BIOGRAPHICAL SKETCH

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NAME: **Mohit Jain MD PhD**

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

POSITION TITLE: Assistant Professor of Medicine & Pharmacology

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
Boston University, Boston, MA	B.A.	05/97	Medical Sciences
Boston University School of Medicine, Boston, MA	Ph.D.	06/00	Mol and Cell Physiology
Boston University School of Medicine, Boston, MA	M.D.	05/03	Medicine
Brigham & Women's Hospital, Boston, MA	Resident	06/06	Internal Medicine
Brigham & Women's Hospital, Boston, MA	Fellow	06/11	Cardiology
Broad Institute of Harvard & MIT, Cambridge, MA	Postdoc	06/11	Metabolomics / Sys Bio

A. Personal Statement.

Dr. Jain is currently a tenure-track Assistant Professor of Medicine and Pharmacology at the University of California, San Diego School of Medicine. He obtained his M.D. and Ph.D. from Boston University School of Medicine, with his graduate work in physiology and metabolic biochemistry focusing on the enzyme, glucose-6-phosphate dehydrogenase and its role in cardiac physiology and redox metabolism. He subsequently performed training in clinical biomedicine including Internal Medicine and Cardiology at Brigham and Women's Hospital. His postdoctoral work was performed at the Broad Institute and Harvard Medical School Department of Systems Biology in the HHMI laboratory of Dr. Vamsi Mootha, developing methods for large scale LC-MS based metabolomics and integrative computational analysis, and the application of these approaches to define the role of metabolism in normal tissue physiology and human disease pathophysiology. Dr. Jain's work continues to focus on leveraging his background in physiology, biomedicine and mass spectrometry based metabolomics to understand global metabolic dysregulation and to identify metabolic target for disease intervention. Recent publications detailing his proficiency in mass spectrometry based metabolomics and large scale data handling include:

1. **Jain M*,** Nilsson R*, Sharma S, Madhusudhan N, Kitami T, Souza AL, Kafri R, Kirschner MW, Clish CB, Mootha VK. Metabolic profiling identifies a key role for glycine in rapid cancer cell proliferation. *Science*. 336:1040-4. 2012.
2. Nilsson R*, **Jain M***, Madhusudhan N, Gustafsson Sheppard N, Strittmatter L, Kampf C, Huang J, Asplund A, Mootha VK. Metabolic enzyme expression highlights a key role for MTHFD2 and the mitochondrial folate pathway in cancer. *Nature Commun.* 5:3128. 2014.
3. **Jain M**, Ngoy S, Sheth S, Swanson R, Rhee EP, Liao R, Clish CB, Mootha VK, Nilsson R. A systematic survey of lipids across mouse tissues. *Am J of Physiol Endocrinol Metab.* 306:E854-68. 2014.

B. Positions and Honors.

Professional Positions

1994 - 1997 **Boston University's Accelerated Seven-Year Liberal Arts / Medical Education Program**
Bachelor of Arts Medical Science - Summa Cum Laude

1997 - 2003 **Boston University School of Medicine**
Doctorate of Medicine - Magna Cum Laude / Alpha Omega Alpha

1998 - 2000 **Boston University School of Medicine, Division of Graduate Medical Sciences**
Doctorate of Philosophy – Molecular and Cellular Physiology

2003 - 2006 **Brigham & Women's Hospital, Harvard Medical School**
Internship / Residency in Internal Medicine – Department of Medicine

2006 - 2011 **Brigham & Women's Hospital, Harvard Medical School**
Fellow in Cardiovascular Medicine / Cardiometabolism – Cardiovascular Division

2008 - 2013 **The Broad Institute and the**
Department of Systems Biology, Harvard Medical School
Postdoctoral Research Fellow – Laboratory of Vamsi Mootha, M.D.

