BIOGRAPHICAL SKETCH

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NAME: Natarajan, Sathish Kumar

eRA COMMONS USERNAME (credential, e.g., agency login): natarajan.sathish

POSITION TITLE: Assistant Professor

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)	END DATE MM/YYYY	FIELD OF STUDY
University of Madras, Chennai, Tamilnadu	BS	05/1999	Biochemistry
University of Madras, Chennai, Tamilnadu	MS	05/2001	Biochemistry
Dr. MGR Medical University, Chennai, Tamilnadu	PHD	10/2008	Biomedical Sciences
University of Nebraska-Lincoln	Postdoc	07/2012	Proline Metabolism
University of Nebraska Medical Center	Postdoc/Instructor	12/2015	Palmitoleate Protection

A. Personal Statement

I am an Associate Professor in the Department of Nutrition & Health Sciences, University of Nebraska-Lincoln and my research focus is to improve the outcome of newborn in mothers infected with Zika virus (ZIKV) and to establish dietary palmitoleate as an effective nutrition intervention for the prevention of placenta and fetal brain injury and congenital Zika Syndrome**.** As a Principal Investigator of this application**,** I will provide overall direction for the project that aims to a) determine the signaling mechanism of palmitoleate protection against ZIKV-induced endoplasmic reticulum (ER) stress; b) investigate the role of ZIKV-induced inflammation and inflammasome activation in trophoblasts and neuronal cells; and c) ascertain the protective role of dietary palmitoleate against ZIKV-induced apoptosis using *in vitro* and *in vivo* experimental approaches. I have broad background and expertise in studying the mechanism of cell injury with ZIKV infection, protective nutrient signaling and apoptotic signaling pathways, mitochondrial function, and mitochondrial fatty acid oxidation disorders, which positions me well to lead this project. I have established the pro-apoptotic role of FoxO3 and microRNA-34a in cholangiocyte lipoapoptosis in metabolic dysfunction-associated steatotic liver disease (MASLD) and have identified that **palmitoleate** protects against palmitate-induced cholangiocyte lipoapoptosis and trophoblast lipoapoptosis. I have recently demonstrated that ZIKV infection induces ER stress and apoptosis to placental trophoblasts and neuronal cells; established omega-3 fatty acid metabolites regulate placental trophoblast function; demonstrated that placenta and liver lipotoxicity in acute fatty liver of pregnancy (AFLP); established that proline and pipecolate metabolism promote cell survival signaling pathways like mTORC2-AKT. As a recognition for my contributions, I have been invited to serve as an *ad hoc* grant reviewer for the NICHD, special emphasis panel in NIEHS, early career reviewer to NIDDK, Graduate Fellowship Panel reviewer to NSF and DoD. I have 62 peer-reviewed publications, 1 preprint, 1 editorial comment and 1 book chapter. These articles have been placed in journals like Hepatology, Cell Death & Disease, Cell Death & Discovery, Molecular Psychiatry, Vaccines, Molecular Nutrition Food Research, AJP Liver Physiology, Journal of Lipid Research, International Journal of Molecular Sciences, and Journal of Virology. I have been cited in 2,746 documents including editorial comments (Source: Scopus.com, ID#9035955300; h-index:23). **In summary,** I have necessary expertise, leadership to mentor graduate students and postdoctoral fellow training to successfully complete the proposed project.

Ongoing projects that I would like to highlight include

Current

Nexus of Virology, Immunology, & Bioengineering (NVIBE-Phase 2) Funding, UNL

- **Grant Title:** Dietary Palmitoleate protects against Orthoflavivirus infection-induced placenta, fetal brain and brain damage, 07/01/2025-06/30/2026
- Role: Principal Investigator

Rural Drug Addiction Research Center-Pilot Award, UNL

- **Grant Title:** Therapeutic efficacy of dietary palmitoleate supplementation to mitigate maternal oxycodone-induced placenta and fetal brain damage**.** 05/01/2025-04/30/2027
- Role: Principal Investigator

DHHS/NIH/NIDA -1R01DA064132-01

- **Grant Title:** Synergistic Effect of Nicotine and Antiretrovirals on Placental Development , 07/01/2025 - 06/30/2030
- Role: Co-investigator (PI: Bade AN)

Agricultural Research Division-Hatch Multistate Enhanced Program, NUramp#49434

- **Grant Title:** Dietary Palmitoleate protects against maternal obesity-induced complications, 10/01/2023-09/30/2027
- Role: **Principal Investigator**

