BIOGRAPHICAL SKETCH

NAME: Testani, Jeffrey Moore

eRA COMMONS USER NAME testanij

POSITION TITLE: Associate Professor of Medicine

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Florida	B.S.	05/00	Microbiology & Cell Science
University of Florida	M.D.	06/04	Medicine
Hospital of the University of Pennsylvania		07/07	Internal Medicine
Hospital of the University of Pennsylvania		07/09	Cardiovascular Medicine
University of Pennsylvania	M.T.R.	07/11	Research Fellow/Masters in Translational Research
Hospital of the University of Pennsylvania		07/12	Advanced Heart Failure & Cardiac Transplantation

A. Personal Statement

My clinical training is as an advanced heart failure and cardiac transplantation physician with formal research training in patient oriented translational research. My research program is supported by NIH and investigator-initiated industry sources and uses techniques of both translational and clinical research to further the mechanistic understanding of cardiac-renal interactions, fluid and sodium homeostasis, and diuretic resistance in heart failure. The primary approach of my current research program is prospective mechanistic human studies in heart failure patients. Notably, we have enrolled over 700 patients and conducted over 1300 intense biospecimen collections resulting in the approximately 500,000 biospecimens currently housed in our biorepository. Furthermore, my lab has extensive expertise in biomarker research has established and maintains an extensive bioassay resource with the capability to determine an extensive range of analytes in biological samples with complexity ranging from simple urine chemistries to complex analytes such as ultra-trace lithium by inductively coupled plasma mass spectrometry, deuterium concentration by nuclear magnetic resonance and isotope dilution mass spectrometry, high dimension multiplex protein assays, and large and small molecules by liquid chromatography mass spectrometry. We have also served as the core lab for two multicenter industry studies and one NIH multicenter study. As a result, my lab is well qualified to assist as a collaborator on the TENSION trial team.

B. Positions and Honors

Positions and Employment

2011-2012 Fellow-Instructor, Hospital of the University of Pennsylvania, Philadelphia, PA
2012-2018 Assistant Professor of Medicine, Yale University School of Medicine, New Haven, CT
2012- Director, Heart Failure Research, Yale University School of Medicine, New Haven, CT
2018- Associate Professor of Medicine (tenure track), Yale University School of Medicine, New Haven, CT

Other Experience

2010- Journal Reviewer: Circulation, Circulation: Heart Failure Journal of the American College of Cardiology, European Journal of Heart Failure, The Lancet, European Heart Journal, Clinical Journal of the American Society of Nephrology, American Journal of Physiology, Journal of the American College of Cardiology: Heart Failure, New England Journal of Medicine

2015-	Grant Reviewer, Israel Science Foundation (ISF); The Netherlands Comprehensive Cardiovascular Research Program; UK National Institute for Health Research (NIHR) Invention for Innovation (i4i); NIH Special Emphasis Panel, ZDK1 GRB-9 O2; NIDDK PAR-09-247
2015-2016	Annual Scientific Session Program Committee, Heart Failure Society of America
2017-	Steering Committee, Sotagliflozin Heart Failure Outcomes Study (Sanofi)
2017-	Journal of The American College of Cardiology Heart Failure, Editorial Board
2018-2019	Temporary member NIDDK-D study section
2019	Guest Associate Editor (Standing member), Circulation

Honors

2000	Suma Cum Laude, University of Florida, Gainesville, FL
2003	Alpha Omega Alpha (elected as third year student) University of Florida College of Medicine, Gainesville, FL
2004	Suma Cum Laude, University of Florida College of Medicine, Gainesville, FL

C. Contributions to Science

Complete List of Published Work in MyBibliography (N=139) Can Be Found At:
https://www.ncbi.nlm.nih.gov/myncbi/10OKlTLG-8_QK/bibliography/public/