2011 - 2013 **Instructor of Medicine, Harvard Medical School**

2011 - 2013 **Associate physician, Cardiovascular Division, Brigham and Women's Hospital**

2013 - **Assistant Professor of Medicine and Pharmacology,**
University of California at San Diego School of Medicine

Honors and Awards

Boston University Distinguished Sophomore Award, 1995
Fellow Finalist - New England Cardiovascular Research Competition, 1997
American Heart Association Medical Student Research Fellowship, 1997
Alpha Epsilon Delta Award for Academic and Social Achievement, 1997
Elected to the Golden Key International Honour Society, 1997
Wotiz Award for Academic Excellence, 2000
Heart Failure Society of America Trainee Grant, 2000
Elected to the Association of Pathology Chairs Honors Society, 2001
Groupe Foundation Award, 2001
Boston University School of Medicine Chapter of Alpha Omega Alpha, 2002
Susan J Narajan MD/PhD Award, 2002
Boston University School of Medicine – Internal Medicine Award, 2003
NIH K08 Mentored Research Career Development Award, 2011
Lerner Research Award, 2012
William Guy Forbeck Scholar Award, 2012
American Society for Clinical Investigation Young Physician Scientist Award, 2014
ABSciex Innovation Advisory Board Member, 2014
Mary Kay Foundation Scholar Award, 2014
Sidney Kimmel Foundation for Cancer Research Scholar Award, 2014
V Foundation Scholar, 2014
Doris Duke Clinical Scientist Development Award, 2015

C. Contribution to Science.

Contributes to science are broadly spaced across technical and scientific accomplishments as described below. Full list of published work is available at the following URL:

http://www.ncbi.nlm.nih.gov/sites/myncbi/1rIqbHGoqBskz/bibliography/47443535/public/?sort=date&direction=ascending

I. Development of high throughput mass spectrometry based metabolomics / lipidomics

Mass spectrometry enables the comprehensive monitoring of small molecules in complex biospecimens, allowing for measure of endogenous small molecule metabolites as well as those small molecules that originate from dietary and environmental exposures. Such approaches, however, are limited by analytical time and corresponding expense. Dr. Jain has developed high throughput systems that enable the rapid screening of small molecules in complex specimens using mass spectrometry and applied these approaches to understand the role of metabolism in normal tissue physiology and disease pathobiology. This work has included detailing of the nutritional requirements of rapidly proliferating cancer cells as well as lipid metabolites present across mammalian tissues.

Jain M*, Nilsson R*, Sharma S, Madhusudhan N, Kitami T, Souza AL, Kafri R, Kirschner MW, Clish CB, Mootha VK. Metabolic profiling identifies a key role for glycine in rapid cancer cell proliferation. *Science*. 336:1040-4. 2012.

Jain M, Ngoy S, Sheth S, Swanson R, Rhee EP, Liao R, Clish CB, Mootha VK, Nilsson R. A systematic survey of lipids across mouse tissues. *Am J of Physiol Endocrinol Metab.* 306:E854-68. 2014.

Ivanisevic J, Elias D, Deguchi H, Averell PM, Kurczy M, Johnson CH, Tautenhahn R, Zhu Z, Watrous J, **Jain M**, Griffin J, Patti GJ, Siuzdak G. Arteriovenous Blood Metabolomics: A Readout of Intra-Tissue Metabostasis. *Sci Reports*. 5:12757. 2015.

Nilsson R and **Jain M**. Simultaneous tracing of carbon and nitrogen isotopes in human cells. *Mol Biosyst*. 2016 Apr 21. PMID: 27098229

II. Application of large scale data integration for biological understanding

The development of massive parallel biological assays has now enable the routine generation of massive data from a single experiment. Computational analysis of such data, however, has lagged and has limited the biological insight that is derived from such experimental approaches. Dr. Jain has developed approaches for the analysis of large scale data across multiple data modalities, including DNA sequencing, epigenetic modification, mRNA expression, small molecule metabolites, protein levels, compound screening, and functional RNAi genomic screening, in each case leveraging large scale data to drive biological understanding, with subsequent traditional experimental validation. In each instance, Dr. Jain has contributed to data analysis and experimental validation.

Calvo S, **Jain M**, Xie X, Sheth SA, Chang B, Goldberger OA, Spinazzola A, Zeviani M, Carr SA, Mootha VK. Systematic identification of human mitochondrial disease genes through integrative genomics. *Nat Genet*. 38:576-82. 2006.

Sharma S, Quintana A, Findlay G, Mettlen M, Baust B, **Jain M**, Nilsson R, Rao A, Hogan PG. An siRNA screen for NFAT activation identifies septins as coordinators of store operated Ca2+ entry. *Nature*. 499:238-42. 2013.

