BIOGRAPHICAL SKETCH

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NAME	POSITION TITLE
Srinivasan Dasarathy	Professor of Medicine
eRA COMMONS USER NAME dasaras	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Jawaharlal Institute of Post Graduate Medical Education and Research; Pondicherry, India	MB, BS	1977-1983	Medicine
	M.D.	1984-1987	Internal Medicine
All India Institute of Medical Sciences; New Delhi	D.M.	1987-1990	Gastroenterology

A. Personal Statement.

Dr. Dasarathy is a transplant hepatologist with a joint appointment with the Department of Pathobiology at the Lerner Research Institute in the Cleveland Clinic with a long-standing interest in determining the mechanisms of skeletal muscle loss in liver disease and has extensive experience with human, animal and in vitro cell models. Dr. Dasarathy is a clinical hepatologist with commitment to clinical care of patients with end stage liver disease as well as being a co investigator in the NIH funded Non Alcoholic Steatohepatitis (NASH) network, a co investigator in the NIAAA funded Novel Mechanisms in Alcoholic Hepatitis network and a PI of a research component of the NIAAA P50 Cleveland Alcohol Center. He has been actively involved in the development of the current submission of the Clinical Translational grant for the alcoholic hepatitis network and will be the PI on this submission for the Cleveland site.

He leads the liver transplant nutrition clinic at the Cleveland Clinic and has also established an inpatient nutrition program for the management of hospitalized cirrhotic patients. His commitment to and interest in research in alcohol related disorders are shown by his continued work in the field of skeletal muscle loss in alcoholic liver disease requiring interdisciplinary interactions. He also coauthored the recent EASL and ESPEN guidelines on Nutrition and Liver Diseases that will be published early 2018.

He discovered novel signaling pathways and regulatory mechanisms in the skeletal muscle following portacaval anastomosis in the rat and ethanol feeding in mice. He has performed detailed *in vivo* kinetic and metabolic studies in both rodents and humans and shown dysregulated autophagy in the skeletal muscle of patients with alcoholic liver disease and mice fed alcohol. He has used a wide variety of molecular, cellular and animal based techniques (e.g. cloning, mutagenesis, Western blotting, microscopy, metabolic tracers, *in-vivo* transfections, tissue specific inducible knockout transgenic mice and several models of ethanol induced muscle atrophy) and generated reagents to evaluate the signaling responses to ethanol induced skeletal muscle loss. He showed that ethanol is directly metabolized in the skeletal muscle and activates upstream regulators of autophagy. He also generated a number of reporter assays and tagged constructs for myostatin, AMPK and mTORC1 activator, Ras homologue enriched in brain (RhEB). He discovered that alcohol-feeding results in lower tricarboxylic acid cycle intermediates in the skeletal muscle and showed increased mitochondrial fission in mice fed ethanol. The PI also has cross-disciplinary interactions with well established investigators on ethanol induced molecular and metabolic changes as well as mitochondrial studies.

In addition, Dr. Dasarathy has also trained a number of new investigators, both clinical and basic, in the field of alcoholic liver disease who are in the process of transitioning to be independent investigators. His recent work on modeling the prevalence and incidence of alcoholic liver disease emphasizes the impact of alcohol abuse on the future trends in liver disease.

B. Positions and Employment

7/90 – 1/92 Pool Officer, Central Scientific Research Institute, New Delhi, India
1/92 – 7/97 Assistant Professor, Department of Gastroenterology, All India Institute of Medical Sciences, New Delhi, India

7/97 – 6/99	Internal Medicine Resident, MetroHealth Medical Center
7/99 - 6/01	Gastroenterology Fellow, MetroHealth Medical Center
7/01 – Present	Assistant Professor, Department of Medicine, Case Western Reserve University
7/06 – Present	Staff, Department of Gastroenterology, Cleveland Clinic Foundation

Other Experience

2001-present-	Reviewer for Hepatology, Journal of Hepatology, Liver Transplantation, American Journal of Gastroenterology, Journal of Clinical Gastroenterology, American Journal of Physiology.
2001- present	Member AASLD, AGA
2007-2010	Member, Education Committee, American Association of Study of Liver Diseases
2010-2011	Member, International Relations Committee, American Association of Study of Liver Diseases
2010-2019	Special Government Employee, Food and Drugs Administration, Clinical Trials Section
2012-	Review Panel American Heart Association.