USDA NIFA-AFRI Standard Grant, 2023-67017-40223

- **Grant Title:** Bioactive Components of Macadamia Nut Protects against Maternal Obesity-induced Complications, 06/01/2023-05/31/2028
  Role: **Principal Investigator**

Citations:

1. Muthuraj PG, Krishnamoorthy C, Anderson-Berry A, Hanson C, **Natarajan SK***. Novel Therapeutic Nutrient Molecules that Protects against Zika virus with a special note on palmitoleate. *Nutrients*. **2023**, 15(1), 124; ***Corresponding author.** PMID: 36615782, PMCID: PMC9823984
2. Muthuraj PG, Sahoo PK, Kraus M, Bruett T, Annamalai AS, Pattnaik A, Pattnaik AK, Byrareddy SN, **Natarajan SK***. Zika virus Infection Induces Endoplasmic Reticulum Stress and Apoptosis in Placental Trophoblasts. *Cell Death Discov.* **2021**, **7,** 24. ***Corresponding author**. PMID**:** 33500388**,** PMCID: PMC7838309**.** ***This manuscript was highlighted as Cell Death Discovery Readers' choice article on the basis of readership and citing metrics in 2020-2022.***
3. Muthuraj PG, Pattnaik A, Sahoo PK, Islam MT, Pattnaik AK, Byrareddy SN, Hanson C, Anderson-Berry A, **Natarajan SK***. Palmitoleate Protects against Zika virus-induced Placental Trophoblast Apoptosis. *Biomedicines*. **2021**, *9*(6), 643; ***Corresponding author.** PMID: 34200091, PMCID: PMC8226770
4. Annamalai A, Pattnaik A, Sahoo B, Guinn, Z, Bullard B, Weaver E, Steffen D, **Natarajan SK**, Petro T, Pattnaik A. An Attenuated Zika Virus Encoding Non-Glycosylated Envelope (E) and Non-Structural Protein 1 (NS1) Confers Complete Protection against Lethal Challenge in a Mouse Model *Vaccines*. **2019** Sep 12;7(3):112. PMID:31547297, PMCID: PMC6789518

B. Positions, Scientific Appointments and Honors

Positions and Scientific Appointments

2025-	Member, Rural Drug Abuse Research Center, UNL
2024- present	**Associate Professor, Department of Nutrition & Health Sciences, UNL, Lincoln, NE**
2023	Member, Nebraska Food for Health Center, UNL, Lincoln, NE
2022	*ad hoc* reviewer for the Special Emphasis Panel, ZRG1-DKUS-J (06) study section, NIEHS
2021	*ad hoc* reviewer for the Pregnancy and Neonatology (PN) study section, NICHD
2020	Topic *Editor-in-chief* for an issue on "Novel Therapeutic Nutrient Molecules' Biomedicines, Nutrients, Current Issues in Molecular Biology, Reports and Metabolites *Journals* *ESI* reviewer for the Hepatobiliary pathophysiology (HBPP) study section, NIDDK
2018 – present	Guest Editor for a Special Issue in *Biomedicine* journal Member, Nebraska Center for Virology, UNL, Lincoln, NE Member, Child Health Research Institute, UNMC, Omaha, NE Member, Fred, and Pamela Buffet Cancer center, UNMC
2018	USDA-NIFA Study section panelist for the Function and Efficacy of Nutrients in Agriculture and Food Research Initiative (AFRI) Competitive grants program

2017 *ad hoc* reviewer for the National Defense Society for Engineering Graduate Fellowship Evaluation Panel and Department of Defense (DoD)

2016- 2023 Assistant Professor, University of Nebraska-Lincoln, Lincoln, NE
Member, Nebraska Prevention of Obesity Diseases, UNL, Lincoln, NE
Member, Nebraska Redox Biology Center, UNL, Lincoln, NE
Member, Nebraska Center for Virology, UNL, Lincoln, NE

2016 – present *ad hoc* reviewer for National Science Foundation (NSF) Graduate Research Fellowship Program

2014 Ad hoc reviewer, Well-Being Women Foundation, London, UK

Honors

2023 Dinsdale Family Faculty Award, Institute of Agriculture and Natural Resources, UNL

2022 Annual Research Symposium Alumni Presentation, Biochemistry and Molecular Biology, University of Nebraska Medical Center