1. One of my most significant contributions to the medical literature focused on better understanding the importance of the mechanism underlying renal dysfunction in determining the associated prognosis and therapeutic approach to these patients. Prior to 2010 the prevailing wisdom was that, regardless of mechanism, renal dysfunction or worsening renal function was an ominous prognostic sign and should be avoided at all costs. With a series of ~40 papers we systematically challenged that paradigm, demonstrating that the mechanism underlying the renal dysfunction was critically important in determining prognosis. For example, we demonstrated that worsening renal function after stimuli such as aggressive diuresis, reduction in blood pressure, starting an angiotensin converting enzyme inhibitor, etc. was more or less free from prognostic disadvantage, whereas unprovoked worsening renal function portended a dismal prognosis. Furthermore, we also published a number of papers describing mechanistic drivers of renal dysfunction in heart failure, with our most recent papers showing an absence of renal tubular injury as a primary contributor. This body of work has been credited by many as a catalyst to the change in thinking that has occurred in the area of cardio-renal interactions.
   a. **Testani JM**, Coca SG, Shannon RP, Kimmel SE and Cappola TP. Influence of renal dysfunction phenotype on mortality in the setting of cardiac dysfunction: analysis of three randomized controlled trials. *European journal of heart failure*. 2011;13:1224-30. PMC3248247
   b. Hanberg JS, Sury K, Wilson FP, Brisco MA, Ahmad T, Ter Maaten JM, Broughton JS, Assefa M, Tang WH, Parikh CR and **Testani JM**. Reduced Cardiac Index Is Not the Dominant Driver of Renal Dysfunction in Heart Failure. *J Am Coll Cardiol*. 2016;67:2199-208. PMC4867078
   c. Ahmad T, Jackson K, Rao VS, Tang WHW, Brisco-Bacik MA, Chen HH, Felker GM, Hernandez AF, O'Connor CM, Sabbisetti VS, Bonventre JV, Wilson FP, Coca SG and **Testani JM**. Worsening Renal Function in Acute Heart Failure Patients Undergoing Aggressive Diuresis is Not Associated with Tubular Injury. *Circulation*. 2018 Jun 19;137(25):e853. PMC6066176
   d. Rao VS, Ahmad T, Brisco-Bacik MA, Bonventre JV, Wilson FP, Siew ED, Felker GM, Anstrom KK, Mahoney DD, Bart BA, Tang WHW, Velazquez EJ and **Testani JM**. Renal Effects of Intensive Volume Removal in Heart Failure Patients With Preexisting Worsening Renal Function. *Circulation Heart failure*. 2019;12:e005552. PMC6585463

2. One of the primary goals of our laboratory has been to understand the mechanism of diuretic resistance in contemporarily treated heart failure patients. Notably, most of our understanding of diuretic resistance is based on animal models or non-HF human populations. It is often thought that reduced diuretic delivery, due to poor cardiac output, low serum albumin, or renal dysfunction, are the major drivers of diuretic resistance in heart failure. However, we recently have begun to systematically query these commonly held beliefs, finding may to not hold true in human HF. Notably, diuretic delivery appears to be a quantitatively relatively minor contributor to diuretic resistance. Rather, resistance at the renal tubular level appears to be common and the primary driver quantitatively of diuretic resistance. Recently we have been working toward understanding the tubular location and molecular

mechanisms for the resistance. Using endogenous lithium clearance to determine proximal tubular sodium reabsorption, we confirmed that, similar to rodent models, the major driver of loop diuretic resistance is, in fact, enhanced distal tubular sodium reabsorption.