Honors

7/84	**During Undergraduate Education**: Rajah of Panagal Medal for the best outgoing graduate of the University of Madras; Dr. A. Lakshmanaswamy Mudaliar Medal for the best graduate in Obstetrics and Gynecology; Dr. A.C. Asirwada Nadar Memorial Prize for General Surgery; Dr. (Miss) Govindarajula Prize for the best graduate in Internal Medicine; Prof. (Dr.) Lalitha Kameswaran Prize for the best graduate in pharmacology
10/90	Awarded the Searle Best Paper Award at the Annual Conference of the Indian Society of Gastroenterology, for the paper entitled " Prognostic value of serial fibronectin and complement in fulminant hepatitis".
12/94	Dr Dharamvir Dutta Memorial Oration for the research in the development of therapy of portal hypertension
1997	Dr. SS Misra award National Academy of Medical Sciences, India Hoechst Om Prakash award by the Indian Society of Gastroenterology
1998	Peter Adam Award for Research; MetroHealth Medical Center

C. Selected peer-reviewed publications: complete list of Published work in My Bibliography: https://www.ncbi.nlm.nih.gov/myncbi/collections/bibliography/42135789/?reload=addfrompubmed&sortby=date&groupby=citation_type

Demonstrate that alcoholic liver disease is of high clinical significance

The impact of alcohol use and abuse on the prevalence of alcoholic liver disease is likely to increase over the next decade making al. Additionally, we evaluated the interobserver variability of histological characteristics in alcoholic hepatitis. The PI also collaborates with other members of the P50 Cleveland Alcohol Center.

Guirguis J, Chhatwal J, Dasarathy J, Rivas J, McMichael D, Nagy LE, McCullough AJ, **Dasarathy S**. Clinical Impact of Alcohol-Related Cirrhosis in the Next Decade: Estimates Based on Current Epidemiological Trends in the United States. Alcohol Clin Exp Res. 2015 Nov;39(11):2085-94. doi: 10.1111/acer.12887. Epub 2015 Oct 25. PubMed PMID: 26500036; PubMed Central PMCID: PMC4624492

Horvath B, Allende D, Xie H, Guirguis J, Jeung J, Lapinski J, Patil D, McCullough AJ, Dasarathy S, Liu X. Interobserver Variability in Scoring Liver Biopsies with a Diagnosis of Alcoholic Hepatitis. Alcohol Clin Exp Res. 2017 Sep;41(9):1568-1573. doi: 10.1111/acer.13438. Epub 2017 Jul 28. PubMed PMID: 28654190.

Dasarathy S, Brown JM. Alcoholic Liver Disease on the Rise: Interorgan Cross Talk Driving Liver Injury. Alcohol Clin Exp Res. 2017 May;41(5):880-882. doi:10.1111/acer.13370. Epub 2017 Apr 10. PubMed PMID: 28295407; PubMed Central PMCID: PMC5405002.

Demonstrate that autophagy causes skeletal muscle loss in alcoholic liver disease.

A number of mechanisms contribute to sarcopenia including impaired protein synthesis and increased autophagy. The PI has conducted studies in patients with cirrhosis, animal models and *in vitro* studies in myotubes to demonstrate that ethanol causes sarcopenia by dysregulated autophagy. These studies *provide*

preliminary evidence in support of the proposed studies, the availability of the necessary reagents and models as well as the research team in place for successful completing of the proposed aims.

1. Tsien C, Davuluri G, Singh D, Allawy A, Ten Have GA, Thapaliya S, Schulze JM, Barnes D, McCullough AJ, Engelen MP, Deutz NE, **Dasarathy S**. Metabolic and molecular responses to leucine-enriched branched chain amino acid supplementation in the skeletal muscle of alcoholic cirrhosis. Hepatology. 2015 Jun;61(6):2018-29. doi: 10.1002/hep.27717. Epub 2015 Feb 27. PubMed Central PMCID: PMC4441611
2. Thapaliya S, Runkana A, McMullen MR, Nagy LE, McDonald C, Naga Prasad SV, **Dasarathy S**. Alcohol-induced autophagy contributes to loss in skeletal muscle mass. Autophagy. 2014 Apr;10(4):677-90. doi: 10.4161/auto.27918. Epub 2014 Jan 31. PubMed PMID: 24492484; PubMed Central PMCID: PMC4091154
3. Stern RA, Ashwell CM, **Dasarathy S**, Mozdziak PE. The effect of hyperammonemia on myostatin and myogenic regulatory factor gene expression in broiler embryos. Animal. 2015 Feb 18:1-8. [Epub ahead of print] PubMed PMID: 25689990. PMC4491445.
4. Qiu J, Tsien C, Thapalaya S, Narayanan A, Weihl CC, Ching JK, Eghtesad B, Singh K, Fu X, Dubyak G, McDonald C, Almasan A, Hazen SL, Naga Prasad SV, **Dasarathy S**. Hyperammonemia-mediated autophagy in skeletal muscle contributes to sarcopenia of cirrhosis. Am J Physiol Endocrinol Metab. 2012 Oct 15;303(8):E983-93. doi: 10.1152/ajpendo.00183.2012. Epub 2012 Aug 14. PMCID: PMC3469607