2016 Thematic Best Poster Award, American Society for Biochemistry and Molecular Biology

2015 Travel Award to attend American Association for the Study of Liver Disease (AASLD) and Industry Colloquium, Novel Targets and Therapies in Liver Disease

2004 Shakuntala Amir Chand Prize, Indian Council of Med Research (ICMR). Ministry of Education, Government of India

C. Contribution to Science

1. **Zika Virus induces endoplasmic reticulum** (**ER) stress and apoptosis in placental trophoblasts and Neuronal cells**: Zika virus (ZIKV) infection in pregnant women is highly associated with Congenital Zika Syndrome and the development of microcephaly, intra uterine growth retardation and ocular damage in the fetus. Recent advances in ZIKV infection suggest that the virus is transmitted to the fetal organs including brain via infecting the placenta. Infection of the placenta during the first and second trimester plays a crucial role in ZIKV transmission from maternal circulation to the fetus resulting in Congenital Zika Syndrome. We have recently demonstrated that ZIKV induces the activation of ER stress and MAPK kinases. Activation of JNK plays a critical role in ZIKV-induced placental trophoblast apoptosis. We also have preliminary data to show that ZIKV induces apoptosis in neuroblastoma cell and retinal pigmental epithelial cells. Further, we also demonstrated that palmitoleate supplementation dramatically protects ZIKV-induced placental trophoblast and neuronal cell apoptosis. The identification of palmitoleate protection against ZIKV-induced apoptosis will result in potential nutrient therapy against placenta and fetal brain injury caused due to ZIKV infection. Our team has previously collaborated and have published co-authored manuscripts.

    a. Muthuraj PG, Sahoo PK, Kraus M, Bruett T, Annamalai AS, Pattnaik A, Pattnaik AK, Byrareddy SN, **Natarajan SK***. Zika virus Infection Induces Endoplasmic Reticulum Stress and Apoptosis in Placental Trophoblasts. *Cell Death Discov.* **2021**, 7**,** 24. ***Corresponding author**. PMID**:** 33500388**,** PMCID: PMC7838309. *This manuscript is highlighted as Cell Death Discovery Readers' choice article on the basis of readership and citing metrics in 2020-2022.*
    b. Muthuraj PG, Pattnaik A, Sahoo PK, Islam MT, Pattnaik AK, Byrareddy SN, Hanson C, Anderson-Berry A, **Natarajan SK***. Palmitoleate Protects against Zika virus-induced Placental Trophoblast Apoptosis. *Biomedicines*. **2021**, *9*(6), 643; ***Corresponding author.** PMID: 34200091, PMCID: PMC8226770
    c. Muthuraj PG, Krishnamoorthy C, Anderson-Berry A, Hanson C, **Natarajan SK***. Novel Therapeutic Nutrient Molecules that Protects against Zika virus with a special note on palmitoleate. *Nutrients*. **2023**, 15(1), 124; ***Corresponding author.** PMID: 36615782, PMCID: PMC9823984
    d. Krishnamoorthy C, Sahoo PK, Delaney T, Hanson C, Anderson-Berry A, **Natarajan SK*** Zika virus induce endoplasmic reticulum stress and apoptosis in neurons and protective role of palmitoleate. bioRxiv 2025.01.22.634157; doi: https://doi.org/10.1101/2025.01.22.634157. ***Corresponding author.**

2. **Free Fatty Acid-induced Trophoblast and Cholangiocyte Lipoapoptosis:** Maternal obesity and metabolic dysfunction-associated steatotic liver disease (MASLD) patients have elevated concentrations of circulating saturated free fatty acids (FFAs). We have demonstrated that toxic FFAs induce caspase-

dependent trophoblast lipoapoptosis. Lipoapoptosis is defined as programmed cell death induced by high levels of fatty acid exposure. I have also established the pro-apoptotic role of FoxO3 and microRNA-34a in cholangiocyte lipoapoptosis in MASLD, Palmitoleate, an omega-7 monounsaturated fatty acid , has been shown to be protective against hepatocyte, cholangiocyte and trophoblast lipoapoptosis. These data suggest that palmitoleate treatment can also be a nutritional therapy for the prevention of obesity-induced complications.