a. Ter Maaten JM, Rao VS, Hanberg JS, Perry Wilson F, Bellumkonda L, Assefa M, Sam Broughton J, D'Ambrosi J, Wilson Tang WH, Damman K, Voors AA, Ellison DH and **Testani JM**. Renal tubular resistance is the primary driver for loop diuretic resistance in acute heart failure. European journal of heart failure. 2017, Jan 19. PMC6231236
b. Rao VS, Planavsky N, Hanberg JS, Ahmad T, Brisco-Bacik MA, Wilson FP, Jacoby D, Chen M, Tang TW, Cherney DZ, Ellison DH, **Testani JM**. Compensatory distal reabsorption drives diuretic resistance in human heart failure. J Am Soc Nephrol. 2017 Jul 24. PMC5661276
c. Charokopos A, Griffin M, Rao VS, Inker L, Sury K, Asher J, Turner J, Mahoney D, Cox ZL, Wilson FP and **Testani JM**. Serum and Urine Albumin and Response to Loop Diuretics in Heart Failure. *Clinical journal of the American Society of Nephrology : CJASN*. 2019;14:712-718. PMC6500945
d. Cox ZL, Hung R, Lenihan DJ and **Testani JM**. Diuretic Strategies for Loop Diuretic Resistance in Acute Heart Failure: The 3T Trial. *JACC Heart failure*. 2019.PMC7058489

3. I have also contributed to the developing understanding of the association between loop diuretics and mortality in patients with heart failure. We were the first to demonstrate that the cardio-renal response and efficacy of decongestion appears to interact with the mortality risk associated with high dose loop diuretics, and, by inference, that the association was more than just confounding by indication. Moreover, we have described that the dose of loop diuretic is only important prognostically when interpreted in the context of the resultant diuretic response, which we have termed diuretic efficiency (fluid output per mg of diuretic administered). Notably, using this metric we have demonstrated, and several authors have subsequently validated, that even very high doses of loop diuretic in the context of a good diuretic response are free from an adverse prognostic risk. This early work has led to my current scientific focus of better understanding the mechanisms for diuretic resistance and sodium avidity and developing new approaches to remove sodium from patients without loop diuretics.

a. **Testani JM**, Cappola TP, Brensinger CM, Shannon RP and Kimmel SE. Interaction between loop diuretic-associated mortality and blood urea nitrogen concentration in chronic heart failure. *J Am Coll Cardiol*. 2011;58:375-82. PMC3980479
b. **Testani JM**, Brisco MA, Turner JM, Spatz ES, Bellumkonda L, Parikh CR and Tang WH. Loop diuretic efficiency: a metric of diuretic responsiveness with prognostic importance in acute decompensated heart failure. *Circulation Heart failure*. 2014;7:261-70. PMC4386906
c. Griffin M Rao VS, Ivey-Miranda J, Fleming J, Mahoney D, Maulion C, Suda N, Siwakoti K, Ahmad T, Jacoby D, Riello R, Bellumkonda L, Cox Z, Collins S, Jeon S, Turner JM, Wilson FP, Butler J, Inzucchi SE**, Testani JM**. Empagliflozin in Heart Failure: Diuretic and Cardio-renal Effects. Circulation. 2020; Epub May 15. PMID: 32410463
d. Rao VS, Turner JM, Griffin M, Mahoney D, Asher J, Jeon S, Yoo PS, Boutagy N, Feher A, Sinusas A, Wilson FP, Finkelstein F and **Testani JM**. First in Human Experience with Peritoneal Direct Sodium Removal Using a Zero Sodium Solution: A New Candidate Therapy for Volume Overload. *Circulation*. 2020. Mar 31;141(13):1043-1053 PMID: 31910658

4. I have contributed to a better understanding of the measurement of and effects of decongestion on cardio-renal function and survival in heart failure. Some of my work in this domain has included the description of the remarkably poor fidelity of fluid output and change in weight as used in routine clinical practice and clinical trials of decompensated heart failure. Furthermore, our group developed a natriuretic prediction calculation technique, with a web based calculator (www.cardiorenalresearch.net), that can forecast the cumulative amount of sodium and fluid that will result from a loop diuretic just an hour after administration (the focus of the current application). My most significant contribution toward this area was my initial description of hemoconcentration as a tool to monitor decongestion and its association with worsening renal function but substantially improved outcomes. This work has motivated numerous studies validating our results, is highly cited with citations appearing in the *New England Journal of Medicine* and the *Lancet*, and has been followed by calls by prominent members of the heart failure community to use hemoconcentration in clinical care of heart failure patients (PMID: 24937157).