Develop tools and reagents and characterize models to examine the mechanisms of sarcopenia in liver disease

The PI has been consistently working on understanding signaling abnormalities focusing on both skeletal muscle protein synthesis and skeletal muscle autophagy in liver disease. Studies on signaling pathways, translating the signaling abnormalities to functional consequences have shown that both ethanol and hyperammonemia due to cirrhosis contribute to a well characterized and defined transcriptional program that ultimately results in sarcopenia or loss of skeletal muscle mass.

1. Qiu J, Thapaliya S, Runkana A, Yang Y, Tsien C, Mohan ML, Narayanan A, Eghtesad B, Mozdziak PE, McDonald C, Stark GR, Welle S, Naga Prasad SV, **Dasarathy S**. Hyperammonemia in cirrhosis induces transcriptional regulation of myostatin by an NF-κB-mediated mechanism. Proc Natl Acad Sci U S A. 2013 Nov5;110(45):18162-7. doi: 10.1073/pnas.1317049110. Epub 2013 Oct 21. PMCID: PMC3831479.
2. **Dasarathy S**, Muc S, Runkana A, Mullen KD, Kaminsky- Russ K, and McCullough AJ. Alteration in body composition in the portacaval anastamosis rat is mediated by increased expression of myostatin. Am J Physiol Gastroint Liver Phys. 2011; 301: G731-8.
3. Dasarathy S, Muc S, Hisamuddin K, Edmison JM, Dodig M, McCullough AJ, Kalhan SC. Altered expression of genes regulating skeletal muscle mass in the portacaval anastomosis rat. Am J Physiol Gastrointest Liver Physiol. 2007 Apr;292(4):G1105-13. PubMed PMID: 17185634
4. Dasarathy S, Mullen KD, Dodig M, Donofrio B, McCullough AJ. Inhibition of aromatase improves nutritional status following portacaval anastomosis in male rats. J Hepatol. 2006 Aug;45(2):214-20. Epub 2006 Apr 5. PubMed PMID: 16684577.

Studies in patients with liver disease

Prior to the PI contributions, the clinical literature did not have a clear definition of malnutrition in liver disease and this was a contributing factor to the lack of therapies. The PI used the term sarcopenia in liver disease after careful deliberation because the term sarcopenia only refers to muscle loss even though it is used most often in the context of aging. However, there is now nearly universal acceptance of the term sarcopenia in liver disease due to its high prevalence and clinical significance. This is a relatively new area and the PI has commented on the *significance of the problem* in a number of invited reviews in high impact publications. The focus of the proposed studies is to directly translate many of the PI's recent discoveries on the mechanisms of skeletal muscle loss in cirrhosis. The PI has conducted a number of human studies including tracer kinetics, whole body metabolism, body composition etc.

1. Issa D, Alkhouri N, Tsien C, Shah S, Lopez R, McCullough A, **Dasarathy S**. Presence of sarcopenia (muscle wasting) in patients with nonalcoholic steatohepatitis. Hepatology. 2014 Jul;60(1):428-9. doi: 10.1002/hep.26908. Epub 2014 May 27. PubMed PMID: 24990106.
2. Tsien C, Garber A, Narayanan A, Shah SN, Barnes D, Eghtesad B, Fung J, McCullough AJ, **Dasarathy S**. Post-liver transplantation sarcopenia in cirrhosis: a prospective evaluation. J Gastroenterol Hepatol. 2014 Jun;29(6):1250-7. doi:10.1111/jgh.12524. PubMed PMID: 24443785; PubMed Central PMCID: PMC4024321.
3. Glass C, Hipskind P, Tsien C, Malin SK, Kasumov T, Shah SN, Kirwan JP, **Dasarathy S**. Sarcopenia and a Physiologically Low Respiratory Quotient in Cirrhotic Patients: A Prospective Controlled Study. J Appl Physiol. 2013 Jan 3. [Epub ahead of print] PubMed PMID: 23288550.
4. Tsien C, Shah SN, McCullough AJ, **Dasarathy S**. Reversal of sarcopenia predicts survival after a transjugular intrahepatic portosystemic stent. Eur J Gastroenterol Hepatol. 2013 Jan;25(1):85-93. doi: 10.1097/MEG.0b013e328359a759.PubMed PMID: 23011041.

