BIOGRAPHICAL SKETCH

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NAME: Uma Sundaram, M.D.

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

POSITION TITLE: Professor of Medicine, Biochemistry, Microbiology and Immunology

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
The Johns Hopkins University, Baltimore, MD	B.E.S.	06/1980	Bio Engineering
The Medical College of Ohio, Toledo, OH	M.D.	06/1983	Medicine

A. Personal Statement:

The goals of the Marshall University School of Medicine's (MUSOM) Obesity Research Center of Appalachia (ORCA; https://jcesom.marshall.edu/research/orca) are to promote obesity and related diseases research emphasizing cellular transport by the next generation of biomedical investigators and enhance the necessary infrastructure to accomplish this at MUSOM.

My training and career to date has ideally positioned me to serve as the Principal Investigator and Program Director of the Center of Biomedical Research Excellence (COBRE) ORCA. I have demonstrated a commitment to basic, clinical and translational research since my undergraduate training in Bioengineering at Johns Hopkins University during which my research at the National Institutes on Aging led to multiple co-authored publications in blood brain barrier drug entry and distribution modeling. Since graduating from the Medical College of Ohio, completing my residency in internal medicine at the University of Michigan and gastroenterology subspecialty training at Yale University, I have been actively involved in patient care, teaching and research funded by NIH, AGA, AHA, and CCFA. Over the years investigator initiated and multi center prospective clinical studies have been in Hepatitis C, inflammatory bowel disease, peptic ulcer disease and Barrett's esophagus. The basic and translational research has been funded by NIH RO1s and currently an NIH RO1 (DK 67420) to study regulation of glucose and Na homeostasis as it pertain to diseases such as obesity and hypertension. Most recently, I was the Principal Investigator of the newly funded NIGMS IDeA Clinical Translational Research (CTR) U54 grant (1 U54 RR033567-01) at the West Virginia Clinical and Translational Science Institute (WVCTSI).

I have been equally active in education of healthcare professionals. I established and served as the Director of the Digestive Disease Fellowship Training Program at West Virginia University (WVU), the only GI fellowship training program in WV. Over the past 16 years, 33 MDs, MD/PhDs or PhDs have received training in my laboratory as well as 27 medical residents and gastroenterology fellows who have received clinical research training under my tutelage. All of these trainees have presented studies at national meetings; many have published in peer reviewed journals and have academic appointments.

Administratively, I have held numerous leadership positions over the years. More recently, from 2008 to 2013, I served as Assistant Vice President in WVU Health Science Center (HSC) and was responsible for assessing, coordinating, and promoting research in all clinical departments in the Schools of Medicine, Nursing, Dentistry, and Pharmacy at WVU. As the Founding Director of the WVCTSI since its inception in 2008, my mission had been to bring together and promote collaborative approaches across many departments, schools, medical institutions and clinical enterprises in WV to promote clinical translational research and education. As the principle investigator, I am proud to say that we succeeded

in obtaining the NIGMS IDeA CTR U54 in 2012. I have learned a lot from these different experiences from building high performing cross cutting teams, to effectively managing and communicating to broad constituencies, to developing, articulating and executing a vision for clinical and translational research.