a. **Testani JM**, Brisco MA, Kociol RD, Jacoby D, Bellumkonda L, Parikh CR, Coca SG and Tang WH. Substantial Discrepancy Between Fluid and Weight Loss During Acute Decompensated Heart Failure Treatment. *Am J Med*. 2015;128:776-83.e, PMC4475432
b. **Testani JM,** Hanberg JS, Cheng S, Rao V, Onyebeke C, Laur O, Kula A, Chen M, Wilson FP, Darlington A, Bellumkonda L, Jacoby D, Tang WH and Parikh CR. Rapid and Highly Accurate Prediction of Poor Loop Diuretic Natriuretic Response in Patients With Heart Failure*. Circulation Heart failure.* 2016;9:e002370. PMC4741370
c. **Testani JM**, Chen J, McCauley BD, Kimmel SE and Shannon RP. Potential effects of aggressive decongestion during the treatment of decompensated heart failure on renal function and survival. *Circulation*. 2010;122:265-72. PMC3025294
d. **Testani JM**, Brisco MA, Chen J, McCauley BD, Parikh CR and Tang WH. Timing of hemoconcentration during treatment of acute decompensated heart failure and subsequent survival: importance of sustained decongestion. *J Am Coll Cardiol*. 2013;62:516-24. PMC3892152

5. A massive literature exists describing the relationship between hyponatremia and adverse outcomes in patients with heart failure. However, there is no direct mechanism by which the kidney can sense sodium, rather salt appears to be sensed by the kidney through the chloride anion. My group was the first to describe how hypochloremia is strongly associated with adverse outcomes, diuretic resistance, and neurohormonal activation. Notably, after accounting for serum chloride, serum sodium is no longer associated with adverse prognostic significance. We also have performed and published a pilot study where we administered a sodium free chloride salt, lysine chloride, to patients with diuretic resistance and heart failure. In that study we observed what appeared to be a significant improvement in volume status and downregulation of renal sodium chloride transporters. These early findings provide optimism that manipulating chloride homeostasis may be a viable therapeutic strategy, a hypothesis we intend to study further. We have contributed to a total of 8 published or in press manuscripts on chloride in HF at this point and are actively expanding our understanding of chloride homeostasis with an RO1 funded series of studies.
a. Grodin JL, Simon J, Hachamovitch R, Wu Y, Jackson G, Halkar M, Starling RC, **Testani JM*** and Tang WH*. Prognostic Role of Serum Chloride Levels in Acute Decompensated Heart Failure. *J Am Coll Cardiol*. 2015;66:659-66.*** Both corresponding authors** PMID: 26248993
b. **Testani JM**, Hanberg JS, Arroyo JP, Brisco MA, Ter Maaten JM, Wilson FP, Bellumkonda L, Jacoby D, Tang WH and Parikh CR. Hypochloraemia is strongly and independently associated with mortality in patients with chronic heart failure. *European journal of heart failure*. 2016;18:660-8, PMC5471359
c. Ter Maaten JM, Damman K, Hanberg JS, Givertz MM, Metra M, O'Connor CM, Teerlink JR, Ponikowski P, Cotter G, Davison B, Cleland JG, Bloomfield DM, Hillege HL, van Veldhuisen DJ, Voors AA and **Testani JM**. Hypochloremia, Diuretic Resistance, and Outcome in Patients With Acute Heart Failure. *Circulation Heart failure*. 2016;9. PMID: 27507112
d. Hanberg JS, Rao V, Ter Maaten JM, Laur O, Brisco MA, Perry Wilson F, Grodin JL, Assefa M, Samuel Broughton J, Planavsky NJ, Ahmad T, Bellumkonda L, Tang WH, Parikh CR and **Testani JM**. Hypochloremia and Diuretic Resistance in Heart Failure: Mechanistic Insights. *Circulation Heart failure*. 2016;9. PMC4988527

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

Ongoing Research Support

R01HL148354 **Testani (PI)** **07/2019 – 06/2023**

"Cardio-Renal Effects of Torsemide vs. Furosemide: A TRANSFORM-HF Mechanistic Sub-Study"

The overarching goal of this proposal is to rigorously characterize candidate mechanisms by which torsemide may influence outcome within the TRANSFORM-HF population.

