BIOGRAPHICAL SKETCH
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NAME: Ramanathan, Arvind
eRA COMMONS USER NAME (agency login): ARVINDR
POSITION TITLE: Assistant Professor, Buck Institute for Research on Aging,
Director of Metabolomics
Adjunct Professor Leonard Davis School of Gerontology University of Southern California

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

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
Mumbai University, Mumbai	BS	09/1993	Chemistry
Indian Institute of Technology, Mumbai	MS	09/1995	Biotechnology
New York University, New York, New York	PHD	04/2002	Chemistry

A. Personal Statement

Dr. Ramanathan has extensive training in mass spectrometry-based metabolomics, metabolism, cancer biology and cell signaling. In his post-doctoral research he pioneered the use of metabolomics for elucidating the regulation of metabolism in cancer cells in response to oncogenic and metabolic perturbations. The laboratory develops relative and absolute quantitation, and flux measurements of metabolites from tissue and biofluids using human subject samples and from vertebrate and invertebrate models. Using metabolomics and tissue culture models, the lab is elucidating the fundamental role of branched chain amino acid (BCAA) catabolism in regulating mitochondrial biogenesis and metabolism in skeletal muscle. In this context his laboratory is working on a disease arising from an inborn error in metabolism called Maple Syrup Urine Disease (MSUD). As the director of metabolomics his laboratory has developed sample preparation and analytical approaches to analyze metabolites (using biofluids and tissues) from model organisms including mice, *C. elegans* and Drosophila. He has also established HPLC-ESI-MS- MS protocol to perform drug metabolism studies in *C.elegans*. Ongoing collaborations have resulted in recent publications using *C. elegans* to understand age related glycation end products (AGE) and Vitamin D signaling.

a) Mark, K.A., Dumas, K. J., Bhaumik,D., Schilling, B., Davis, S., Ronnen Oron, T., Sorensen, D., J., Lucanic, M., Brem, R.B., Melov, S., **Ramanathan**, **A**., Gibson, B., Lithgow, G. L., Vitamin D Promotes Protein Homeostasis and Longevity via the Stress Response Pathway Genes SKN-1, IRE-1, and XBP-1 *PMID 27783938, PMC journal in process*
b) Chaudhuri, J., Bose, N., Gong, J., Gong, Hall, D., Rifkind, A., Bhaumik, D., Peiris, T. H., Chamoli, M., Le, C., Liu, J., Lithgow, G., **Ramanathan, A**., X. Z. Shawn Xu, Kapahi, P., Conserved TRPA1-Nrf2 signaling mediates reactive α-dicarbonyl detoxification. (**accepted for publication, Current Biology 2016**) PMC5135008 (Available 2017-11-21)
c) Gutierrez MA, Davis SS, Rosko A, Nguyen SM, Mitchell KP, Mateen S, Neves J, Garcia TY, Mooney S, Perdew GH, Hubbard TD, Lamba DA, **Ramanathan A**., A novel AhR ligand, 2AI, protects the retina from environmental stress. Sci Rep. 2016 Jul 1;6:29025. PMC4929558
d) S Sonnet D, N O'Leary M, A Gutierrez M, M Nguyen S, Mateen S, Hsu Y, P Mitchell K, J Lopez A, Vockley J, K Kennedy B, **Ramanathan A.,** Metformin inhibits Branched Chain Amino Acid (BCAA) derived ketoacidosis and promotes metabolic homeostasis in MSUD..Sci Rep. 2016 Jul 4;6:28775. PMC4931503

B. Positions and Honors

Positions and Employment

1993 - 1995 Research Fellow, K.K. Rao Laboratory, Biotechnology Center, Indian Institute of Technology, Mumbai
1995 - 1999 Research Fellow, David C. Schwartz Laboratory, Dept. of Chemistry , New York, NY
1999 - 2002 Research Scientist, David C. Schwartz Laboratory, Biotechnology Center, Madison, WI

2002 - 2010	Research Scientist I, Stuart Schreiber's Laboratory, Chemical Biology Program, Cambridge, MA
2011 -	Assistant Professor, Buck Institute for Research on Aging, Novato, CA

