BIOGRAPHICAL SKETCH

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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

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. I am also a member and grant recipient of the NIH-funded Stanford Diabetes Research Center and have access to core facilities such as the Diabetes Genomics Analysis Core facility. The objective of the proposed research training grant 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, and molecular biology. We have discovered a role for insulin receptor signaling in the kidney to augment SGLT2 expression and glucose reabsorption. This work established the physiologic relevance of the pathway for which Dr. Shi now proposes to explore the mechanism. I have mentored predoctoral (19), and postdoctoral (20) trainees, including a recent K08 awardee, and of whom several have publications based on our work and five are now academic faculty. I participate as a mentor for basic science trainees at national meetings through Kidney STARS at Kidney Week and the APS-Renal Section of the Experimental Biology Annual Meeting and have advocated for funding for basic science nephrology trainees both in periodicals and on social media. I received a Gottschalk award and know the value of funding of young investigators. Thus, I was honored to be asked by Ms. Le to mentor her basic science research and to provide scientific, technical and career assistance related to being a renal scientist. Taken together, with my scientific background, motivation, complementary collaborations, and mentorship experience, I am well qualified to sponsor Ms. Le and provide her with the necessary tools to fulfill her training goals.

The five most relevant publications for this work are included below. These include five manuscripts with a former mentee as first-author. I have included a link to my bibliography is available for the complete list of publications.

1. 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. PMCID: PMC4451330. * published as *Innovative Methodology*

2. 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)

3. Nizar JM, **Bhalla V**, “Molecular Mechanisms of Sodium-Sensitive Hypertension in the Metabolic Syndrome”, *Current Hypertension Reports*, 2017 Aug; 19(8):60, PMCID: PMC4867314.

4. 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. PMCID: PMC6032076 [Available on 2019-06-01]. * published as *Innovative Methodology*

5. 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.

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
09/08-05/20	Stanford University	Assistant Professor of Medicine, Tenure Track
06/20-	Stanford University	Associate Professor of Medicine, Tenure Track
09/12-	Stanford University	Director, Nephrology, Medical Student Curriculum
05/14-	Stanford University	Founder, 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
01/19-	Journal of Clinical Investigation Insight

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

Guest Editor

2018-2020	Current Opinion in Nephrology and Hypertension

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
04/13-05/17	Child Health Research Institute, Stanford University
06/14	2014/10 ZDK1 GRB-G (O1) 1 - NIDDK-KUH-Fellowship Review
04/15-02/18	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)
02/19-Current	NIH, Member, KUH Fellowship Application Review Committee

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
06/18-06/20	American Heart Association	- Chair, Kidney and Cardiovascular Disease Council
06/18-06/20	American Heart Association	-Liaison, Hypertension Council
07/16-06/18	American Heart Association	-Member, Council Operations Committee
2018-Current	American Heart Association Hypertension Conference	-Vice-Chair, Program Committee
12/19-Current	American Society of Nephrology	-Kidney Week 2020 / 2021 (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.

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.

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.

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*.

Complete List of Published Work in MyBibliography
https://www.ncbi.nlm.nih.gov/myncbi/1Rgp10wCrIeA4/bibliography/public/

D. Additional Information: Research Support and/or Scholastic Performance
Current
Bhalla (Project co-I)(Center PI: Turakhia, Project PI: Wang)
American Heart Association – Strategic Focused Research Network: Health Technology 7/01/20 – 06/30/24

Heart Health Technology Center: Innovation to Implementation
Goal: We will use technology on unmeet-needs in healthcare, quickly and inexpensively to iterative development and tests, implement in a larger scale and train future leaders in an interdisciplinary way between cardiovascular and technology. The project will focus on a digital, provider- and patient-facing interface to efficiently manage blood pressure in patients with hypertension.

Bhalla (co-PI)
Stanford Medicine Translational and Clinical Innovation Fund 04/01/20-03/31/22

Exploiting Sugars to Elude a Genetic Defect- Precision Therapy for Precision Medicine
Role: co-Principal Investigator
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.

Bhalla (PI)
National Collegiate Inventors & Innovators Alliance-VentureWell Grants, 20497-20 05/01/20- 01/31/21
A Novel Urine Dipstick for the Detection of Acute Kidney Injury
Goal: Dr. Bhalla will utilize funds to train an undergraduate to further validate and to commercialize a novel device for detection of acute kidney injury biomarkers.

Bhalla (co-PI)
Vascular Dynamics, Inc. 03/25/19-03/31/25
CALM-2 – Controlling and Lowering Blood Pressure with the Mobius HD
Goal: The co-site PI's will evaluate eligible individuals with treatment-resistant hypertension to device placement vs. sham procedure for this international, multi-center, randomized, blinded clinical trial to test the principle that modulation of baroreceptor activity can reduce blood pressure.

Bhalla (PI)
NIH NIDDK R01 DK110385-01A1 09/15/18 – 06/30/22
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 02/01/19 – 01/31/23
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.

Bhalla (PI)
P30 DK079307 02/01/19 – 01/31/21
University of Pittsburgh / Mount Sinai George O'Brien Kidney Center Pilot Proposal
Wnt4(+) Cell Fate Mapping and ENaC Activity in Furosemide-treated Mice
Goal: The PI will test the role of Wnt4(+) cells to reprogram towards principal cells in the setting of diuretics.

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.