BIOGRAPHICAL SKETCH

NAME: Leaf, David E.

eRA COMMONS USER NAME: DELEAF

POSITION TITLE: Associate 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 a physician-scientist, Associate Professor of Medicine at Harvard Medical School (HMS), and Director of Clinical and Translational Research in Acute Kidney Injury (AKI) in the Division of Renal Medicine at Brigham and Women's Hospital (BWH). My lab (www.leaflab.org) conducts clinical and translational research in AKI, investigating novel risk factors for its development and therapies for its prevention (1–3). I am the PI of three R01 grants investigating novel therapies to prevent AKI and reduce mortality in critically ill patients. I also have experience successfully leading large multicenter epidemiologic studies, most recently exemplified by a project in which I coordinated the efforts of >400 collaborators across 68 institutions to generate comprehensive data on critically ill patients with COVID-19 (4).

Ongoing and recently completed projects:

R01DK126685
Leaf (PI)
7/1/22 – 5/31/26
Hepcidin-Ferroportin-Iron Axis in Cardiac Surgery-associated Acute Kidney Injury

R01DK125786
Leaf (PI)
9/1/20 – 6/30/25
Deferoxamine for the Prevention of Acute Kidney Injury

R01HL144566
Leaf (PI)
7/1/19 – 6/30/23
Precision Medicine Approach to Vitamin D3 Administration in Critical Illness

K23DK106448
Leaf (PI)
7/15/15 – 4/30/20
Dysregulated Mineral Metabolism in AKI

Citations:

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. PMCID: PMC7065830. ***Equal contribution**

2. **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
3. **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
4. Gupta S, Hayek SS, Wang W, Chan L, Mathews KS, Melamed ML, Brenner SK, Leonberg-Yoo A, Schenck EJ, Radbel J, Reiser J, Bansal A, Srivastava A, Zhou Y, Sutherland A, Green A, Shehata AM, Goyal N, Vijayan A, Velez JCQ, Shaefi S, Parikh CR, Arunthamakun J, Athavale AM, Friedman AN, Short SAP, Kibbelaar ZA, Abu Omar S, Admon AJ, Donnelly JP, Gershengorn HB, Hernán MA, Semler MW, **Leaf DE**; STOP-COVID Investigators. Factors Associated with Death in Critically Ill Patients with Coronavirus Disease 2019 in the US. JAMA Intern Med. 2020;180(11):1-12.

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2022-Present	Associate Professor of Medicine, HMS
2021-Present	Founding Member, American Society of Onconephrology
2021-Present	Member, Harvard Catalyst Scientific Review Committee, HMS
2020-Present	Editorial Board, *Kidney International*
2020	Abstract Chair for Onco-Nephrology, American Society of Nephrology Kidney Week
2019-Present	Director of Clinical and Translational Research in Acute Kidney Injury, Renal Division, BWH
2019	Ad hoc Reviewer, NIH/NIDDK X01 Study Section (ZDK1 GRB-S)
2018-Present	Member, Institutional Review Board, Mass General Brigham
2018-Present	Member, Immune-Related Adverse Events Working Group, Dana-Farber Cancer Institute
2017-Present	Editorial Board, *Clinical Journal of the American Society of Nephrology*
2016-2022	Assistant Professor of Medicine, HMS
2016	Ad hoc Reviewer, NIH/NIDDK R21 Study Section (ZRG1 DKUS-R 55 R)
2015-2016	Instructor in Medicine, HMS
2015-2020	Course Director, Renal Clinical Conference, Renal Division, BWH
2014-Present	Associate Physician, Renal Division, BWH
2013-2015	Member, Education Committee, BWH
2010-Present	Member, American Society of Nephrology
2010-Present	Ad hoc Reviewer for >60 journals, including *New England Journal of Medicine* and *JAMA*