Nilsson R*, **Jain M***, Madhusudhan N, Gustafsson Sheppard N, Strittmatter L, Kampf C, Huang J, Asplund A, Mootha VK. Metabolic enzyme expression highlights a key role for MTHFD2 and the mitochondrial folate pathway in cancer. *Nature Commun*. 5:3128. 2014.

Knoechel B, Roderick JE, Williamson KE, Zhu J, Lohr JG, Cotton MJ, Gillespie SM, Fernandez D, Ku M, Wang H, Piccioni F, Silver SJ, **Jain M**, Pearson D, Kluk MJ, Ott CJ, Shultz LD, Brehm MA, Greiner DL, Gutierrez A, Stegmaier K, Kung AL, Root DE, Bradner JE, Aster JC, Kelliher MA, Bernstein BE. An epigenetic mechanism of resistance to targeted therapy in T-cell acute lymphoblastic leukemia. *Nature Gen.* 46:364-70. 2014.

III. Elucidating the metabolic basis for heart failure

The fundamental basis for the development of acquired heart failure remains controversial with numerous signaling processes implicated. While metabolic changes have been noted with the development of heart failure in cellular, small animal and human models, it is unclear if metabolic remodeling is a direct driver of cardiovascular dysfunction, and if so the mechanisms by which this occur. Dr. Jain has worked to understand the role of metabolism in the cardiovascular system, detailing the role for the enzyme glucose-6-phosphate dehydrogenase in cardiac redox metabolism and ischemic injury, as well as the role of metabolic remodeling in mediating *in vivo* cardiac dysfunction in mouse models of heart disease.

Jain M, Brenner DA, Cui L, Lim CC, Wang B, Pimentel DR, Koh S, Sawyer DB, Leopold JA, Handy DE, Loscalzo J, Apstein CS, Liao R. Glucose-6-phosphate dehydrogenase modulates cytosolic redox status and contractile phenotype in adult cardiomyocytes. *Circ Res*. 93:e9-16. 2003.

Jain M, Cui L, Brenner DA, Wang B, Handy DE, Leopold JA, Loscalzo J, Apstein CS, Liao R. Increased myocardial dysfunction after ischemia-reperfusion in mice lacking glucose-6-phosphate dehydrogenase. *Circulation*. 109:898-903. 2004.

Jain M, Jakubowski A, Cui L, Shi J, Su L, Bauer M, Guan J, Lim CC, Naito Y, Thompson JS, Sam F, Ambrose C, Parr M, Crowell T, Lincecum JM, Wang MZ, Hsu YM, Zheng TS, Michaelson JS, Liao R, Burkly LC. A novel role for tumor necrosis factor-like weak inducer of apoptosis (TWEAK) in the development of cardiac dysfunction and failure. *Circulation*. 119:2058-68. 2009.

Luongo TS, Lambert JP, Yuan A, Zhang X, Gross P, Song J, Shanmughapriya S, Gao E, **Jain M**, Houser SR, Koch WJ, Cheung JY, Madesh M, Elrod JW. The Mitochondrial Calcium Uniporter Matches Energetic Supply with Cardiac Workload during Stress and Modulates Permeability Transition. *Cell Rep*. 12:23-34. 2015

IV. Identification of mitochondrial glycine metabolism as a critical determinant of cancer cell proliferation.

Metabolic dysregulation stands among the key hallmarks that define a cancerous cell relative to its normal counterpart, though the specific metabolic pathways altered with cancer transformation and their biosynthetic and bioenergetic roles in promoting cancer cell phenotypes has remained unknown. Using mass spectrometry based metabolomics and integrative meta-analysis of metabolic enzyme expression across diverse tumor cell lines and tumor samples, Dr. Jain has comprehensively mapped the metabolic remodeling that occurs with cellular transformation. Moreover, through association of metabolic activities to cancer cell phenotypes, Dr. Jain has identified mitochondrial glycine metabolism and the enzyme methylenetetrahydrofolate dehydrogenase (MTHFD2) as cancer-specific metabolic processes that enable rapid cancer cell proliferation.

Jain M*, Nilsson R*, Sharma S, Madhusudhan N, Kitami T, Souza AL, Kafri R, Kirschner MW, Clish CB, Mootha VK. Metabolic profiling identifies a key role for glycine in rapid cancer cell proliferation. *Science*. 336:1040-4. 2012.

