BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. DO NOT EXCEED FIVE PAGES.

NAME: Paulmurugan, Ramasamy

eRA COMMONS USER NAME (credential, e.g., agency login): paulmur8

POSITION TITLE: Associate Professor of Radiology

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
Madurai Kamaraj University, Madurai, India	B.Sc.	05/1989	Zoology, Botany, Chemistry
University of Madras, Madras, India	M.Sc.	09/1991	Biomedical Genetics
National Environmental Engineering Research Institute (NEERI), University of Madras, Madras, India	Jr. Project Fellowship	12/1993	Molecular Virology
National Environmental Engineering Research Institute (NEERI), University of Madras, Madras, India	Sr. Research Fellowship	08/1996	Molecular Virology
National Environmental Engineering Research Institute (NEERI), University of Madras, Madras, India	Ph.D.	11/1997	Biomedical Genetics (Molecular Virology

A. Personal Statement

I am currently an Associate Professor under the Molecular Imaging Program at Stanford (MIPS), in the Department of Radiology at Stanford University. I have more than 16 years of experience in the use of different *in vivo* imaging modalities (Bioluminescence, Fluorescence, PET, SPECT and CT) for monitoring different cellular events in mice and rats. My research group mainly focuses on developing new imaging assays for studying different cellular signal transduction networks in living animals. Specifically, we are interested in developing imaging assays to study post-translational modifications of proteins, such as protein-methylation, protein-phosphorylation, and protein-sumoylation, in living animals. We have applied our extensive experience in molecular biology to develop several *in vivo* imaging assays, which can be used for monitoring basic cellular processes, such as drug modulated protein-protein interactions, protein-phosphorylation, protein-methylation, protein sumoylation, and protein folding, in living animals. We have developed split-reporter protein complementation systems for various reporter genes (luciferases, fluorescent proteins, and thymidine kinase), and currently use them to design various imaging sensors to study various cellular processes. Mainly we are using these assays for studying protein cross talks involved in estrogen receptor signaling, Nrf2- mediated drug resistance in cancer therapy, p53-sumoylation in cancer, imaging tumor microenvironment in cancers, imaging cytokine signaling in cancer, and APP and Tau protein sumoylations in Alzheimer's disease. My research group is also working on imaging gene- and microRNA-based therapeutics in cancers (breast cancer, hepatocellular carcinoma, and glioma). We are currently exploring the role of the Nrf2-pathway for acquired chemoresistance in cancer therapy, as well as the activation of cellular Nrf2 to improve antioxidant potentials of cancer therapy and stress-mediated β-cell apoptosis in diabetes. In addition, my lab collaborates with Dr. Willmann's lab in developing ultrasound-microbubble (US-MB) triggered drug delivery strategies for improved cancer therapy, and Dr. Massoud's lab in developing super selective microRNA delivery to brain to improve glioma therapy.

We have shown tremendous progress in developing novel strategies and technologies to study estrogen receptor biology using reporter protein complementation sensors which we are planning to use in this grant for addressing ERα and ERβ homo- and heterodimerizations and the associated downstream ERE- and alternate signaling (AP1, Sp1 and NF-kB) mechanisms to accurately predict the biology of ER-signaling in breast cancers that co-express both the ERs or ERβ alone.

B. Positions and Honors

Positions and Employment

1996-1999 Scientist B and Head, Environmental Biotechnology Division, Rajiv Gandhi Centre for Biotechnology, Trivandrum, Kerala, India

1999-2003 Scientist C and Head, Environmental Biotechnology Division, Rajiv Gandhi Centre for Biotechnology, Trivandrum, Kerala, India

2001-2003 Post-doctoral Visiting Scientist, Crump Institute for Molecular Imaging, Department of Molecular and Medical Pharmacology, UCLA, Los Angeles, CA, USA
2003-2009 Senior Research Scientist, Department of Radiology, Molecular Imaging Program at Stanford (MIPS), Stanford University, Stanford, CA, USA
2009-2016 Assistant Professor, Department of Radiology, MIPS, Stanford University, Stanford, CA, USA
2016- Associate Professor, Department of Radiology, MIPS, Stanford University, Stanford, CA, USA