a. **Natarajan SK***, Bruett T, Muthuraj PG, Sahoo PK, Power J, Mott JL, Hanson C, Anderson-Berry A. Saturated Free Fatty Acids induce Placental Trophoblast Lipoapoptosis. *PlosOne* **2021,** Apr 22; 16(4): e0249907. ***Corresponding author.** PMID: 33886600, PMCID: PMC8062006

b. **Natarajan SK**, Ingham SA, Mohr AM, Wehrkamp CJ, Ray A, Roy S, Cazanave SC, Phillippi MA, Mott JL. Saturated free fatty acids induce cholangiocyte lipoapoptosis. *Hepatology*. **2014** Dec;60(6):1942-56. PMID: 24753158. PMCID: PMC4553418. ***This manuscript was highlighted by an editorial comment by Martinez AK, Glaser SS, Hepatology. 2014 Dec; 60(6): 1809-1811.***

c. **Natarajan SK***, Stringham BA, Mohr AM, Wehrkamp CJ, Lu S, Phillippi MA, Harrison-Findik D, Mott JL. FoxO3 increases miR-34a to cause palmitate-induced cholangiocyte lipoapoptosis. *Journal of Lipid Research;* **2017**, 58(5):866-875. PMID: 28250026. PMCID: PMC5408604 ***Corresponding author**

d. Kim Y, **Natarajan SK**, Chung S. Gamma-tocotrienol attenuates the hepatic inflammation and fibrosis by suppressing endoplasmic reticulum stress in mice. *Mol. Nutr. Food Res.* **2018** Nov; 62(21): e1800519. PMID: 30183139.

3. **Omega-3 fatty acid metabolism in the placenta.** Our work demonstrated that omega-3 fatty acid-derived lipid mediators regulate placental trophoblast function. We have also demonstrated the expression of Resolvin D2 (RvD2) receptor, GPR18 expression in placental trophoblasts and have observed an increase in membrane localization of GPR18 with RvD2 supplementation in trophoblasts. Our data also showed that RvD1 and RvD2 derived from docosahexaenoic acid (DHA) were increased in maternal circulation in settings of adverse health or inflammation. Further, we observed the role of RvD2 in the inflammation resolution in trophoblasts. We have also recently demonstrated that both omega-3 and omega-6 derived oxylipins influence fetal birth length and weight percentiles.

   a. Hahka T*, Sekar D, Sahoo PK, Ravi A, Freel C, Krishnamoorthy C, Ramamurthy S, Rapoza R, Drakowski R, Akbar A, VanOrmer M, Thoene M, Hanson CK, Nordgren T, **Natarajan SK***, Anderson Berry A. RvD2 mitigates TNFα-Induced mitochondrial reactive oxygen species through NRF2 signaling in placental trophoblasts. *Front Physiol.* **2025** Apr 2;16:1547940. doi: 10.3389/fphys.2025.1547940. PMID: 40241717 * **Corresponding author.**

   b. Thompson M, Ulu A, Yuil-Valdes AG, Mukherjee M, Thoene M, VanOrmer M, Slotkowski R, Lyden E, Anderson-Berry A, Hanson CK, Nordgren TM, **Natarajan SK*.** Omega-6 and Omega-3 Fatty Acid-Derived Oxylipins from the Lipoxygenase Pathway in Maternal and Umbilical Cord Plasma at Delivery and Their Relationship with Infant Growth. *Int J. Mol. Sci*. 2. **2022**, 23(2), 708; ***Corresponding author.**

   c. Woodard V, Thoene M, Van Ormer M, Thompson M, Hanson C, **Natarajan, SK,** Mukherjee M, Yuil-Valdes A, Nordgren TM, Ulu A, Jackson KH, Anderson-Berry, A. Intrauterine Transfer of Polyunsaturated Fatty Acids in Mother–Infant Dyads as Analyzed at Time of Delivery. *Nutrients* **2021**, *13 (3)*, 996. PMID: 33808763, PMCID: PMC8003544.

   d. Ulu A, Sahoo PK, Yuil-Valdes AG, Mukherjee M, VanOrmer M, Muthuraj PG, Thompson M, Anderson-Berry A, Hanson CK, **Natarajan SK***, Nordgren TM*. Omega-3 Fatty Acid-derived Resolvin D2 regulates Human Placental Vascular Smooth Muscle and Extravillous Trophoblast Activities. *Int. J. Mol. Sci.* **2019** Sep; 20(18):4402. ***Co-Corresponding authors,** PMID: 31500240. PMCID: PMC6770915.

