BIOGRAPHICAL SKETCH

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NAME: Estela Jacinto

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

POSITION TITLE: 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)*	Completion Date MM/YYYY	FIELD OF STUDY
University of the Philippines	B.S.	06/1986	Zoology
University of California, San Diego	Ph.D.	09/1997	Biomedical Sciences Mentor: Michael Karin
Biozentrum, Univ. of Basel, Switzerland	Post-doc	11/2004	Molecular Biology Mentor: Michael N. Hall

A. Personal Statement

Research in my lab aims to understand how nutrients and growth factors control intracellular signaling pathways and how these pathways are coupled to cellular metabolism and gene expression. We specifically focus on the mTOR signaling pathway and how it plays a role in metabolism in T cells using cellular and animal models. Our goal is to understand how cells rewire metabolic processes in response to genetic and environmental changes in order to develop better therapeutic strategies against diseases arising from metabolic dysfunction. As a graduate student in Michael Karin's lab, I elucidated how the JNK/MAPK pathway controls T cell activation. As a post-doctoral fellow in the lab of Michael Hall, I have identified and characterized the rapamycin-insensitive protein complex in mammals (mTORC2). Since I started my lab at Rutgers-, we identified new components and functions of mTORC2. My lab has been at the forefront of the mTOR, particularly mTORC2, signaling field. Recently, we discovered that mTORC2 activation is enhanced during nutrient-limiting conditions to promote flux through the hexosamine biosynthetic pathway (HBP). We generated several animal models to further address the role of mTORC2 and the HBP in metabolism in T cells.

Since coming to Rutgers (formerly UMDNJ 2004-2013), I have trained or am currently training a total of 10 post-doctoral fellows, 4 Ph.D. graduate students, 1 medical student, 15 M.S. students, 34 undergraduate students, 2 high school students and 6 lab technicians/research assistant. In addition, I have also supervised 23 rotation graduate students and have served on thesis committees of 11 Ph.D. candidates and 5 M.S. candidates. Two of my Ph.D. graduate students were awarded the Dean's Research Award for Outstanding Research Publication by a Graduate Student. Two of my post-doctoral fellows were awarded a Post-doctoral Fellowship from NJ Commission on Cancer Research. Three of my graduate students were also funded by an administrative supplement to enhance diversity from my NIH grants. All of my former post-doctoral and graduate trainees have obtained scientific positions in industry or academia. Most of my MS or undergrads go to medical or graduate school. I have been nominated by one of my undergraduate work-study students as a Supervisor of the year (2006). I am also a member of the Molecular Biosciences (MBS) Graduate Program Admissions Committee (since 2012) and have also served in the Recruitment Committee and Qualifying Exams Committee of that program. I have also participated in the development of the Fundamentals of Biosciences curriculum for first year MBS graduate students and the integrated course curriculum for first year medical students. I am fully committed to train students and fellows in the basic sciences, focusing on immunity-related research, that will prepare them to pursue basic, clinical and/or translational research. Ongoing projects that I would like to highlight include:

1 R01 GM137493-01 (PI: Jacinto) 4/1/2020-3/31/24
NIH/NIGMS
mTORC2 signaling in metabolism and cell fate
The aims of the proposed project are to elucidate how mTORC2 and the HBP play a role in controlling αβ-T cell versus γδ-T cell development.
Supplement for Diversity Student 4/1/2022-3/31/2023
3R01GM137493-03S1

NJCCR Pediatric Research Grant (PI:Jacinto) 6/1/2022-5/31/2024
Award No. COCR22PRG009
Targeting mTOR and metabolism in lymphoma

B. Positions and Honors

Positions, Scientific Appointments:

