BIOGRAPHICAL SKETCH

NAME: Leaf, David E.

eRA COMMONS USER NAME: DELEAF

POSITION TITLE: Assistant Professor of Medicine

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Pennsylvania, Philadelphia, PA	BA	05/2004	Psychology
NYU School of Medicine, New York, NY	MD	06/2008	Medicine
Columbia Univ. Medical Center, New York, NY	Residency	06/2011	Internal Medicine
Harvard Medical School, Boston, MA	MMSc	05/2014	Clinical Investigation
Brigham and Women's Hospital and Massachusetts General Hospital, Boston, MA	Fellowship	06/2015	Nephrology

A. Personal Statement

I am an academic physician-scientist, Assistant Professor of Medicine at Harvard Medical School, and Director of Clinical and Translational Research in Acute Kidney Injury (AKI) in the Division of Renal Medicine at Brigham and Women's Hospital. My lab (www.leaflab.org) conducts patient-oriented and translational research in AKI, investigating novel risk factors for its development and therapies for its prevention. In particular, I am interested in dysregulated iron homeostasis and mineral metabolism as potential contributors to AKI and as therapeutic targets for AKI prevention.

I have expertise conducting translational studies in human AKI (1–4), including studies of disordered iron homeostasis in AKI (2,3). I have experience enrolling cardiac surgery patients into research studies, including collecting pre- and postoperative biospecimens and adjudicating and analyzing perioperative clinical outcomes (3). I also have experience conducting randomized controlled trials (RCTs) in critically ill patients, both as the PI of ACTIVATE-AKI, an ongoing, investigator-initiated, phase II RCT of vitamin D metabolites funded by the NIH/NIDDK (NCT02962102), and as the PI of R01HL144566, an ancillary study to the Vitamin D to Improve Outcomes by Leveraging Early Treatment (VIOLET) trial. Finally, I have experience leading large collaborative studies, including a recently published study (4) that coordinated the efforts of 31 authors across 18 institutions to generate novel data on immunotherapy-associated AKI.

1. Hayek SS,* **Leaf DE,*** Tahhan AS,* Raad M, Sharma S, Waikar SS, Sever S, Camacho A, Wang X, Dande RR, Ibrahim NE, Baron RM, Altintas MM, Wei C, Sheikh-Hamad D, Pan JS, Holliday M, Januzzi JL, Weisboard SD, Quyyumi AA, Reiser J. Soluble Urokinase Receptor and Acute Kidney Injury. N Engl J Med. 2020;382(5):416-426. ***Equal contribution**
2. **Leaf DE,** Rajapurkar M, Lele SS, Mukhopadhyay B, Boerger EAS, Mc Causland FR, Eisenga MF, Singh K, Babitt JL, Kellum JA, Palevsky PM, Christov M, Waikar SS. Iron, Hepcidin, and Death in Human Acute Kidney Injury. J Am Soc Nephrol. 2019;30(3):493-504. PMCID: PMC6405140
3. **Leaf DE,** Rajapurkar M, Lele SS, Mukhopadhyay B, Rawn J, Frendl G, Waikar SS. Increased plasma catalytic iron in patients may mediate acute kidney injury and death following cardiac surgery. Kidney Int. 2015; 87(5):1046-54. PMCID: PMC5137505
4. Cortazar FB, Kibbelaar ZA, Glezerman IG, Abudayyeh A, Mamlouk O, Motwani SS, Murakami N, Herrmann SM, Manohar S, Shirali AC, Kitchlu A, Shirazian S, Assal A, Vijayan A, Renaghan AD, Ortiz-Melo DI, Rangarajan S, Malik AB, Hogan JJ, Dinh AR, Shin DS, Marrone KA, Mithani Z, Johnson DB, Hosseini A, Uprety D, Sharma S, Gupta S, Reynolds KL, Sise ME, **Leaf DE**. Clinical Features and Outcomes of Immune Checkpoint Inhibitor-Associated AKI: A Multicenter Study. J Am Soc Nephrol. 2020;31(2):435-446.