Other Experience and Professional Memberships

2001 Member, Academy of Molecular Imaging
2002 Member, Society of Molecular Imaging
2009 American Society of Gene and Cell Therapy (ASGCT)
2016 International Society for Bioluminescence and Chemiluminescence (ISBC)

Honors

1991 Best Research Fellow, NEERI, CSIR, Nagpur, India
1999 Young Scientist Award, Government of Kerala, India
2003 Travel Award, Academy of Molecular Imaging for Best Paper Presentation, San Diego, CA, USA
2005 Travel Award, Academy of Molecular Imaging for Best Paper Presentation, Orlando, FL, USA
2005 Travel Award, Society of Molecular Imaging for Best Paper Presentation, Cologne, Germany
2006 Travel Award, Academy of Molecular Imaging for Best Paper Presentation, Orlando, FL, USA

International Patents Filed

2007 R. Paulmurugan, S.S. Gambhir. Self-complementing firefly luciferase enzyme fragments for studying cellular events in living animals (Publication #: 20070161067)
2007 S.S. Gambhir, R. Paulmurugan. Protein Phosphorylation Imaging Systems, Methods of Making Phosphorylation Imaging Systems, and Methods of Use Thereof. US Patent #: 7834148 (Publication #: 20070275428)
2008 S.S. Gambhir, R. Paulmurugan. Ligand-regulable transactivation systems, methods of use thereof, methods of detecting estrogen receptor ligands, and methods of differentiating estrogen receptor ligand agonists and antagonists. US Patent #: 7709253 (Publication #: 20080034445)
2009 R. Paulmurugan, S.S. Gambhir. Estrogen receptor intramolecular folding systems, Estrogen receptor intramolecular folding sensors, Methods of use thereof, methods of detecting ER ligands, and methods of detecting ER agonists and antagonists. No Patent # (Original Publication #: 20090044286; also published as 8178654 B2)
2009 T. F. Massoud, R. Paulmurugan, S.S. Gambhir: Split Herpes Simplex Virus Type 1 Thymidine Kinase for Noninvasive PET Reporter Complementation Imaging of Protein-Protein Interactions No Patent # (Publication #: 20090075313)
2010 S.S. Gambhir, R. Paulmurugan. Ligand-regulable transactivation systems, methods of use thereof, methods of detecting estrogen receptor ligands, and methods of differentiating estrogen receptor ligand agonists and antagonists. US Patent #: 8076159 (Publication #: 20100169993)
2011 S. Bhaumik, S.S. Gambhir, R. Paulmurugan, S. Yaghoubi, B-C Ahn, N. Parashurama. Composition and Method for Imaging Stem Cells. (Publication #: 20110059439)

C. Contribution to Science

1. **Reporter gene assays for imaging protein-protein interactions.** My early publications address my training in molecular virology and molecular biology. Later I used my experience in molecular biology to develop reporter gene assays/sensors for studying protein-protein interactions in living animals by molecular imaging. The sensors are mainly based on reporter protein complementation. From these studies I developed optimal split-reporter complementation systems for various optical reporters, such as firefly luciferase, renilla luciferase, gaussia luciferase, enhanced green fluorescent protein, and monomeric red fluorescent protein, and for PET reporter, the Thymidine Kinase (HSV1-sr39TK).

    a. Paulmurugan R, Umezawa Y, Gambhir SS. Noninvasive imaging of protein-protein interactions in living subjects by using reporter protein complementation and reconstitution strategies. Proc Natl Acad Sci USA. 2002 Nov 26;99 (24):15608-13. PMCID PMC137764.
    b. Paulmurugan R, Gambhir SS. Monitoring protein-protein interactions using split synthetic renilla luciferase protein-fragment-assisted complementation. Anal Chem. 2003 Apr 1;75:1584-9. PMCID: PMC4154785.

c. Paulmurugan R, Massoud TF, Huang J, Gambhir SS. Molecular imaging of drug-modulated protein-protein interactions in living subjects. Cancer Res. 2004 Mar 15;64(6):2113-19.PMCID: PMC4154786.
d. Massoud TF, Paulmurugan R, Gambhir SS. A molecularly engineered split reporter for imaging protein-protein interactions with positron emission tomography. Nat Med. 2010 Aug;16(8):921-6. PMCID: PMC2917476.