2018-present	Professor, Dept. of Biochemistry and Molec. Biol., Rutgers-RWJ Medical School
2011-2018	Associate Professor (tenured), Dept. of Physiology and Biophysics/renamed Dept of Biochemistry and Molecular Biology, Rutgers –RWJMS, Piscataway, NJ
2004-2011	Assistant Professor, Dept. of Physiology and Biophysics, UMDNJ-RWJMS, Piscataway, NJ
1997-2004	Post-Doctoral Fellow, Dept. of Biochemistry, Biozentrum, Univ. of Basel, Switzerland
1991-1997	Graduate Student, Dept. of Pharmacology, Univ. of California, San Diego
1990-1991	Research Associate, Clontech Laboratories, Palo Alto, CA
1989	Research Technician, Richardson Researches, Hayward, CA
1988	Research Technician, Sogetal Inc., Hayward, CA

Other Professional Activities

2020-2022	ACS TBE study section, Co-chair
2021	PLOS Genetics, Guest Editor
2021	Genes (Special Issue: Signaling and Gene Regulation in Metabolism), Guest Editor
2019	Genes (Special Issue: Cellular Control of Growth Signaling), Guest Editor
2013-2019	NIH CSRS Study Section, Member
2014-present	Journal of Biological Chemistry (Editorial Board)
2011-present	Frontiers in Cellular and Molecular Oncology (Editorial Board)
2010-2016	ACS Tumor Biochemistry and Endocrinology Study Section Member (Chair 2014)

Honors and Awards

2022	NJCCR Pediatric Research Grant “Targeting mTOR and metabolism in lymphoma”
2020	NIH/NIGMS R01 “mTORC2 signaling in metabolism and cell fate”
2018	Extended Service Award (for Admissions Committee of Rutgers MBS Program)
2015	Edward J. Ill Outstanding medical research scientist award for basic biomedical research
2014-2018	NIH/NIGMS R01 “The regulation of cell metabolism and proliferation by mTOR complex 2”
2013	Foundation of UMDNJ Excellence in Research Award
2012-2017	NIH/NCI R01 “Cotranslational functions of mTOR”
2011	2010 Signaling Breakthroughs of the Year (for EMBO J. paper), Science Signaling
2011-2014	Stand Up to Cancer Innovative Research Grants “Targeting protein quality control for cancer therapy”
2009-2013	Investigator Award, Cancer Research Institute “mTOR targets in T lymphocyte development”
2008-2013	NIH/NIGMS R01 “The regulation of cell survival by the rapamycin-insensitive mTOR complex”
2007-2011	Research Scholar Grant, American Cancer Society “Mammalian TOR and SIN1 in tumor growth and metastasis”
2006-2008	NJ Commission on Cancer Research “Phosphorylation of target of rapamycin complexes in growth regulation”
2006	Rutgers Univ. Supervisor of the Year Nominee
2005-2008	Scientist Development Grant, American Heart Association “The regulation of actin cytoskeleton organization by the target of rapamycin (TOR)”
2004	Best Poster Award, Cell Growth Meeting, Instituto Juan March, Madrid, Spain

2004 Fellowship from the Novartis Foundation
1998-2002 Cancer Research Institute Postdoctoral Fellowship
1994 Travel Award, Immunology Course, Naples, Italy
1993-1994 Graduate Fellowship from Tobacco Research Foundation

C. Contributions to Science:

***As a post-doc in the lab of Michael N. Hall (Biozentrum, Switzerland; discoverer of target of rapamycin [TOR]), I have elucidated how TOR controls growth via protein phosphatases. I also contributed to the discovery of mTORC2 (mTOR complex 2).**
mTORC2 is the long sought-after protein kinase that targets an oncogene that is often deregulated in cancer (Akt). My studies have revealed that the function of yeast TORC2 in actin cytoskeleton reorganization is also conserved in mammals. mTORC2, in contrast to mTORC1, is not inhibited directly by rapamycin. A number of mTOR drugs, particularly inhibitors that can target both mTORC1 and mTORC2 are currently under clinical trials for different cancer types.