Studies to demonstrate expertise in metabolic and tracer studies.

The PI has performed a number of metabolic studies in human subjects using tracers to quantify the kinetics of amino acids and fatty acids and metabolites. The published studies show that the PI has the necessary expertise to perform studies to quantify metabolic intermediates and assays using gas and liquid chromatography-mass spectrometry.

1. **Dasarathy S**, Yang Y, McCullough AJ, Marczewski S, Bennett C, Kalhan SC. Elevated hepatic fatty acid oxidation, high plasma fibroblast growth factor 21, and fasting bile acids in nonalcoholic steatohepatitis. Eur J Gastroenterol Hepatol. 2011 May;23(5):382-8.
2. **Dasarathy S**, Kasumov T, Edmison JM, Gruca LL, Bennett C, Duenas C, Marczewski S, McCullough AJ, Hanson RW, Kalhan SC. Glycine and urea kinetics in non-alcoholic steatohepatitis in human: effect of intralipid infusion. *Am J Physiol Gastrointest Liver Physiol* 2009 Sep;297(3):G567-G575.
3. Kumar A, Davuluri G, Silva RNE, Engelen MPKJ, Ten Have GAM, Prayson R, Deutz NEP, Dasarathy S. Ammonia lowering reverses sarcopenia of cirrhosis by restoring skeletal muscle proteostasis. Hepatology. 2017 Jun;65(6):2045-2058. doi: 10.1002/hep.29107. Epub 2017 Apr 28. PubMed PMID: 28195332; PubMed Central PMCID: PMC5444955
4. Davuluri G, Allawy A, Thapaliya S, Rennison JH, Singh D, Kumar A, Sandlers Y, Van Wagoner DR, Flask CA, Hoppel C, Kasumov T, Dasarathy S. Hyperammonaemia-induced skeletal muscle mitochondrial dysfunction results in cataplerosis and oxidative stress. J Physiol. 2016 Dec 15;594(24):7341-7360. doi:10.1113/JP272796. Epub 2016 Oct 23. PubMed PMID: 27558544; PubMed Central PMCID: PMC5157075.

C. Research Support

Ongoing Research Support

UO1 DK 061732. 2014-2019.
NIH
Clinical Research Network in Non Alcoholic Steatohepatitis (NASH)
The goal of this study is to examine the natural course of non alcoholic fatty liver disease and study the therapeutic effects of novel agents.
Role: Co Principal Investigator

UO1 AA021893 2012-2018
NIH
Clinical Research Network in Alcoholic Steatohepatitis.
To identify the natural history and examine novel therapies for sever alcoholic hepatitis.
Role. Co-investigator

9RO1 GM119174 2017-2021
Mechanisms of Malnutrition in Cirrhosis

The goal of these ongoing studies is to determine the molecular mechanisms of skeletal muscle loss in cirrhosis.
Role PI

P50 AA024333 PI Laura Nagy 2016-2021

Sarcopenia of alcoholic liver disease: Regulation of skeletal muscle autophagy by alcohol
The goal of these studies is to identify the molecular mechanisms by which ethanol induced mitochondrial dysfunction results in ROS mediated autophagy and to develop leucine enriched amino acids to reverse sarcopenia in alcoholic cirrhosis.
Role PI

R21 AR 71046 PI Davuluri 2017-2019
Hyperammonemia reduces skeletal muscle protein synthesis via a beta catenin-cMYC mediated impaired ribosomal biogenesis.
The goal of these exploratory studies is to determine how hyperammonemia in cirrhosis results in ribosomal dysfunction and impaired mRNA translation
Role. Co PI

Recently Completed Research Support

2 UO1 DK 061732-08. 2009-2014
NIH
Clinical Research Network in Non Alcoholic Steatohepatitis (NASH)
The goal of this study is to examine the natural course of non alcoholic fatty liver disease and study the therapeutic effects of novel agents.
Role: Co Investigator 20% effort

RO1 DK083414
NIH 2011-2016
Mechanisms of malnutrition in cirrhosis with portosystemic shunting
The goals of this study are to examine the mechanisms of skeletal muscle loss in cirrhosis using a combination of tracer methodology and molecular biology tools in vivo and in vitro cell systems.
Role: PI 20% effort

R21 AA 022742 2014-2016
Alcohol induces muscle autophagy by a novel AMPK independent PI3K mediated mechanism.
The goal of this study is to identify novel regulation of skeletal muscle autophagy by alcohol and acetaldehyde mediated protein adducts that induce autophagy and sarcopenia in alcoholic liver disease.
Role: Principal investigator 5% effort