4. **Placenta and Liver Lipotoxicity in Acute Fatty Liver of Pregnancy**: I have developed and established an animal model for microvesicular steatosis and demonstrated that the administration of the peroxisome proliferator, clofibrate, results in protection against the oxidative injury seen in the liver subcellular organelles and decreases hepatic microvesicular steatosis. Later, my work revealed a novel mechanism of

placental damage in acute fatty liver of pregnancy (AFLP), a rare autosomal recessive disease that occurs during the third trimester of pregnancy. AFLP is a catastrophic illness resulting in progressive maternal liver dysfunction and secondary systemic compromise that poses a significant challenge to the fetus and mother. We had shown that defect due to genetic mutation in fatty acid oxidizing enzymes results in placental mitochondrial damage/dysfunction and oxidative stress in the placenta and systemic oxidative stress, which acts as a source of maternal liver damage in AFLP patients. Further, we had demonstrated that arachidonic acid from the placenta of AFLP patient's damages hepatocyte mitochondria by enhancing the levels of mitochondrial-derived free radicals, in an in vitro culture system. More importantly, the arachidonic acid also resulted in lipoapoptosis of cultured hepatocytes as evidenced by an increase in the caspase 3 activity. My work clearly showed that lipoapoptosis occurs even at low concentrations of toxic arachidonic acids reflective of pathology observed in AFLP patients.

a. **Natarajan SK**, Ibdah JA. Role of 3-Hydroxy Fatty Acid-Induced Hepatic Lipotoxicity in Acute Fatty Liver of Pregnancy. *Int J Mol Sci.* **2018** Jan 22;19(1) PMID: 29361796; PMCID: PMC5796265.

b. **Natarajan SK**, Thangaraj KR, Goel A, Eapen CE, Balasubramanian KA, Ramachandran A. Acute Fatty Liver of Pregnancy: An Update on Mechanisms. *Obstet Med.* **2011** Sep;4(3):99-103. PMID: 27579101; PMCID: PMC4989602.

c. **Natarajan SK**, Thangaraj KR, Eapen CE, Ramachandran A, Mukhopadhya A, Mathai M, Seshadri L, Peedikayil A, Ramakrishna B, Balasubramanian KA. Liver Injury in Acute Fatty Liver of Pregnancy: Possible Link to Placental Mitochondrial Dysfunction and Oxidative Stress. *Hepatology*. **2010** Jan;51(1):191-200. PMID: 20034024.

d. **Natarajan SK**, Eapen CE, Pullimood AB, Balasubramanian KA. Oxidative Stress in Experimental Liver Microvesicular Steatosis: Role of Mitochondria and Peroxisomes. *J Gastroenterol Hepatol.* **2006** Aug;21(8):1240-9. PMID: 16872304.

5. **Established that proline and pipecolate metabolism promote cell survival.** Proline catabolism can lead to the formation of superoxide and induces apoptosis while biosynthesis or accumulation of proline appears to be protective against oxidative stress. These opposing properties suggest proline has a pivotal role in mediating redox homeostasis under different conditions. We have provided evidence that proline supplementation protects mammalian cells via Akt-FoxO3 signaling pathways for cell survival during stress. Similar to proline, pipecolate also protects mammalian cells against oxidative stress-induced cell death. My work for the first time showed that pipecolate oxidase is present in the mitochondria besides to its home, peroxisomes. Identifying nutrients and small molecules that are cytoprotective related to current proposal.

a. **Natarajan SK**, Zhu W, Liang X, Zhang L, Demers AJ, Zimmerman MC, Simpson MA, Becker DF. Proline Dehydrogenase is Essential for Proline Protection against Hydrogen Peroxide-induced Cell Death. *Free Radic Biol Med*. **2012** Sep 1;53(5):1181-91. PMID: 22796327; PMCID: PMC3432146.

b. **Natarajan SK**, Becker DF. Role of Apoptosis-inducing Factor, Proline Dehydrogenase, and NADPH Oxidase in Apoptosis and Oxidative Stress. *Cell Health Cytoskelet*. **2012** Feb 1; 2012(4):11-27. PMID: 22593641; PMCID: PMC3351110.

c. Liang X, Zhang L, **Natarajan SK**, Becker DF. Proline mechanisms of stress survival. *Antioxid. Redox Signal*. **2013**; 19(9): 998-1011. PMID: 23581681; PMCID: PMC3763223.

Complete List of Published Work in NCBI My Bibliography: (Total of 62 publications)

https://www.ncbi.nlm.nih.gov/myncbi/sathish%20kumar.natarajan.1/bibliography/public/