Other Experience and Professional Memberships

Honors

2011	Hillblom early investigator grant
2005	Pinnacle Grant, Smith Family Foundation

C. Contribution to Science

Biochemical products of cellular metabolism (metabolites), along with proteins and RNA are the central components for cellular function. Therefore to understand the global metabolic state of cells, it is important to measure levels and reaction fluxes of metabolites. Intracellular signaling plays an important role in coordinating metabolism with the proliferative and developmental state of the cell. A central player, mTOR, functions in a cellular nutrient-sensing network by receiving inputs derived from both nutrients and growth factors. It then directs outputs to the appropriate down-stream effectors of metabolism. The over all goal of my research is to address fundamental gap in our knowledge of the global physiological relationships between cell proliferation, cell differentiation and cellular signaling in disease using metabolomics.

1. Elucidating the effect of genetic variation on cancer metabolism, using a serially transduced cell line model of tumorigenesis and metabolic profiling - With my colleagues, I developed an LC-MS/MS based metabolomic profiling technology; we designed a platform for a targeted, semi-quantitative measurement of 205 endogenous metabolites. I have co-authored manuscripts detailing work where we applied this technology to profile metabolites from human plasma (Lewis et. al. 2008) and mammalian cells (Ramanathan *et. al.* 2010). We discovered that metabolic profiling of the inhibition of mitochondrial function in cells, uncovered biomarkers of mitochondrial disease that were also validated in human patients. This is an exciting avenue for the discovery of new biomarkers of mitochondrial disease in the future. We have also used high-throughput approaches of assaying for cellular metabolism in order to discover mechanisms of drug induced mitochondrial dysfunction (Wagner et. al. 2008). I uncovered fundamental insights into cancer-cell metabolism by investigating a cell-line model of tumorigenesis (Ramanathan *et. al.* 2005). This study probed cancer genotype in increasingly tumorigenic cells using deep metabolic profiling and the resulting correlations provided a firm foundation for the well-known Warburg effect. I demonstrated that oncogenes drive metabolism, increasingly towards aerobic glycolysis, resulting in increased: 1) sensitivity to inhibitors of glycolysis (targeting hexokinase and phosphoglucose isomerase) and 2) resistance to inhibitors of respiration (targeting ATP synthase). I have also characterized the global metabolic effects of the cancer type M2 pyruvate (Christofk *et. al.* 2008).

a) Christofk H.R., Vander Heiden M.G., Harris M.H., **Ramanathan A**., Gerszten R.E., Wei R., Fleming M.D., Schreiber S.L., Cantley L.C. The M2 splice isoform of pyruvate kinase is important for cancer metabolism and tumour growth. Nature, 2008, 452, 230-233 PMID: 18337823

b) **Ramanathan A.,** Wang C., Schreiber S.L. Perturbational profiling of a cell-line model of tumorigenesis by using metabolic measurements. Proc. Natl. Acad. Sci. U.S.A. 2005, 102, 5992- 5997

2. Discovering a direct mechanism of control of mitochondrial function my mTOR- Studies have shown that treatment with rapamycin (a small molecular inhibitor of mTOR) does not result in a decrease in mitochondrial content (Schieke et.al. 2006) even after 8 hours, indicating that mTOR mediated transcriptional regulation might not be the point of metabolic control in certain cells. Using metabolic profiling, we investigated whether mTOR affects immediate control over cellular metabolism by post-translational mechanisms. Inhibiting the FKBP12/rapamycin-sensitive subset of mTOR functions in leukemic cells rapidly induced aerobic glycolysis and a decrease in uncoupled mitochondrial respiration. mTOR is in a complex with the mitochondrial outer-membrane protein Bcl-xl and VDAC1. Bcl-xl is a kinase substrate for mTOR *in vitro* (Ramanathan et.al. 2009). Our studies reveal that mTOR controls mitochondrial function by modulating Bcl-xl in the outer mitochondrial membrane and that inhibition of mTOR induced a state of increased dependence on aerobic glycolysis in leukemic cells as judged by the synergy between the glycolytic inhibitors and rapamycin in reducing levels of

intracellular ATP. A high-throughput screen of approximately 3000 bioactive natural products in L6 myoblast cells revealed five small molecule inhibitors of glycolytic metabolism, the combination of rapamycin and four of the compounds displayed synergy in reducing the levels of intracellular ATP in leukemia cells (Ramanathan et.al. submitted).