2. **Imaging cellular signaling networks in living animals.** The molecular imaging assays and sensors I developed using various bioluminescence reporters were later applied to studying the biological complexities associated with estrogen receptor signaling, activation of Hsp90 chaperon complex, activation c-myc, and phosphorylation of Akt. Estrogen receptors respond and activate downstream target genes' expressions in response to estrogen. While estradiol is an endogenous estrogen regulates estrogen receptor pathways, various estrogen analogues, estrogen mimetics, and environmental estrogens also significantly activate estrogen receptor signaling and induce carcinogenesis. In addition, the recent discovery of the second estrogen receptor, the estrogen receptor beta (ER-β), adds additional complexity to ER biology. I used reported complementation to study ligand-induced ER-folding and ER-α/ER-β cross talk in cells and living animals. Similarly, Hsp90 α/β -p23 interaction and Akt phosphorylation systems were used for drug screening.

   a. Paulmurugan R, Gambhir SS. An intramolecular folding sensor for imaging estrogen receptor-ligand interactions. Proc Natl Acad Sci USA. 2006 Oct 24;103 (43):15883-8. PMCID: PMC1635097.
   b. Chan CT, Paulmurugan R, Gheysens OS, Kim J, Chiosis G, Gambhir, SS. Molecular imaging of the efficacy of heat shock protein 90 inhibitors in living subjects. Cancer Res. 2008 Jan 1;68(1):216-26. PMCID: PMC4146344.
   c. Paulmurugan R, Tamrazi A, Katzenellenbogen JA, Katzenellenbogen BS, Gambhir SS. A human estrogen receptor (ER) alpha mutation with differential responsiveness to nonsteroidal ligands: novel approaches for studying mechanism of ER action. Mol Endocrinol. 2008 Jul;22(7):1552-64. PMCID: PMC2453600.
   d. Chan CT, Paulmurugan R, Reeves RE, Solow-Cordero D, Gambhir SS. Molecular imaging of phosphorylation events for drug development. Mol Imaging Biol. 2009 May-Jun;11(3):144-58. PMCID: PMC4154800.

3. **Imaging Nrf2-Keap1 antioxidant signaling in drug resistance and cancer therapy.** Transcription factor Nrf2 plays a major role in maintaining intracellular ROS level to maintain cellular homeostasis. Activation of Nrf2 by antioxidants is a potent way to improve β-cell function in diabetes. However, Nrf2 demonstrates the opposite effect in cancer therapy and drug resistance. Hence, we are working on finding the mechanism to activate/inhibit the Nrf2 pathway to improve cancer therapy.

   a. Paulmurugan R, Oronsky B, Brouse CF, Reid T, Knox S, Scicinski J. Real time dynamic imaging and current targeted therapies in the war on cancer: a new paradigm. Theranostics. 2013 May 25;3(6):437-47. PMCID: PMC3677414.
   b. Ramkumar KM, Sekar TV, Bhakkiyalakshmi E, Foygel K, Rajaguru P, Berger F, Paulmurugan R. The impact of oxidative stress on islet transplantation and monitoring the graft survival by non-invasive imaging. Curr Med Chem. 2013;20(9):1127-46.

