BIOGRAPHICAL SKETCH

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NAME: Gama, Vivian

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

POSITION TITLE: Associate 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
Universidad de los Andes, Colombia	BS	01/1999	Microbiology
University of Wisconsin-Milwaukee	MS	09/2002	Clinical Laboratory Sciences
Case Western Reserve University	PHD	01/2009	Pharmacology
University of North Carolina at Chapel Hill	Postdoctoral Fellow	08/2015	Neuronal and stem cell apoptosis

A. Personal Statement

Broad questions of how mitochondrial structure/function and apoptosis execution programs are coordinated to regulate cell fate have been the major theme of my training and guide my lab's research program. Since starting my laboratory 5.5 years ago at Vanderbilt University, I have expanded these studies to examine how mitochondrial-related molecular mechanisms are involved in maintaining stem cell pluripotency/multipotency, and self-renewal. Many mitochondrial proteins do not only function under stress conditions but also have critical functions during the life of stem cells, and during neuronal development. Despite the irrefutable link between mitochondrial dysfunction and human disease, the exact mechanisms by which mitochondrial morphology and function influence human brain development remain largely unexplored. My laboratory is inspired to reveal the intricate mechanisms by which mitochondrial health and metabolism are linked to the normal development of the human central nervous system. We are approaching this fascinating topic from the unique angle of examining the function of the BCL-2 family in organelle dynamics and metabolism. Elucidating these basic molecular mechanisms has clear implications for development and disease. Another focus of our laboratory is on a rare disease caused by mutations in the gene DNML1, encoding the Dynamin related protein 1, a GTPase that is essential for mitochondrial fission. Most of these mutations are heterozygous missense mutations affecting either the GTPase (catalytic domain) or the stalk domain (regulating protein-protein interactions and folding). Children present with heterogeneous symptoms including developmental delay, muscle tone abnormalities, seizures, and ataxia. The specific mechanisms by which deficient fission of the mitochondria affects mitochondrial functions such as metabolism, mitophagy or cell death have not been determined. It is also not known whether or how DRP1 dysfunction affects the identity or function of neural progenitors, intermediate progenitors or mature neurons during brain development. We are using classical biochemical and cellular approaches, state-of-the-art imaging techniques patient-derived pluripotent stem cell-derived model systems like brain organoids and oligospheres, as well as CRISPR-based inducible systems. Given our scientific background, model systems experimental tools as well as the research environment at Vanderbilt University, our laboratories are uniquely positioned to gain fundamental insight into how abnormal mitochondrial fitness affects early neurogenesis.

I am passionate about mentoring and guiding trainees to discover their inherent talents and allowing them to set their own paths with my unwavering support. As an international graduate student, postdoctoral fellow, and faculty member, I focused particularly on students from underrepresented backgrounds in STEM struggling to adapt to the rigorous graduate school life. Since starting my independent position at Vanderbilt five and half years ago, first as an Assistant Professor, and now as an Associate Professor, I have been fortunate to have mentored eight graduate students (7 women; 5 students from underrepresented backgrounds in STEM) and fourteen undergraduate students (11 women; 7 students from underrepresented backgrounds in STEM). All of the graduate trainees in my laboratory have contributed to peer-reviewed publications and all have received their own research funding – from either the National Institutes of Health (i.e., Training grants (T32), F31 pre-doctoral fellowships, and/or Blueprint D-SPAN F99/K00), the American Heart Association pre-doctoral fellowships, or the HHMI Gilliam Fellowship. Four senior graduate students in the laboratory, graduated with their Ph.D., and most

importantly, four of them secured positions in industry (1), academia (2), or scientific writing (1). Six undergraduate mentees trained in my laboratory have contributed to manuscripts lead by their laboratory mentors. In addition to mentoring members of my own laboratory, I also serve as an auxiliary mentor for graduate students who have completed their first year. As faculty members, it is important that we continue developing mentoring skills through the various resources available. This awareness-raising helped me identify personal assumptions, biases, and privileges that may affect mentoring relationships. My laboratory aims to have a strong emphasis on nurturing future scientists while pursuing exciting and undiscovered directions in the field of mitochondrial biology.