Honors

2021	Editors' Choice Article, *Journal of the American Society of Nephrology*
2019	Chair's Research Award, Department of Medicine, BWH
2018	Outstanding Reviewer Award, *Clinical Journal of the American Society of Nephrology*
2018	Young Investigator Award, National Kidney Foundation (declined due to a competing grant)
2018	Carl W. Gottschalk Research Scholar Award, American Society of Nephrology
2015	Chair's Research Award, Department of Medicine, BWH
2015	Fellow of the American Society of Nephrology
2014	Excellence in Teaching Award, HMS
2013	Excellence in Teaching Award, HMS
2011	Excellence in Research Award, Columbia University Medical Center
2008	Andrew Alan Friedland Memorial Award for Excellence in Internal Medicine, NYU School of Medicine (SOM)
2008	Excellence in Physiology and Neuroscience Basic Science Research Award, NYU SOM
2008	Excellence in Research Award, NYU SOM
2004	Phi Beta Kappa, University of Pennsylvania
2004	Summa cum laude, University of Pennsylvania

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, 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. COVID-19 Critical Illness

The Study of the Treatment and Outcomes in Critically Ill Patients with COVID-19 (STOP-COVID) is a multicenter cohort study led by Dr. Leaf that enrolled 5154 critically ill adults with COVID-19 admitted to intensive care units at 68 hospitals across the US. Dr. Leaf coordinated the efforts of >400 attendings, fellows, residents, and medical students to collect detailed data on these patients, and published the first nationwide studies on COVID-19 critical illness in the US. These studies (22 to date) identified risk factors for death and acute organ injury, interhospital variation in treatment and outcomes, and therapies that may improve survival, and have been featured in national media including *CNN*, *The NY Times*, *USA Today*, and *The Washington Post*.

a. Gupta S, Hayek SS, Wang W, Chan L, Mathews KS, Melamed ML, Brenner SK, Leonberg-Yoo A, Schenck EJ, Radbel J, Reiser J, Bansal A, Srivastava A, Zhou Y, Sutherland A, Green A, Shehata AM, Goyal N, Vijayan A, Velez JCQ, Shaefi S, Parikh CR, Arunthamakun J, Athavale AM, Friedman AN, Short SAP, Kibbelaar ZA, Abu Omar S, Admon AJ, Donnelly JP, Gershengorn HB, Hernán MA, Semler MW, **Leaf DE**; STOP-COVID Investigators. Factors Associated with Death in Critically Ill Patients with Coronavirus Disease 2019 in the US. JAMA Intern Med. 2020;180(11):1-12. PMCID: PMC7364338.
b. Gupta S, Wang W, Hayek SS, Chan L, Mathews KS, Melamed ML, Brenner SK, Leonberg-Yoo A, Schenck EJ, Radbel J, Reiser J, Bansal A, Srivastava AS, Zhou Y, Finkel D, Green A, Mallappallil M, Faugno AJ, Zhang J, Velez JCQ, Shaefi S, Parikh CR, Charytan DM, Athavale AA, Friedman AN, Redfern RE, Short SAP, Correa S, Pokharel KK, Admon AJ, Donnelly JP, Gershengorn HB, Douin DJ, Semler MW, Hernán MA, **Leaf DE**; STOP-COVID Investigators. Association Between Early Treatment with Tocilizumab and Mortality Among Critically Ill Patients with COVID-19. JAMA Intern Med. 2021;181(1):41-51. PMCID: PMC7577201.
c. Hayek SS, Brenner S, Azam TU, Shadid HR, Anderson E, Berlin H, Pan M, Meloche C, Feroze R, O'Hayer P, Kaakati R, Bitar A, Padalia K, Perry D, Blakely P, Gupta S, Shaefi S, Srivastava A, Charytan DM, Bansal A, Mallappallil M, Melamed ML, Shehata AM, Sunderram J, Mathews KS, Sutherland AK, Nallamothu BK, **Leaf DE**; STOP-COVID Investigators. In-hospital cardiac arrest in critically ill patients with covid-19: multicenter cohort study. BMJ. 2020;371:m3513. PMCID: PMC7525342.
d. Al-Samkari H, Gupta S, Leaf RK, Wang W, Rosovsky RP, Brenner SK, Hayek S, Berlin H, Kapoor R, Shaefi S, Melamed ML, Sutherland A, Radbel J, Green A, Garibaldi BT, Srivastava A,

Leonberg-Yoo A, Shehata AM, Flythe JE, Rashidi A, Goyal N, Chan L, Mathews KS, Hedayati S, Dy R, Toth-Manikowski SM, Zhang J, Mallappallil M, Redfern RE, Bansal A, Short SAP, Bauer KA, Hernán MA, **Leaf DE**; STOP-COVID Investigators. Thrombosis, Bleeding, and the Observational Effect of Early Therapeutic Anticoagulation on Survival in Critically Ill Patients with COVID-19. Ann Intern Med. 2021;174(5):622-632. PMCID: PMC7863679.