B. Positions and Honors

Positions and Employment

2014-present Associate Physician, Renal Division, Brigham and Women's Hospital (BWH)
2015-2016 Instructor in Medicine, Harvard Medical School

2016-present Assistant Professor of Medicine, Harvard Medical School
2019-present Director of Clinical and Translational Research in Acute Kidney Injury, Renal Division, BWH

Other Experience and Professional Memberships

2010-present Member, American Society of Nephrology
2010-present Ad hoc Reviewer for >30 journals, including N Engl J Med and JAMA
2013-2015 Member, Education Committee, BWH
2015-present Course Director, Renal Clinical Conference, Division of Renal Medicine, BWH
2016 Ad hoc Reviewer, NIH/NIDDK R21 Study Section (ZRG1 DKUS-R 55 R)
2017-present Editorial Board, Clinical Journal of the American Society of Nephrology
2017-2018 Member, Abstract Selection Committee, American Society of Nephrology Kidney Week
2018-present Member, Partners Human Research Committee (Institutional Review Board for BWH/MGH)
2019 Ad hoc Reviewer, NIH/NIDDK X01 Study Section (ZDK1 GRB-S)
2020-present Editorial Board, Kidney International

Honors

2004 Summa cum laude, University of Pennsylvania
2004 Phi Beta Kappa, University of Pennsylvania
2008 Excellence in Research Award, NYU School of Medicine (SOM)
2008 Excellence in Physiology and Neuroscience Basic Science Research Award, NYU SOM
2008 Andrew Alan Friedland Memorial Award for Excellence in Internal Medicine, NYU SOM
2011 Excellence in Research Award, Columbia University Medical Center
2011 Diplomate, American Board of Internal Medicine
2013 Excellence in Teaching Award, Harvard Medical School
2014 Excellence in Teaching Award, Harvard Medical School
2015 Fellow of the American Society of Nephrology
2015 Chair's Research Award, BWH, Department of Medicine
2018 Carl W. Gottschalk Research Scholar Award, American Society of Nephrology
2018 Young Investigator Award, National Kidney Foundation (declined due to a competing grant)
2018 Outstanding Reviewer Award, Clinical Journal of the American Society of Nephrology
2019 Chair's Research Award, BWH, Department of Medicine

C. Contributions to Science

1. Clinical and translational studies of catalytic iron, hepcidin, and heme oxygenase-1 in AKI
   Catalytic iron, also known as labile iron, is a toxic, nonphysiologic species of iron that plays a key role in the pathogenesis of AKI in animal models. We were the first to translate these findings to humans by establishing that plasma catalytic iron levels increase rapidly during cardiac surgery, likely due to hemolysis from cardiopulmonary bypass, transfusion of red blood cells, and other factors. These studies further established that higher levels of catalytic iron in the immediate postoperative setting are an early and independent predictor of AKI and death following cardiac surgery. Additionally, in a cohort of 807 critically ill patients with established AKI requiring dialysis – the largest study conducted to date on catalytic iron and AKI in humans – we found that higher levels of catalytic iron and lower levels of hepcidin, the master regulator of systemic iron homeostasis, are each independently associated with a greater risk of 60-day mortality. Finally, we established that a common polymorphism in heme oxygenase-1 (HO-1), the rate limiting enzyme in the degradation of heme, is independently associated with AKI following cardiac surgery.