a) **Ramanathan A**. and Schreiber S.L. Direct control of mitochondrial function by mTOR. Proc. Natl. Acad. Sci. USA 2009, 106, 22229- 22232*:* PMC2796909

3. Discovering the inter-relationships between metabolic and differentiation networks - We sought to determine how carbon metabolism is integrated into the cellular differentiation network. Using automated, image-based RNAi screening and metabolic profiling, we discovered three metabolic enzymes whose knock-down induce differentiation of mouse C2C12 myoblasts *dominant over growth factor signaling*: phosphoglycerate kinase (Pgk), hexose-6-phosphate dehydrogenase (H6pd) and ATP citrate lyase (Acl) (Ramanathan *et. al.* 2010). We found that H6pd induces differentiation in a calcium-calcineurin dependent fashion; and that Acl effects differentiation by modulating chromatin acetylation and cholesterol metabolism. These enzymes and the pathways they regulate provided novel targets for the control of myogenic differentiation in myoblasts and rhabdomyosarcoma cells (Ramanathan et. al. 2010).

a) **Ramanathan A**., Bracha A., Huang S., Ingber D. and Schreiber S.L. Carbon metabolism mediated myogenic differentiation. Nat. Chem. Biol 2010, 6.202-204 (Featured on cover of issue). PMC2822028

4. Metabolomics technology and biomarker discovery - Metabolomics is a comprehensive analysis of endogenous naturally occurring biomolecules. We have developed directed MS/MS based assays to discover biomarkers of mitochondrial dysfunction in mitochondrial and cardiovascular disease.

a) Lewis G.D., Wei R., Liu E., Yang E., Shi X., Martinovic M., Farrell L., Asnani A., Cyrille M., **Ramanathan A**., Shaham O., Berriz G., Lowry P.A., Palacios I.F., Taşan M., Roth F.P., Min J, Baumgartner C., Keshishian H, Addona T, Mootha VK, Rosenzweig A, Carr SA, Fifer MA, Sabatine M.S., Gerszten R.E. Metabolite profiling of blood from individuals undergoing planned myocardial infarction reveals early markers of myocardial injury. J. Clin. Invest., 2008, 118, 3503- 3512 PMC2525696
b) Shaham O., Goldberger O., **Ramanathan A**., Clish C., Sims K.B. and Mootha V.M. A plasma signature of human mitochondrial disease revealed through metabolic profiling of spent cell culture media. Proc Natl Acad Sci U S A. 2010 Jan 26;107(4):1571-5. doi: 10.1073/pnas.0906039107. Epub 2010 Jan 8. PMC2824369
c) Wagner B.K., Kitami T., Gilbert T.J., Peck D., **Ramanathan A**., Schreiber S.L., Golub T.R., Mootha VK. Large-scale chemical dissection of mitochondrial function. Nat. Biotechnol. 2008, 26, 343- 351 PMC2715872

5. Targeting AhR signaling against diseases of retinal degeneration- Retinal degeneration is a physiological phenomenon that is a feature of various disease conditions such as dry and neovascular age-related macular degeneration, retinitis pigmentosa, and diabetic retinopathy. Such conditions involve the degeneration of the retinal pigmented epithelial (RPE) layer of the retina, which consequently results in the death of rod and cone photoreceptors that they support, structurally and functionally. This, in turn, inevitably leads to legal or complete blindness. Therefore, developing therapeutic strategies to preserve cellular homeostasis in the RPE despite degenerative conditions would be a favorable asset in the clinic. The aryl hydrocarbon receptor (AhR) is a conserved, environmental ligand-dependent, per ARNT-sim (PAS) domain containing bHLH transcription factor that mediates adaptive response to stress via its downstream transcriptional targets. The activation of this signaling pathway results in the expression of a battery of detoxifying factors, including CYP450 enzymes. Using *in silico* and *in vitro* assays, a novel synthetic ligand of AhR that protects RPE cells from lipid peroxidation cytotoxicity mediated by 4-hydroxynonenal (4HNE). Additionally, metabolic characterization of this molecule by LC-MS suggests that 2AI alters the lipid metabolism of RPE cells, enhancing the intracellular levels of palmitoleic acid. Finally, we show that, as a downstream effector of 2AI-mediated AhR activation, palmitoleic acid protects RPE cells from 4HNE-mediated stress, and light mediated eye degeneration in *Drosophila*.