MUSOM is at the epicenter of numerous health care disparities in one of the poorest regions of the United States (Central and Southern Western WV, Eastern KY and Southeastern OH). Most of healthcare disparities here are a result of rampant obesity and related diseases. Given my interest in obesity related biomedical research and experience in organizing multi-institutional programmatic approaches to address health care disparities, I was recruited to MUSOM as the Vice Dean in 2013. I was charged with developing resources, facilities, and personnel to collaboratively address obesity as a focus of research at MUSOM. First we formed the Appalachian Clinical and Translational Science Institute at Marshall University (ACTSI; http://jcesom.marshall.edu/research/actsi) to advance research and education to improve the health of Central Appalachia. Then we formed the Department of Clinical and Translational Sciences (http://jcesom.marshall.edu/research/dcts) to provide an academic home for ACTSI and for the Univ. of Kentucky/Marshall Univ. Clinical and Translational Science Award (UL1TR00011719; MU PI: Uma Sundaram/UK PI: Phil Kern). Based on institutional junior investigators interest and senior investigators strength in obesity research at MUSOM and its ideal location to address this problem it became clear a center of excellence was needed. Thus, we formed ORCA and are applying for the COBRE to promote obesity and related diseases research emphasizing cellular transport by the next generation of biomedical investigators and enhance the necessary infrastructure to accomplish this at MUSOM. This in conjunction with the $8 million commitment by MUSOM will be a significant start to address this problem which would not only benefit WV, but also all other rural areas of this country. I believe my education, training, academic career to date and my commitment to basic, clinical and translational research, mentorship of trainees, and numerous administrative leadership positions over the years have ideally prepared me for the challenges of directing the COBRE ORCA.

B. Positions and honors

Positions:

1989-1995	Assistant Professor of Internal Medicine Yale University School of Medicine
1995-2001	Tenured Associate Professor of Internal Medicine and Physiology & Cell Biology Associate Director, Division of Digestive Diseases Ohio State University College of Medicine
2001-2004	Professor of Medicine with Unlimited Tenure Professor of Pharmacology and Physiology Chief, Digestive and Liver Diseases Unit University of Rochester Medical Center
2004 – 2013	Professor of Medicine, Microbiology, Immunology and Cell Biology Chief, Section of Digestive Diseases (-- 2012) Director, WVU Inflammatory Bowel Disease Center Director, WVU Digestive Disease Fellowship Program West Virginia University School of Medicine
2008 – 2013	Assistant Dean, WVU School of Medicine Assistant Vice President, WVU Health Science Center Founding Director, WV Clinical and Translational Science Institute
2013 –	Vice Dean Chairman, Department of Clinical and Translational Sciences Director, Appalachian Clinical and Translational Science Institute Joan C Edwards School of Medicine, Marshall University

Recent Honors:

2001-2	NIH, NIDDK – GMA 2 Study Section Ad Hoc Member
2004	AGA, Roche Research Scholar Award Committee, Member
2001-4	AGA, Research Scholar Award Committee Member
2002	NIH, Nutrition Study Section Ad Hoc Member
2002	NIH, ZDK1 GRB-6 Study Section Member
2002-6	NIH, NIDDK – CIGP Study Section Member
2002-4	AGA, Elsevier Research Initiative Award Chairman

2004 NIH, NIDDK – GMPB Study Section Ad Hoc Member
2004-5 VA Merit Review Committee Member
2007 Dean's Award for Excellence in Research, WVU School of Medicine
2007 NIH ZDK1 GRB-R M2 Study Section Member
2008 NIH ZDK1 GRB-G J1 Study Section Member
2008 NIH ZRG1-DIG C Study Section Member
2009 NIH CMBK ARRA SBIR Study Section
2009-10 VA Merit Review, Gastroenterology Study Section
2009 ZRG1 DKUS-E Study Section Member
2010 NIH NIDDK PPG Study Section
2010 NIH ZDK1 GRB-6 (J1) Study Section Member
2011 ZRG1 DKUS-C Study Section Member
2011 NIH ZDK1 GRB-N (O5) Study Section Member
2013 NIH, NIGMS IDeA CTR U54 Study Section Member
2013 NIH, CTSA Study Section Member
2013 National External Advisory Board, Research Centers in Minority Institutions Translational Research Network
2013 NIH, ZTR1 CG-1 01 Study Section Member
2014 NIH, NIAID, ZAI1 LG-M Study Section Member
2015 NIH, NCATS, ZTR1 CI-3 (01) Study Section Member
2015 NIH, NCATS, ZTR1 CI-8 (01) Study Section Member
2015 NIH, NIDDK, ZRG1 DKUS-N (10) Study Section Member
2015 NIH, NIDDK, ZTR1 CI-8 (01) Study Section Member