   a. **Leaf DE,** Rajapurkar M, Lele SS, Mukhopadhyay B, Rawn J, Frendl G, Waikar SS. Increased plasma catalytic iron in patients may mediate acute kidney injury and death following cardiac surgery. Kidney Int. 2015;87(5):1046-54. PMCID: PMC5137505
   b. **Leaf DE,** Rajapurkar M, Lele SS, Mukhopadhyay B, Boerger EAS, Mc Causland FR, Eisenga MF, Singh K, Babitt JL, Kellum JA, Palevsky PM, Christov M, Waikar SS. Iron, Hepcidin, and Death in Human Acute Kidney Injury. J Am Soc Nephrol. 2019;30(3):493-504. PMCID: PMC6405140
   c. **Leaf DE**, Body, SC, Muehlschlegel JD, McMahon GM, Lichtner P, Collard CD, Shernan SK, Fox AA, Waikar SS. Length Polymorphisms in Heme Oxygenase-1 and Risk of AKI following Cardiac Surgery. J Am Soc Nephrol. 2016;27(11):3291-97. PMCID: PMC5084897

d. Sharma S, **Leaf DE.** Iron Chelation as a Potential Therapeutic Strategy for AKI Prevention. J Am Soc Nephrol. 2019;30(11):2060-71. PMCID: PMC6830795

2. Clinical and translational studies of FGF23, vitamin D, and disordered mineral metabolism in AKI
These studies were the first to establish that circulating levels of the osteocyte-derived, vitamin D-regulating hormone, fibroblast growth factor 23 (FGF23), are elevated in critically ill patients and in patients undergoing cardiac surgery, and that higher levels are an early and independent marker of AKI and death. We further demonstrated that elevated FGF23 is a potential mechanism of 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D (1,25D) deficiency in critical illness. Finally, we demonstrated in a randomized, double-blind, placebo-controlled trial that administration of 1,25D to critically ill patients with severe sepsis upregulates leukocyte RNA expression of human cathelicidin antimicrobial peptide 18 (hCAP-18). Prior studies had demonstrated effects of 1,25D on hCAP-18 in vitro, but we were the first to demonstrate these effects in vivo. We are currently conducting a larger follow-up trial, funded by the NIH/NIDDK, to test whether administration of activated vitamin D metabolites prevents AKI in critically ill patients (NCT02962102; *n*=150).

   a. **Leaf DE,** Wolf M, Waikar SS, Chase H, Christov M, Cremers S, Stern L. FGF-23 Levels in patients with AKI and risk of adverse outcomes. Clin J Am Soc Nephrol. 2012;7:1217-23. PMCID: PMC3408118
   b. **Leaf DE**, Christov M, Jüppner H, Siew E, Ikizler TA, Bian A, Chen G, Sabbisetti VS, Bonventre JV, Cai X, Wolf M, Waikar SS. Fibroblast growth factor 23 levels are elevated and associated with severe acute kidney injury and death following cardiac surgery. Kidney Int. 2016;89(4):939-48. PMCID: PMC4801748
   c. **Leaf DE,** Jacob KA, Srivastava A, Chen ME, Christov M, Jüppner H, Sabbisetti VS, Martin A, Wolf M, Waikar S. Fibroblast Growth Factor 23 Levels Associate with AKI and Death in Critical Illness. J Am Soc Nephrol. 2017;28(6):1877-85. PMCID: PMC5461795
   d. **Leaf DE,** Raed A, Donnino MW, Ginde AA, Waikar SS. Randomized Controlled Trial of Calcitriol in Severe Sepsis. Am J Respir Crit Care Med. 2014;190(5):533-41. PMCID: PMC4214090

3. Clinicopathologic features of immune checkpoint inhibitor-associated AKI
Immunotherapy, and in particular the immune checkpoint inhibitors (ICPis), have revolutionized oncology and are now considered first-line therapies for a number of malignancies. However, these medications can cause a unique spectrum of autoimmune toxicities, including AKI. We published the first multicenter description (>180 citations) of the clinicopathologic features of ICPi-associated AKI (ICPi-AKI). More recently we published the most comprehensive description of ICPi-AKI to date, which included 138 patients with ICPi-AKI from 18 centers across the U.S. and Canada. This study revealed several novel insights into ICPi-AKI, including risk factors for its development, prognostic factors for its recovery, treatment options, and long-term survival outcomes. Additionally, the study included critical information on the safety of ICPi rechallenge following an episode of ICPi-AKI, and found that the majority of patients rechallenged do not develop recurrent AKI. These findings have major implications for cancer patients, particularly those who suffer from ICPi-AKI and who may have limited alternative therapeutic options apart from ICPi rechallenge.