R01HL139629 **Testani (PI)** **04/2018 – 02/2023**

"Mechanism and Effects of Manipulating Chloride Homeostasis in Heart Failure"

The goal of this work is to better understand the therapeutic impact and mechanism of action of chloride supplementation in heart failure.

R01HL128973 **Testani (PI)** **08/2015-05/2021**
"Diagnosing and Targeting Mechanisms of Diuretic Resistance in Heart Failure"
The goal is to understand the mechanisms of diuretic resistance in patients with heart failure and develop tools to rapidly detect and determine the mechanism underlying diuretic resistance. In no cost extension.

R21HL143092 **Testani (PI) Rao (MPI)** **08/2018 – 07/2021**
"*Urine galectin-3 as a biomarker of cardio-renal phenotype and prognosis"*
The goal of this work is to evaluate if urine galectin-3 indeed can serve as a marker of renal fibrosis and phenotype.

IIS2016-10532 (Boehringer Ingelheim) **Testani (PI)** **04/2017-08/2021**
"Empagliflozin in heart failure: Diuretic and cardio-renal effects"
The goal of this work is to better understand the cardio-renal and diuretic actions of the new class of anti-diabetic agents, the sodium glucose cotransporter (SGLT-2) inhibitors.

Abbott **Testani (PI)** **9/2016-05/2022**
"MOMENTUM III biorepository and core laboratory"
To systematically bank blood and urine from a multinational ventricular assist device trial for future cardio-renal and other biomarker investigations.

Abbott **Testani (PI)** **2/2020-02/2022**
"Mechanisms of Changes in Renal Function Following Continuous-Flow LVAD Support""
To characterize the trajectory of renal function post LVAD and rigorously investigate the mechanisms involved in changes in renal function over time during continuous-flow LVAD support.

3IVE LABS LLC **Testani (PI)** **11/2018 – 11/2020**
"Cardio-renal effects of negative renal pelvis pressure in experimental congestive heart failure"
The goal of this project is to develop a large animal model of venous congestion and investigate the ability of negative renal pelvis pressure therapy to rescue the phenotype.

Otsuka **Testani (PI)** **10/2018 – 10/2023**
"Positive Structural Remodeling of the Kidney through Vasopressin Antagonism- A TROUPER sub-study"
In this project we are utilizing urinary exosomes/microvesicles to investigate the effect of tolvaptan on renal tubular levels of sodium transporters.

Merck ISP 59625 **Testani (PI)** **7/2020 – 6/2022**
"Ertugliflozin in acute heart failure: Cardio-renal and diuretic effects"
The purpose of this study is to understand the value of add on SGLT-2 inhibition to acute heart failure and the mechanisms underlying the long term cardio-renal effects.

Bristol Myers Squibb **Testani (PI)** **4/2020 – 4/2022**
"Mechanistic insights into persistent congestion and cardio-renal interaction in heart failure"
The purpose of this study is to characterize the molecular drivers of diuretic resistance in our existing biorepositories of diuretic resistant heart failure patients.

BI ECR 1811 (Boehringer Ingelheim) **Testani (PI)** **12/2020-12/2023**
"Cardio-renal effects of empagliflozin in worsening heart failure"
The goal of this work is to better understand the impact of empagliflozin on patients with worsening heart failure and the underlying cardio-renal mechanisms leading to enhanced diuresis without over diuresis.

Selected Completed Research Support (Last 3 years):

U01FD005969 **Testani (PI) Prasad (MPI)** **09/2016 – 08/2017**
"Evaluating predictive methods and product performance in Healthy Adults for Pediatric Patients, Case Study: Furosemide"
The goal of this work is to better understand the effects of dosing liquids on furosemide absorption and develop a pharmacokinetic and pharmacodynamic model to predict the implications of different dosing liquids.