C. Contributions to Science:

1. **In the mammalian small intestine villus cells absorb and crypt cells secrete.** In the late 1980s technology did not exist to separate viable and pure villus and crypt cells from the intestine. Our lab perfected this technique and subsequently demonstrated that in isolated intact villus cells and in brush border membrane (BBM) prepared from these cells that coupled NaCl occurs via the dual operation of Na:H and Cl:HCO3 exchange on the BBM. In contrast, the crypt cells only had Cl:HCO3 exchange on the BBM and thus are not capable of coupled NaCl absorption. *Effect of Secretogogues and Absorptagogue.* We demonstrated that coupled NaCl was inhibited by serotonin by inhibiting Cl:HCO3, but not Na:H exchange. Unlike serotonin, whose effects are mediated by calcium, forskolin, whose effects are mediated via cAMP, reduced coupled NaCl absorption by inhibiting Na:H, but not Cl:HCO3 exchange on the BBM of villus cells. In contrast, in crypt cells both serotonin and forskolin stimulated basolateral membrane (BLM) Na:H exchange. This stimulation alkalinizes the cell, which may stimulate the BBM Cl:HCO3 exchanger and produce HCO3 secretion by the crypt cells. In contrast, an absorptagogue, clonidine, enhanced coupled NaCl absorption by stimulating Na:H, but not Cl:HCO3 exchange on the BBM of villus cells. Also, clonidine inhibited BLM NHE1 in crypt cells resulting in the acidification of these cells, which would subsequently inhibit the BBM Cl:HCO3 exchanger resulting in the inhibition of HCO3 secretion. Thus, these studies illustrated that villus and crypt cells respond uniquely to secretogogues, and absorptagogues.

- Sundaram U, Knickelbein RG, Dobbins JW. Mechanism of intestinal secretion. Effect of serotonin on rabbit ileal crypt and villus cells. *The Journal of Clinical Investigation*. 1991;87:743-746.
- Sundaram U, Knickelbein RG, Dobbins JW. Mechanism of intestinal secretion: effect of cyclic AMP on rabbit ileal crypt and villus cells. *Proceedings of the National Academy of Sciences of the United States of America*. 1991;88:6249-6253.
- Sundaram U. Mechanism of intestinal absorption. Effect of clonidine on rabbit ileal villus and crypt cells. *The Journal of Clinical Investigation*. 1995;95:2187-2194

2. **Unique regulation of NaCl absorption in the chronically inflamed intestine.** At the time it was held that once chronic intestinal inflammation has occurred, altered epithelial cell function resulting in malabsorption and diarrhea are fait accompli. However, we hypothesized that malabsorption and diarrhea are not the irrevocable end results of chronic intestinal inflammation, but actively regulated processes. Thus, to study the regulation of electrolyte and nutrient malabsorption, we developed a mammalian animal model of chronic small intestinal inflammation from which we can isolate relatively

pure and viable villus and crypt cells. The rabbit model of chronic small intestinal inflammation has many of the characteristics of human inflammatory bowel disease (IBD). First, we determined that coupled NaCl absorption in villus cells is diminished secondary to the inhibition of Cl:HCO3 (DRA) but not Na:H exchange (NHE3). Subsequently, we determined that the inhibition of Cl:HCO3 exchange in villus cell BBM is due to decreased affinity for Cl and HCO3, rather than altered transporter numbers. Finally, since Cl channels (CFTR) have shown to affect the functioning of Cl:HCO3 in epithelial cells, we demonstrated that CFTR expression is unaffected in the chronically inflamed rabbit intestine. To determine if these changes in the chronically inflamed intestine are dynamic regulatable processes, we treated rabbits with the broad spectrum immune modulator, methylprednisolone, which indeed reversed the inhibition of Cl:HCO3 exchange and thus the inhibition of NaCl in the chronically inflamed intestine. These data indicate that the inhibition of coupled NaCl in the chronically inflamed intestine is secondary to the inhibition of Cl:HCO3, but not Na:H exchange on the BBM of villus cells and that it is actively regulated by immune inflammatory mediators.