Ongoing projects that I would like to highlight include:

1R35GM128915-01, MIRA, **NIH/NIGMS**
Gama, Vivian (PI)
08/01/18-07/30/23
The BCL-2 family controls stem cell identity by regulating mitochondrial dynamics and priming

1R01MH123971-01, **NIH/MH**
Gama, Vivian/Bellan, Leon (MPI)
07/01/2020 – 06/30/2023
Modeling developmental gradients and supportive tissue signaling networks using iPSC-derived forebrain organoids

1R21CA227483-01A1, **NIH/NCI**
Gama, Vivian (PI)
04/01/19-03/31/22 (NCE)
Assessing the contribution of mitochondrial heterogeneity to gliomagenesis using single cell approaches

Citations:

1. Joshi P, Bodnya C, Rasmussen ML, Romero-Morales AI, Bright A, **Gama V**. Modeling the function of BAX and BAK in early human brain development using iPSC-derived systems. *Cell Death Dis*. 2020 Sep 25;11(9):808. PubMed Central PMCID: PMC7519160.
2. Rasmussen ML, Taneja N, Neininger AC, Wang L, Robertson GL, Riffle SN, Shi L, Knollmann BC, Burnette DT, **Gama V**. MCL-1 Inhibition by Selective BH3 Mimetics Disrupts Mitochondrial Dynamics Causing Loss of Viability and Functionality of Human Cardiomyocytes. *iScience*. 2020 Apr 24;23(4):101015. PubMed Central PMCID: PMC7155208.
3. Romero-Morales A.I., Robertson G.L., Rastogi A., Temuri H., Rasmussen M.L, McElroy G., Hsu L., Almonacid P., Chandel N.S., Cartailler J-P., **Gama V**., Human iPSC-derived cerebral organoids model features of Leigh Syndrome and reveal abnormal corticogenesis. *bioRxiv*. 2020 April. DOI: https://doi-org.proxy.library.vanderbilt.edu/10.1101/2020.04.21.054361. In review at *Development.*
4. Rasmussen ML, Kline LA, Park KP, Ortolano NA, Romero-Morales AI, Anthony CC, Beckermann KE, **Gama V**. A Non-apoptotic Function of MCL-1 in Promoting Pluripotency and Modulating Mitochondrial Dynamics in Stem Cells. *Stem Cell Reports*. 2018 Mar 13;10(3):684-692. PubMed Central PMCID: PMC5918190.

B. Positions, Scientific Appointments and Honors

Positions and Scientific Appointments

2015 -	Assistant Professor, Vanderbilt University, Department of Cell and Developmental Biology, Vanderbilt Center for Stem Cell Biology
2008 - 2015	Postdoctoral Fellow - Dr. M. Deshmukh., Neuroscience Center, UNC-Chapel Hill
2003 - 2008	Ph.D - Dr. S. Matsuyama, Case Western Reserve University
1999 - 2002	M.Sc. Graduate student - Dr. L. Sabatini., Univ. of Wisconsin-Milwaukee.

Honors

2001	Irwin Amrani Scholarship Award for Outstanding Academic Achievement, University of Wisconsin
2002	Excellence in Research Award (1st Place), School of Health Professions - University of Wisconsin
2002	Irwin Amrani Scholarship Award for Outstanding Academic Achievement, University of Wisconsin
2002	Scientific Research Award to the Best Master Thesis, University of Wisconsin
2006	Graduate Student of the Year Award, Pharmacology Department - Case Western Reserve University
2006	Marcus Singer Award for Best Presentation at the Biomedical Graduate Student Symposium, Case Western Reserve University
2006	University Hospitals of Cleveland Award for Outstanding Graduate Student Presentation, Case Western Reserve University
2008	Neinmark Graduate Student Award, AAAS
2008	Marcus Singer Award for Best Presentation at the Biomedical Graduate Student Symposium, Case Western Reserve University
2008	Research Showcase Scholarship to the Best PhD. Research Project, Case Western Reserve University
2010	Best Postdoctoral Fellow Presentation Award, University of North Carolina at Chapel Hill
2011	Best Postdoctoral Fellow Presentation Award, University of North Carolina at Chapel Hill
2012	Postdoctoral Award for Research Excellence, University of North Carolina at Chapel Hill
2013	Pathway of Independence Award (K99/R00), National Institute of Health
2014	Postdoctoral Scholar Award for Excellence in Mentoring, University of North Carolina at Chapel Hill
2015	Van L. Weatherspoon Brain Tumor Research Award, University of North Carolina at Chapel Hill
2015	Finalist to Earl Stadtman Investigators Program, National Institute of Health
2020 - 2020	Leadership Alliance Award, The Leadership Alliance
2020 - 2023	Gilliam Fellow Adviser, Howard Hughes Medical Institute (HHMI)