Featured Commentary:
Tomita M. Systems biology, metabolomics, and cancer metabolism. *Science*. 223: 990-91. 2012.
Chenette EJ. Glycine fuels cancer cells. *Nature Cell Biol*. 14:658. 2012
Villaneuva MT. Metabolism: craving for glycine. *Nature Rev Clinic Oncol*. 9:430. 2012.
Gordon EJ. Getting to the CORE of cancer metabolism. *ACS Chem Biol*. 7:1137. 2012.
Hampton T. Cancer cells' reliance on glycine. *JAMA*. 308:21. 2012.

Nilsson R*, **Jain M***, Madhusudhan N, Gustafsson Sheppard N, Strittmatter L, Kampf C, Huang J, Asplund A, Mootha VK. Metabolic enzyme expression highlights a key role for MTHFD2 and the mitochondrial folate pathway in cancer. *Nature Commun*. 5:3128. 2014.

Sheppard N, Jarl L, Mahadessian D, Strittmatter L, Schmidt A, Madhusudan N, Tegnér J, Lundberg E, Asplund A, **Jain M**, Nilsson R. The folate-coupled enzyme MTHFD2 is a nuclear protein and promotes cell proliferation. *Sci Reports*. 13;5:15029. 2015

D. Research Support

Ongoing

Kimmel Scholars Program (Jain) 7/1/14 – 6/30/16 Sidney Kimmel Foundation
Comprehensive reconstruction of global metabolic enzyme activity in-vivo in human cancer
The goal is to use systems biology to reconstruct *in vivo* metabolic enzyme flux (no overlap with proposal).

Mary Kay Scholar (Jain) 8/1/14 – 7/30/16 Mary Kay Foundation
Targeting MTHFD2 activity for breast cancer therapy
The goal is to test a small molecule inhibition of MTHFD2 in breast cancer models (no overlap with proposal).

V Foundation Scholar (Jain) 11/1/14 – 10/30/16 V Cancer Foundation
Systematic discovery of metabolic vulnerabilities in cancer
The goal is to identify cancer specific metabolic activities (no overlap with proposal).

R01 HL117861 Supplement (Mora) 9/15/14 – 6/30/16 NIH/NHLBI
HDL heterogeneity and function, statin therapy and CVD outcomes
The goal is to identify metabolite biomarkers of HDL function (no overlap with proposal).

R01 MH091448-06 (Okereke) 7/1/15 – 6/30/20 NIH/NIMH
Vital-depression endpoint prevention in the vitamin D and Omega-3 trial
The goal is to identify metabolite biomarkers of mental health related outcomes in human cohorts (no overlap).

AHA Genome-Phenome Award (Cheng) 1/1/15 – 12/30/17 American Heart Association
Chronic Inflammation, Cardiovascular Aging, and Longevity
The goal is to assess inflammatory markers as predictors of CV disease (no overlap with proposal).

R01 HL128135-01 (Liao) 4/1/15 – 3/31/20 NIH/NHLBI
Metabolic Underpinnings of AL Amyloid Cardiomyopathy
The goal is to identify diagnostic markers for amyloid cardiomyopathy (no overlap with proposal).

S10 Shared Instrument Grant (Jain) 4/17/15 – 4/16/16 NIH/Common Fund
RapidFire Mass Spectrometry System
The goal is to acquire a mass spectrometry system for biomedical metabolomics (no overlap with proposal).

Doris Duke Clinical Investigator 7/1/15 – 6/30/18 Doris Duke Foundation
Defining Environmental Determinants of Human Disease
The goal is to use mass spectrometry to identify environmentally derived metabolites that are associated with human disease in clinical cohorts (no overlap with proposal)

Tobacco Related Disease Research Program 7/1/15 – 6/30/18 TRDRP Foundation
Metabolic consequences of tobacco toxicants
The goal is to identify tobacco related toxicants associated with human disease (no overlap with proposal)

Completed

5U01CA138962-06 (Manson) 2/1/15 – 5/30/15 NIH/NCI
Vitamin D and Omega-3 Trial (VITAL)
The goal is to identify metabolite predictors of vitamin D and Omega-3 effects in the VITAL trial.

1K08HL107451 (Jain) 4/22/11 – 3/31/16 NIH/NHLBI
A Systems Approach to Metabolic Dyregulation in the Heart
The goal is to understand metabolic dysregulation in heart failure (no overlap with proposal).