Complete List of Published Work in My NCBI Bibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/arvind.ramanathan.2/bibliography/43513593/public/?sort=date&direction=ascending

D. Research Support

Ongoing Research Support

R01AG057353-01 (MPI: Ramanathan, Jasper) 09/15/17-05/31/22
NIH/NIA
"Proteostasis and metabolism in brain aging"
The aims of this project are: 1) Determine if changes in energy metabolism downstream of JNK/IIS influence protein turnover 2) Assess age-related changes in protein turnover and metabolic flux in long-lived mutants 3) Perform genetic studies to explore the causes of aging and longevity..
Role: Co-investigator

RF1AG057358- 01 (MPI: Lithgow, Anderson) 09/15/17-06/30/22
NIH/NIA
The aims of this project are: 1) Determine the effects of the induction of autophagy by C1 in AD models in the invertebrate nematode worm *C. elegans.* 2) Determine the temporal order of energetic and metabolic dysfunction in *C. elegans* AD models. 3) Determine the temporal order of proteomic changes in *C. elegans* AD models.
Role: Co-Investigator

R01AG209631 (Lithgow) 05/01/14 - 04/30/19
NIH/ NIA
Pharmacology of Lifespan Extension
Identify the mechanism of lifespan extension with focus on vitamin D - shown to maintain protein homeostasis and extend lifespan in *C.elegans*. This will uncover novel mechanisms for interventions in aging and age related disease.
Role: Co-Investigator

R01AG050441-01A1 (Kennedy) 09/30/16-05/31/21
NIH/ NIA
mTORC1 Signaling in Aging and Metabolism
This proposal seeks to understand the relationship between metabolism and aging with respect to the mTOR pathway, identifying key mechanisms underpinning the beneficial effects of reduced mTOR signaling and developing novel therapeutics to prevent disease and/or extend human healthspan.
Role: Investigator

R01NS100529 (Ellerby) 09/30/16-08/31/21
NIH/ NIA
Identifying Factors Regulating Medium Spiny Neuron Differentiation or Maintenance as Therapeutic Targets for Huntington's Disease using Induced Pluripotent StemCells
The aims of this project are: 1) We will characterize the cellular and functional deficits in normal iPSCs, HDiPSCs, and genetically corrected HD-iPSCs to identify therapeutic targets for HD. 2) We will determine factors that mediate differentiation into patch and matrix medium spiny neurons for this cellular HD model and 3) We will determine if netrin or other MSN-related molecules provide therapeutic benefitin HD mouse models.
Role: Co-Investigator

2U01 AG045844-04 (Lithgow) 03/01/17-02/28/22
NIA/NIH
Caenorhabditis Intervention Testing Program – Buck Institute Compound Testing
The Caenorhabditis Intervention Testing Program has been established to identify pharmacological interventions that improve the length of life and/or the quality of aging. By testing genetically diverse animal models, this study seeks to identify interventions likely to be efficacious in a diverse human population. This study may ultimately lead to treatments that protect against physical deterioration, cognitive decline, and disease susceptibility in the elderly human population.

Astellas SRA (PI: Melov) 09/22/17 – 09/22/18
Corporate Agreement
Proprietary

Completed Research Support

R56AG050441-01 (PI: Kennedy) 09/15/15 – 08/31/16
National Institute on Aging
mTORC1 Signaling in Aging and Metabolism
Role: Co-investigator

R21 AG048528 (Lithgow) 09/01/14 – 04/30/16
National Institute on Aging
Vitamin D metabolism and lifespan determination
There is considerable debate about how much vitamin D supplements we should all be taking with some experts believing just about everyone over 65 is vitamin D deficient. If this is true, then it is a major public health issue because low vitamin D levels is associated with increased risk of age-related chronic conditions
Role: Co-investigator

Ramanathan, Hillblom Foundation 07/01/12 - 06/30/15
Ramanathan, Arvind (PI)
Start Up Grant
Metabolic basis of environmental stress signaling in skeletal muscle by achieving the objectives of this proposal, we expect to gain the ability to detect and prevent toxic chemicals from negatively affecting muscle function.
Role: PI