C. Contribution to Science

1. Identification of novel mechanisms regulating mitochondrial-mediated cell death pathways in stem cells. Our research demonstrated that core components of the apoptotic machinery are differentially regulated in stem cells and that this unique regulation is critical for the ability of stem cells to respond rapidly to stress. In particular, we found that undifferentiated human embryonic stem cells are primed for rapid apoptosis by maintaining the pro-apoptotic protein Bax in its active conformation at the Golgi. Remarkably, just two days of differentiation induced significant changes: Bax was no longer in an active state and the cells were no longer highly sensitive to DNA damage. My laboratory also identified MCL-1, an anti-apoptotic protein of the BCL-2 family, as a crucial mitochondrial membrane shaping protein in stem cells. We continue to explore these mechanisms in the context of mitochondrial structure and function. These results have put into focus the dynamic regulation of the apoptotic machinery during stem cell differentiation and the potential for the members of the BCL-2 family to have novel functions in cells.

    a. Joshi P, Bodnya C, Rasmussen ML, Romero-Morales AI, Bright A, **Gama V**. Modeling the function of BAX and BAK in early human brain development using iPSC-derived systems. Cell Death Dis. 2020 Sep 25;11(9):808. PubMed Central PMCID: PMC7519160.

    b. Rastogi A., Joshi P, Contreras E, **Gama V**. Remodeling of mitochondrial morphology and function: an emerging hallmark of cellular reprogramming. Cell Stress. 2019 May 27;3(6):181-194. PubMed Central PMCID: PMC6558935.

    c. Rasmussen ML, Kline LA, Park KP, Ortolano NA, Romero-Morales AI, Anthony CC, Beckermann KE, **Gama V**. A Non-apoptotic Function of MCL-1 in Promoting Pluripotency and Modulating Mitochondrial

Dynamics in Stem Cells. Stem Cell Reports. 2018 Mar 13;10(3):684-692. PubMed Central PMCID: PMC5918190.

d. Dumitru R*, **Gama V***, Fagan BM, Bower JJ, Swahari V, Pevny LH, Deshmukh M. Human embryonic stem cells have constitutively active Bax at the Golgi and are primed to undergo rapid apoptosis. Mol Cell. 2012 Jun 8;46(5):573-83. PubMed Central PMCID: PMC3372694. *Co-first authors

2. Examining novel non-apoptotic functions of MCL-1 and associated proteins of the BCL-2 family in modulating mitochondrial morphology and function in progenitors and differentiated cells. Our discovery that MCL-1 is a mitochondrial shaping protein has been the basis to elucidate whether this function of MCL-1 is maintained or modified in differentiated cells. We found that in human cardiomyocytes MCL-1 is essential for their functionality. On the other hand, while neural stem cells can survive without MCL-1, they lose the expression of key identity markers. We find that MCL-1 interacts with structural components of the mitochondrial cristae. These discoveries will help expand on the function of MCL-1 and related proteins during differentiation.

   a. Cleveland AH., Romero-Morales AI., Azcona LA., Herrero M, Elroy-Stein O, **Gama V***, Gershon TR*. Leukodystrophy resembling Vanishing White Matter Disease is recapitulated by brain-specific depletion of apoptosis regulator MCL-1. bioRxiv. 2020 December 03. Available from: https://doi.org/10.1101/2020.12.02.408138. Accepted to Cell Death and Disease. *Co-corresponding authors.

   b. Rasmussen ML, Taneja N, Neininger AC, Wang L, Robertson GL, Riffle SN, Shi L, Knollmann BC, Burnette DT, **Gama V**. MCL-1 Inhibition by Selective BH3 Mimetics Disrupts Mitochondrial Dynamics Causing Loss of Viability and Functionality of Human Cardiomyocytes. iScience. 2020 Apr 24;23(4):101015. PubMed Central PMCID: PMC7155208.

   c. Rasmussen ML, **Gama V**. A connection in life and death: The BCL-2 family coordinates mitochondrial network dynamics and stem cell fate. Int Rev Cell Mol Biol. 2020;353:255-284. PubMed Central PMCID: PMC7331972.

   d. Crowther AJ*, **Gama V***, Bevilacqua A, Chang SX, Yuan H, Deshmukh M, Gershon TR. Tonic activation of Bax primes neural progenitors for rapid apoptosis through a mechanism preserved in medulloblastoma. J Neurosci. 2013 Nov 13;33(46):18098-108. PubMed Central PMCID: PMC3828463. *Co-first authors.