   a. Cortazar FB, Marrone KA, Troxell ML, Ralto KM, Hoenig MP, Brahmer JR, Le DT, Lipson EJ, Glezerman IG, Wolchok J, Cornell LD, Feldman P, Stokes MB, Zapata SA, Hodi FS, Ott PA, Yamashita M, **Leaf DE.** Clinicopathological features of AKI associated with immune checkpoint inhibitors. Kidney Int. 2016;90(3):638-47. PMCID: PMC4983464
   b. Seethapthy H, Zhao S, Chute DF, Zubiri L, Oppong Y, Strohbehn I, Cortazar FB, **Leaf DE**, Mooradian MJ, Villani AC, Sullivan RJ, Reynolds K, Sise ME. The Incidence, Causes, and Risk Factors of Acute Kidney Injury in Patients Receiving Immune Checkpoint Inhibitors. Clin J Am Soc Nephrol. 2019;14(12):1692-1700.
   c. Cortazar FB, Kibbelaar ZA, Glezerman IG, Abudayyeh A, Mamlouk O, Motwani SS, Murakami N, Herrmann SM, Manohar S, Shirali AC, Kitchlu A, Shirazian S, Assal A, Vijayan A, Renaghan AD, Ortiz-Melo DI, Rangarajan S, Malik AB, Hogan JJ, Dinh AR, Shin DS, Marrone KA, Mithani Z, Johnson DB, Hosseini A, Uprety D, Sharma S, Gupta S, Reynolds KL, Sise ME, **Leaf DE**. Clinical Features and Outcomes of Immune Checkpoint Inhibitor-Associated AKI: A Multicenter Study. J Am Soc Nephrol. 2020;31(2):435-446.

4. Discovery and validation of novel markers and therapeutic targets for AKI
Using an unbiased metabolomics screen, we found that intermediates in the biosynthetic pathway for nicotinamide adenine dinucleotide (NAD+) are upregulated in the urine of mice with AKI. We further established that elevated levels of these intermediates in the urine are independently associated with development of AKI in critically ill patients. In a phase I randomized controlled trial, we found that prophylactic administration of oral nicotinamide decreases the incidence of AKI following cardiac surgery. In a separate study, we investigated the role of soluble urokinase plasminogen activator receptor (suPAR) in AKI. SuPAR is the circulating form of a membrane protein that is expressed on a variety of immunologically active cells, including monocytes and lymphocytes. We measured plasma suPAR in nearly 5,000 patients across three clinical settings: coronary angiography, cardiac surgery, and critical illness. In each setting, higher suPAR levels associated independently and monotonically with a greater risk of AKI. In preclinical models, pharmacologic blocking of suPAR with a monoclonal antibody attenuated AKI, suggesting that suPAR may be pathologically involved in AKI and could be a novel therapeutic target.

    a. Poyan Mehr A, Tran MT, Ralto KM, **Leaf DE**, Washco V, Messmer J, Lerner A, Kher AV, Kim SH, Khoury CC, Herzig SJ, Trovato ME, Simon-Tillaux N, Lynch MR, Thadhani RI, Clish CB, Khabbaz KR, Rhee EP, Waikar SS, Berg AH, Parikh SM. De novo NAD+ biosynthetic impairment in acute kidney injury in humans. Nature Medicine. 2018;24(9):1351-59.
    b. Hayek SS,* **Leaf DE,*** Tahhan AS,* Raad M, Sharma S, Waikar SS, Sever S, Camacho A, Wang X, Dande RR, Ibrahim NE, Baron RM, Altintas MM, Wei C, Sheikh-Hamad D, Pan JS, Holliday M, Januzzi JL, Weisboard SD, Quyyumi AA, Reiser J. Soluble Urokinase Receptor and Acute Kidney Injury. N Engl J Med. 2020;382(5):416-426. ***Equal contribution**

