for primary and secondary forms of hyperaldosteronism, with measurement of renin-angiotensin-aldosterone system activation, is under-utilized. We published the first single-center study in patients with resistant hypertension and now the largest study using a national VA database, that screening for primary aldosteronism is < 2% of all eligible patients. We also examined patient-, provider-, and system-level factors for rates of screening. These studies represent our first step in increasing awareness of aldosterone in the diagnosis and management of hypertension. We have also published select cases of hyperaldosteronism that were revealed or elucidated by novel diagnostic studies, the recall of renin-angiotensin-aldosterone inhibitors, the role of the renin-angiotensin-aldosterone system in the COVID-19 pandemic, renovascular disease, and the concept of aldosterone sensitivity.

- a. Jaffe G, Gray Z, Krishnan G, Stedman M, Zheng Y, Han Jialin, Chertow GM, Leppert JT, and **Bhalla V**, Screening Rates for Primary Aldosteronism in Resistant Hypertension- A Cohort Study, *Hypertension*. 2020 Mar;75(3):650-659. PMID: 32008436 .
- b. Cohen JB, Cohen DL, Herman DS, Leppert JT, Byrd JB, **Bhalla V**. Testing for Primary Aldosteronism and Mineralocorticoid Receptor Antagonist Use Among US Veterans: A Retrospective Cohort Study, *Annals of Internal Medicine*. 2021 Mar;174(3):289-297. doi: 10.7326/M20-4873. PMID: 33370170.
- c. Gray Z, Tu, W, Chertow GM, **Bhalla V**. Aldosterone sensitivity: an opportunity to explore the pathogenesis of hypertension. *Am J Physiol Renal Physiol*. 2021 Mar 1;320(3):F325-F335. PMID: 33491565.
- d. Funes M, **Bhalla V**, Underdiagnosis of Primary Aldosteronism: A Review of Screening and Detection, *American Journal of Kidney Diseases*. 2023 Mar 23; S0272-6386(23)00579-6. doi: 10.1053/j.ajkd.2023.01.447. PMID: 36965825.

**Complete List of Published Work:** <https://www.ncbi.nlm.nih.gov/myncbi/vivek.bhalla.1/bibliography/public/>