3. Revealing the function of the dynamic properties of mitochondria in early human brain development. Our research is focused on understanding how the dynamic properties of the mitochondria (i.e. mitochondrial fragmentation/fusion, motility, mitophagy, apoptosis) are regulated during early human brain development using pluripotent stem cell-derived systems (e.g. neural differentiation, neural rosettes, brain organoids). We are keen in developing tools that allow us to examine these early stages of human development that had remained understudied.

   a. Baum T, **Gama V**. Dynamic properties of mitochondria during human corticogenesis. Development. 2021 Feb 19;148(4) PubMed Central PMCID: PMC7903999.

   b. Romero-Morales A.I., Robertson G.L., Rastogi A., Temuri H., Rasmussen M.L., McElroy G., Hsu L., Almonacid P., Chandel N.S., Cartailler J-P., **Gama V**. Human iPSC-derived cerebral organoids model features of Leigh Syndrome and reveal abnormal corticogenesis. bioRxiv; 2020. DOI: https://doi-org.proxy.library.vanderbilt.edu/10.1101/2020.04.21.054361. In review at Development.

   c. Robertson GL, Romero-Morales AI, Lippmann ES, **Gama V**. Uncovering cell biology in the third dimension. Mol Biol Cell. 2020 Mar 1;31(5):319-323. PubMed Central PMCID: PMC7183789.

   d. Romero-Morales AI*, O'Grady BJ*, Balotin KM, Bellan LM, Lippmann ES, **Gama V**. Spin∞: an updated miniaturized spinning bioreactor design for the generation of human cerebral organoids from pluripotent stem cells. HardwareX. 2019 Oct;6 PubMed Central PMCID: PMC7451502. *Co-first authors

4. Understanding the role of the ubiquitin system regulating cell death in neurons and brain tumor cells. I am interested in revealing novel mechanisms by which cancer cells evade apoptosis. While neurons and cancer cells are vastly different cell types, they both restrict apoptosis to survive long-term. I found cytochrome c to be rapidly targeted for degradation by the E3 ligase PARC (also known as CUL9) selectively in neurons and

brain tumor cells. Cytochrome c was the first substrate of PARC/Cul9 reported in the literature. I also found that Ku70 is a novel regulator of cell death mediated by Bax in cancer cells.

a. Ortolano NA, Romero-Morales AI, Rasmussen ML, Bodnya C, Kline LA, Joshi P, Connelly JP, Rose KL, Pruett-Miller SM, **Gama V**. A proteomics approach for the identification of cullin-9 (CUL9) related signaling pathways in induced pluripotent stem cell models. PLoS One. 2021;16(3):e0248000. PubMed Central PMCID: PMC7951927.
b. Ortolano NA, **Gama V**. Chronicle of a Neuronal Death Foretold: Preventing Aging by Keeping MGRN1 at the Nucleus. Mol Cell. 2017 May 4;66(3):301-303. PubMed PMID: 28475865.
c. **Gama V**, Deshmukh M. Life after MOMP. Mol Cell. 2015 Apr 16;58(2):199-201. PubMed Central PMCID: PMC4879686.
d. **Gama V**, Swahari V, Schafer J, Kole AJ, Evans A, Huang Y, Cliffe A, Golitz B, Sciaky N, Pei XH, Xiong Y, Deshmukh M. The E3 ligase PARC mediates the degradation of cytosolic cytochrome c to promote survival in neurons and cancer cells. Sci Signal. 2014 Jul 15;7(334):ra67. PubMed Central PMCID: PMC4182917.

Complete List of Published Work in My Bibliography (total of 43 publications):

https://www-ncbi-nlm-nih-gov.proxy.library.vanderbilt.edu/myncbi/vivian.gama.1/bibliography/public/