5. Patient safety and quality improvement
These studies assessed patient safety and resource utilization in a variety of clinical settings. We established that patients assigned to low- versus high-visible rooms in the intensive care unit have increased hospital mortality. We demonstrated the effectiveness of an electronic alert that we implemented to decrease the inappropriate ordering of sodium polystyrene sulfonate (Kayexalate) for mild hyperkalemia. Additionally, we examined the utility of serologic and radiographic diagnostic testing in the initial evaluation of acute and chronic kidney diseases, using an evidence-based approach.

    a. **Leaf DE**, Homel P, Factor PH. Relationship between ICU design and mortality. Chest. 2010;137(5):1022-7.
    b. Mendu ML, Lundquist A, Aizer AA, **Leaf DE**, Robinson E, Steele DJ, Waikar SS. The usefulness of diagnostic testing in the initial evaluation of chronic kidney disease. JAMA Intern Med. 2015;175(5):853-6. PMCID: PMC4420699
    c. **Leaf DE**, Cheng XS, Sanders JL, Mendu M, Schiff GD, Mount DB, Bazari H. An electronic alert to decrease Kayexalate ordering. Ren Fail. 2016;38(10):1752-4. PMCID: PMC5114173
    d. **Leaf DE**, Srivastava A, Zeng X, McMahon GM, Croy HE, Mendu ML, Kachalia A, Waikar SS. Excessive diagnostic testing in acute kidney injury. BMC Nephrol. 2016;17:9. PMCID: PMC4714492

Complete List of Published Work in MyBibliography: (>60 total publications)
https://www.ncbi.nlm.nih.gov/sites/myncbi/david.leaf.1/bibliography/49752290/public/?sort=date&direction=descending

D. Additional Information: Research Support and/or Scholastic Performance

Ongoing Research Support

R01 HL144566 Leaf (PI) 7/1/19 – 6/30/23
NIH/NHLBI
Precision Medicine Approach to Vitamin D3 Administration in Critical Illness
This project will use samples and data from the NHLBI PETAL Network-funded Vitamin D to Improve Outcomes by Leveraging Early Treatment (VIOLET) trial to test whether clinical, genetic, and biochemical factors identify patients most likely to benefit from vitamin D3 administration in critical illness.
Role: PI

K23 DK106448 Leaf (PI) 7/15/15 – 4/30/20
NIH/NIDDK
Dysregulated Mineral Metabolism in AKI
This project will test in a phase II, double-blind, randomized controlled trial whether administration of vitamin D metabolites (25-hydroxyvitamin D and 1,25-dihydroxyvitamin D) prevents acute kidney injury in critically ill patients (*n*=150).
Role: PI

Completed Research Support

American Society of Nephrology Leaf (PI) 7/1/18 – 6/30/20
Carl W. Gottschalk Research Scholar Grant
Hepcidin, Dysregulated Iron Homeostasis, and Anemia in Human Acute Kidney Injury
This project tested whether plasma hepcidin levels associate with anemia and death in patients with established AKI.
Role: PI

P30 DK079337 Agarwal (PI) 8/1/15 – 7/31/17
NIH/NIDDK
Dysregulated Mineral Metabolism in Critically Ill Patients with Severe AKI
This project tested the hypotheses that elevated plasma FGF23 and decreased vitamin D metabolite levels are independently associated with increased 60-day mortality and longer duration of renal replacement therapy in patients with severe AKI who enrolled into the Acute Renal Failure Trial Network (ATN) study.
Role: Pilot and Feasibility Award PI