- Sundaram U, West AB. Effect of chronic inflammation on electrolyte transport in rabbit ileal villus and crypt cells. *The American Journal of Physiology*. 1997;272:G732-741.
- Coon S and U Sundaram. Mechanism of glucocorticoid-mediated reversal of inhibition of Cl:HCO3 exchange during chronic ileitis. *American Journal of Physiology*, 2000;278:G570-G577.

3. **Direct reciprocal regulation of villus cell BBM NHE3 and SGLT1.** In intestinal physiology whether any two epithelial cell BBM transporters may directly regulate the functioning of each other is a very novel concept. To test this novel hypothesis, intestinal epithelial cells (IEC-18 cells) were transfected with siRNA for NHE3 or SGLT1. In NHE3 silenced cells, as expected NHE3 activity, mRNA and BBM protein diminished significantly. However, in these cells, SGLT1 activity increased significantly. NHE3 siRNA stimulation of SGLT1 is selective, as Na-amino acid co-transport (ASCT1) was unaffected. Na-K-ATPase was also not affected. The mechanism of SGLT1 stimulation was due to an increase in BBM SGLT1. Thus, these data indicate that a reduction in BBM NHE3 directly stimulates SGLT1. In SGLT1 silenced, SGLT1 activity, mRNA and BBM protein decreased significantly. However, in these cells, NHE3 activity increased significantly. The mechanism of NHE3 stimulation was secondary to an increase in BBM NHE3. Thus, these data demonstrated that a reduction in BBM SGLT1 directly stimulates NHE3. In conclusion, for the first time, this study demonstrated that intestinal epithelial cell BBM NHE3 and SGLT1 may directly regulate the expression and function of each other.

- Coon S, Kekuda R, Saha P, et al. Reciprocal regulation of the primary sodium absorptive pathways in rat intestinal epithelial cells. *American Journal of Physiology Cell physiology*. 2011;300:C496-505.

4. **Unique distribution and selective regulation of glutamine absorption in the normal and chronically inflamed mammalian small intestine.** The amino acid glutamine is the primary nutrient for the intestinal enterocytes and thus, critical for the health of the epithelium. However, how glutamine is assimilated in the normal and/or in the chronically inflamed mammalian small intestine (e.g. IBD) was not known. Glutamine is primarily absorbed via Na-glutamine co-transport (NGcT) on the BBM of enterocytes. We have demonstrated that B^0AT1 or SLC6A19 mediates NGcT on the BBM of villus cells. And in paradigm shift, we demonstrated the only nutrient absorptive process on the BBM of crypt cells, specifically SN2 or SLC38A5, which mediates NGcT in these cells. Further, in the rabbit model of chronic intestinal inflammation resembling IBD we demonstrated that NGcT in total was reduced. This net inhibition was a sum of B^0AT1 inhibition in villus cells and SN2 stimulation in crypt cells. The mechanism of inhibition of B^0AT1 was transcriptional, specifically secondary to a reduction in the number of co-transporters in the villus cell BBM. In contrast, the mechanism of stimulation of SN2 in crypt cells was post-translational, specifically secondary to an increase in the affinity for glutamine from the chronically inflamed intestine. Thus, glutamine assimilation which occurs via distinct transporters in villus and crypt cells is uniquely regulated in the chronically inflamed intestine. Glucocorticoid treatment reversed the alterations indicating that immune inflammatory mediators known to be produced in the chronically inflamed intestine may be responsible for these unique alterations in glutamine absorption.