4. **Imaging Histone methylation in living animals.** Post-translational modifications in histone proteins play major roles in chromatin organization and transcriptional regulation of gene expression in cells. However, while some histone modifications, such as acetylation, phosphorylation, sumoylation, ubiquitination, and citrullination have been well-characterized and documented in the literature, histone methylations that occur in the N-terminal lysine residues of histone 3 and histone 4, which control chromatin structure and gene expression in cells, are poorly understood. We are developing molecular imaging biosensors to study histone methylations in living animals.

   a. Sekar TV., Foygel K, Gelovani JG, Paulmurugan R. Genetically encoded molecular biosensors to image histone methylation in living animals. Anal Chem. 2015 Jan 20;87(2):892-9. PMCID: PMC4303335.
   b. Sekar TV, Foygel K, Devulapally R, Paulmurugan R. Degron protease blockade sensor to image epigenetic histone protein methylation in cells and living animals. ACS Chem Biol. 2015 Jan 16;10(1): 165-74. PMCID: PMC4301175.

5. **MicroRNAs and Gene-directed enzyme prodrugs therapies for cancer treatment.** MiRNA modulation is a new molecular approach to treating various cancers. MiRNAs are a group of gene expression regulators that play a profound role in the pathogenesis and progression of cancers when aberrantly expressed. In cancers, tumor suppressive miRNAs are significantly under-expressed, while oncogenic miRNAs are highly overexpressed. Both also regulate chemoresistance genes. Therapeutic restoration of both miRNAs has the potential to not only slow cancer growth and metastasis, but also render these tumors sensitive to chemo- and radiotherapies. A major challenge to clinical translations of the miRNA therapy is a safe and efficient approach for *in vivo* delivery. My lab is currently working with ultrasound-microbubbles (US-MB) in combination with polymeric nanoparticles to load and deliver microRNAs *in vivo*. Similarly, gene-directed enzyme prodrug therapy is another efficient strategy for cancer therapy where tumor-targeted delivery of an exogenous gene that codes for an enzyme capable of converting a non-toxic prodrug into an activated cytotoxic agent is used to kill cancer cells. We recently showed that HSV1-sr39TK and NTR enzymes expressed as a fusion protein (TK-NTR) can efficiently kill tumor cells in a subcutaneous and metastatic xenograft of a human TNBC tumor (MDA MB231) in mice. In these studies, we achieved a complete removal of tumors by injecting just two doses of prodrug combinations (GCV and CB1954).

   a. Devulapally R, Sekar NM, Paulmurugan R. Formulation of Anti-miR-21 and 4-Hydroxytamoxifen Co-loaded Biodegradable Polymer Nanoparticles and Their Antiproliferative Effect on Breast Cancer Cells. Mol Pharm. 2015 un 1;12(6):2080-92. doi: 10.1021/mp500852s. Epub 2015 Apr 28. PMID: 25880495.
   b. Mullick Chowdhury S, Wang TY, Bachawal S, Devulapally R, Choe JW, Abou Elkacem L, Yakub BK, Wang DS, Tian L, **Paulmurugan** R, Willmann JK. Ultrasound-guided therapeutic modulation of hepatocellular carcinoma using complementary microRNAs. J Control Release. 2016 Aug 5;238:272-280. doi: 10.1016/j.jconrel.2016.08.005. [Epub ahead of print] PMID: 27503707.
   c. Devulapally R, Sekar NM, Sekar TV, Foygel K, Massoud TF, Willmann JK, Paulmurugan R. Polymer nanoparticles mediated co-delivery of antimiR-10b and antimiR-21 for achieving triple negative breast cancer therapy. ACS Nano. 2015 Mar 24;9(3):2290-302. PMCID: PMC4374409.
   d. Sekar TV, Foygel K, Willmann JK, Paulmurugan R. Dual-therapeutic reporter genes fusion for enhanced cancer gene therapy and imaging. Gene Ther. 2013 May; 20(5):529-37.