3. 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 predictor of AKI and death. We further demonstrated that elevated FGF23 is a potential mechanism of decreased 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D (1,25D) levels 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 recently completed a larger follow-up NIH-funded trial (*n*=150) testing whether administration of activated vitamin D metabolites prevents AKI in critically ill patients.

    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

4. Clinicopathologic features of immune checkpoint inhibitor-associated AKI
Immune checkpoint inhibitors (ICPis) have revolutionized oncology and are now considered first-line therapies for a large number of malignancies. However, these medications can cause a unique spectrum of autoimmune toxicities, including AKI. We published the first multicenter studies describing the clinicopathologic features of ICPi-associated AKI (ICPi-AKI). More recently we published the largest and most comprehensive description of ICPi-AKI to date, which included data on 429 patients with ICPi-AKI from 30 sites across 10 countries. 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 data on the safety of ICPi rechallenge following an episode of ICPi-AKI, and found that the vast 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. PMCID: PMC6895474
    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. PMCID: PMC7003302

d. Gupta S, Short SAP, Sise ME, Prosek JM, Madhavan SM, Soler MJ, Ostermann M, Herrmann SM, Abudayyeh A, Anand S, Glezerman I, Motwani SS, Murakami N, Wanchoo R, Ortiz-Melo DI, Rashidi A, Sprangers B, Aggarwal V, Malik AB, Loew S, Carlos CA, Chang W, Beckerman P, Mithani Z, Shah CV, Renaghan AD, De Seigneux S, Campedel L, Kitchlu A, Shin DS, Rangarajan S, Deshpande P, Coppock G, Eijgelsheim M, Seethapathy HS, Lee M, Strohbehn IA, Owen DH, Husain M, García-Carro C, Bermejo S, Lumlertgul N, Seylanova N, Flanders L, Isik B, Mamlouk O, Lin JS, Garcia P, Kaghazchi A, Khanin Y, Kansal SK, Wauters E, Chandra S, Schmidt-Ott KM, Hsu RK, Tio MC, Mothi SS, Singh H, Schrag D, Jhaveri KD, Reynolds KL, Cortazar FB, **Leaf DE**; ICPi-AKI Consortium. Acute Kidney Injury in Patients Treated with Immune Checkpoint Inhibitors. J Immunother Cancer. 2021 Oct;9(10):e003467. PMCID: PMC8496384

5. Discovery and validation of novel markers and therapeutic targets for AKI

Soluble urokinase plasminogen activator receptor (suPAR) is the circulating form of a membrane protein expressed on a variety of immunologically active cells, including monocytes and lymphocytes. We investigated the role of suPAR in AKI by measuring plasma suPAR levels 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 have a pathologic role in AKI and could be a novel therapeutic target. In a separate study, 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 pilot randomized clinical trial, we found that prophylactic administration of oral nicotinamide decreases the incidence of AKI following cardiac surgery.

a. 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. PMCID: PMC7065830. ***Equal contribution**

b. 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. PMCID: PMC6129212

c. Simic P, Kim W, Zhou W, Pierce KA, Chang W, Sykes DB, Aziz NB, Elmariah S, Ngo D, Pajevic PD, Govea N, Kestenbaum BR, de Boer IH, Cheng Z, Christov M, Chun J, **Leaf DE**, Waikar SS, Tager AM, Gerszten RE, Thadhani RI, Clish CB, Juppner H, Wein MN, Rhee EP. Glycerol-3-phopshate is an FGF23 regulator derived from the injured kidney. J Clin Invest. 2020;130(3):1513-1526. PMCID: PMC7269595

Complete List of Published Work in MyBibliography: (127 total publications)
https://www.ncbi.nlm.nih.gov/sites/myncbi/david.leaf.1/bibliography/49752290/public/?sort=date&direction=descending