- Arthur S, Saha P, Sundaram S, Kekuda R, Sundaram U. Regulation of sodium-glutamine cotransport in villus and crypt cells by glucocorticoids during chronic enteritis. *Inflammatory Bowel Disease*. 2012 Nov;18(11):2149-57.
- Saha P, Arthur S, Kekuda R, Sundaram U. Na-glutamine co-transporters B(0)AT1 in villus and SN2 in crypts are differentially altered in chronically inflamed rabbit intestine. *Biochim Biophys Acta*. 2012

Mar;1818(3):434-42.

- Arthur S, Sundaram U. Inducible nitric oxide regulates intestinal glutamine assimilation during chronic intestinal inflammation. *Nitric Oxide*. 2015 Jan 30;44:98-104.

5. **Chronic and selective inhibition of BLM Na-K-ATPase uniquely regulates primary BBM Na absorptive pathways in intestinal epithelial cells.** Assimilation of most nutrients and important vitamins in the mammalian small intestine occur via Na-dependent co-transport process located on the BBM of enterocytes. These co-transport processes require a favorable transmembrane Na+ gradient. BLM Na-K-ATPase in intestinal epithelial cells is responsible for establishing and maintaining high intracellular K+ and low intracellular Na+ concentration. Thus, inhibition of Na-K- ATPase, would be expected to inhibit these processes. Indeed, treatment with ouabain resulted in inhibition of SGLT1 at 1 hour. However, chronic exposure for 24 hours or more resulted in the stimulation of SGLT1. To further characterize this unexpected stimulation of SGLT1, siRNA silencing was utilized to inhibit α1 subunit of Na-K-ATPase. SGLT1 activity was significantly upregulated by Na- K-ATPase silencing, while NHE3 activity remained unaltered. Nevertheless, chronic and specific inhibition of BLM Na-K-ATPase in intestinal epithelial cells increased intracellular Na. The mechanism of stimulation of SGLT1 activity was secondary to an increase in the affinity of the co-transporter for glucose without a change in the number of co-transporters. In conclusion, chronic and specific inhibition of BLM Na-K-ATPase stimulates influx of glucose and Na via BBM SGLT1, but not influx of Na via NHE3. Thus, Na-K-ATPase uniquely regulates BBM primary Na absorptive pathways in the mammalian small intestine.

- Manoharan P, Gayam S, Arthur s, Palaniappan B, Singh S, Dick G and U Sundaram. Chronic and selective inhibition of basolateral membrane Na-K-ATPase uniquely regulates brush border membrane Na absorption in intestinal epithelial cells. *American Journal of Physiology Cell*. 2015; 308(8):C650-6.

URL to a full list of published work as found in My Bibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/12OKi1k5Gu0Ap/bibliograpahy/48986596/public/?sort=date&direction=ascending

A. Research Support

1. **ACTIVE RESEARCH SUPPORT:**

Title: Regulation of Intestinal Na Absorption
PI: Uma Sundaram, MD
Type: RO1, DK 67420
Period: 7/01/09 – 6/30/17
Agency: NIH/NIDDK
Overlap: None

Title: Univ. Kentucky/Marshall Univ. Clinical and Translational Science Award
Marshall PI: Uma Sundaram, MD/ Kentucky PI: Phil Kern, MD
Type: 1 UL1TR000117
Period: 06/01/20123 – 03/1/2016
Agency: NIH/NCATS
Overlap: None

Title: Regulation of Na-Nutrient co-Transport
PI: Uma Sundaram, MD
Type: RO1, DK 58034
Period: 07/01/06 – 06/30/15 – No Cost Extension, Renewal submitted for review
Agency: NIH/NIDDK

2. **PAST 3 YEARS RESEARCH SUPPORT:**

Title: West Virginia Clinical Translational Research Award
PI: Uma Sundaram, MD
Type: 1 U54 RR033567-01
Period: 06/01/2012 – 06/1/2013
Agency: NIH/NIGMS