Complete List of Published Work:

https://www.ncbi.nlm.nih.gov/pubmed/?term=Paulmurugan%20R%5BAuthor%5D&cauthor=true&cauthor_uid=20639890

D. Additional Information: Research Support

Ongoing Research Support

1R01CA209888-01 (Paulmurugan/Willmann/Dahl) 04/01/2016-03/31/2022
NIH
Title: Therapeutic miRNA Modulation of Hepatocellular Carcinoma Using Ultrasound Guided Drug Delivery
Goal: The goal of this grant is to study therapeutic microRNAs delivered by ultrasound microbubble and PLGA-NP in orthotopic human HCC in mice and rabbit to evaluate improved drug responsive profile

1R21 EB022298 (Willmann/Paulmurugan) 04/01/2016-03/31/2018
NIH
Title: 3D Passive Cavitation Imaging-Guided Therapeutic Delivery of MicroRNA into Cancer
Goal: The goal of this grant is to develop 3D passive cavitation to improve US mediated drug and microRNA delivery *in vivo* to improve cancer therapy

1R01 CA16109104 (Martin Porcel-Rodriguez, Mayo Clinic/Paulmurugan-PI-subcontract)
NIH 04/01/2016-03/31/2021
Title: Imaging mitochondrial function of progenitor cells transplanted to the myocardium
Goal: The goal of this grant is to study the function of progenitor cells in the transplanted myocardium *in vivo* by noninvasive molecular imaging.

CCNE-TD Pilot Grant (Paulmurugan/Massoud/Malhotra) 02/01/2017-12/31/2017
NIH
Title: A novel theranostic 'PolyGOLD' nanoparticle customized for intranasal delivery and targeting of glioblastoma
Goal: The goal of this grant is to develop microRNA conjugated Iron-oxide gold nanoparticles for theranostic intranasal delivery for glioma therapy.

Departmental Funding Paulmurugan (PI) 09/01/09 – 12/31/18
Title: Imaging ligand regulated estrogen receptor folding and dimerization in living animals.
The main goal of this grant is to study the ligand regulated estrogen receptor biology in breast cancer
Role: PI

Completed Research Support

GE –Pilot grant **(**Willmann/Paulmurugan) 06/01/2015-06/31/2016
Title: Study of Neuro-modulation using Focused Ultrasound with Concurrent fMRI
The goal of this project is to evaluate the microRNA delivery by Focused Ultrasound with Concurrent fMRI
Role: PI (Multi-PI)

R43 CA183353 Panduranghi (PI) 08/02/14 – 06/30/16
Dual Targeted Human Beta Defensin1 for Improving Chemotherapy
The goal of this grant is targeted delivery of human beta defensin to improve cancer chemotherapy.
Role: PI of sub-contract with Guidepoint Global Research Consultants

Microbiome Seed grant Paulmurugan (PI) 01/01/15 – 06/30/16
Evaluation of microbial distribution, methylation status, and estrogen signaling in primary breast cancer tissues
The purpose of this grant is to evaluate the microbial distribution and estrogen signaling in human breast cancer samples.
Role: PI

Canary Seed grant Utkan Demirci and Paulmurugan 01/01/15 – 06/30/16
Bioprinted Microfluidic Three Dimensional Lung Cancer Microenvironments for Detection of Histone Modification and Cell Migrat
The goal of this proposal is to quantity histone modifications in secreted nucleosomes from bioprinted lung cancer cells grown in a flow culture in before and after treated with anticancer drugs.
Role: Co-PI

CCNE-Pilot Project Paulmurugan (PI) 08/01/14 – 07/31/15
Title: To develop high-sensitive nanoplasmonic sensor for simultaneous quantitation of chromodomains recruitment to two-histone lysine methylation marks (H3K9me3 and H3K4me3)
The purpose of this grant was to develop high sensitive localized nanoplasmonic sensor for measuring the recruitment of chromodomains from royal family structural fold to methylated histone marks in H3 and H4 proteins
Role: PI

R01 CA161091 Paulmurugan (PI) 04/01/12 – 03/31/16
Title: Molecular Sensors for Imaging Histone Methylations in Living Animals
The goal of this grant is to develop *in vivo* imaging methods to study histone methylation specifically in N-tail lysine and arginine.
Role: PI

R21 CA185805 Massoud (PI) 05/01/14 – 04/30/16
Title: Druggable p53 misfolding in cancer: A novel *in vivo* molecular imaging biosensor
The goal of this project is to develop molecular imaging sensors, which sense functional refolding of mutant p53 protein for drug screening in cancer therapy.
Role: PI (Multi-PI)