1. Jacinto, E., Guo, B., Arndt, K.T., Schmelzle, T., and Hall, M.N. TIP41 interacts with TAP42 and negatively regulates the TOR signaling pathway. **Molecular Cell 2001,** 8, 1017-1026. PMID: 11741537 *(cited 281)*

2. Loewith, R., Jacinto, E., Wullschleger, S., Lorberg, A., Crespo, J.L., Bonenfant, D., Oppliger, W., Jenoe, P., and Hall, M.N. Two TOR complexes, only one of which is rapamycin sensitive, have distinct roles in cell growth control. **Molecular Cell 2002,** 10, 457-468. PMID: 12408816 *(cited 2199)*

3. Jacinto, E.[#], Loewith, R.[#], Schmidt, A., Lin, S., Ruegg, M., Hall, A., and Hall, M.N. Mammalian TOR complex 2 (mTORC2) controls the actin cytoskeleton and is rapamycin insensitive. **Nature Cell Biology 2004** 6, 1122-1128. PMID: 15467718. [#] equal contributors *(cited 2560)*

***As an Assistant Professor at UMDNJ, I discovered a crucial component of mTORC2, SIN1, in collaboration with Bing Su (Yale).**
Our **Cell 2006** was the first to demonstrate the function of mTORC2 using a knockout mTORC2 mouse model and secondly it addressed the specific function of Akt phosphorylation by mTORC2. Several papers followed shortly in Dev. Cell and Genes Dev. that also reported knockout mouse models. *Using the SIN1 knockout model, my lab has discovered a novel function of mTORC2 that is conserved from yeast to man (EMBO J, 2008 and EMBO J, 2010). This function involves cotranslational regulation of nascent polypeptides that is important for protein folding and function. This discovery, which identified mTORC2 in the ribosomal compartment has direct implications on how mTORC2 should be targeted for development of cancer therapy. **Science Signaling cited this work as a Signaling Breakthrough of 2010.** As an Associate Professor, my lab has discovered that mTORC2 is involved in insulin resistance not only via regulation of Akt but due to its involvement in the regulation of the insulin receptor substrate (IRS-1) (Mol Cell 2012).

4. Jacinto, E.[#], Facchinetti, V.[#], Liu, D., Soto, N., Wei, S., Jung, S.Y., Huang, Q., Qin, J., and Su, B. SIN1/MIP1 maintains rictor-mTOR complex integrity and regulates Akt phosphorylation and substrate specificity. **Cell 2006** 127, 125-137. PMID: 16962653. [#]equal contributors *(cited 1660)*
(*Highlighted in Dev. Cell 11:433*)

5. Facchinetti, V., Ouyang, W., Wei, H., Soto, N., Lazorchak, A., Gould, C., Lowry, C., Newton, A.C., Mao, Y., Miao, R.Q., Sessa, W.C., Qin, J., Zhang, P., Su, B., and Jacinto, E. The mammalian target of rapamycin complex 2 controls folding and stability of Akt and protein kinase C., **EMBO J. 2008,** 27, 1932-1943. PMCID: PMC2486276. *(cited 621)*

6. Oh, W.J., Wu, C., Kim, S.J., Facchinetti, V., Julien. L.A., Finlan, M., Roux, P.P., Su, B. and Jacinto, E. mTORC2 can associate with ribosomes to cotranslationally phosphorylate and stabilize nascent Akt polypeptide. **EMBO J. 2010**, 29, 3939-3951. PMCID: PMC3020639 *(cited 343)*
(*2010 Signaling Breakthroughs of the Year, Science Signal. 4 (154): 1-7*.
Editors' Choice Highlight: Science Signal. 3, ec369, 2010).

7. Kim, S.J., DeStefano, M.A, Oh, W.J., Wu, C., Vega-Cotto, N.M., Finlan, M., Liu, D., Su, B., and Jacinto, E. mTOR complex 2 regulates proper turnover of insulin receptor substrate-1 via the ubiquitin ligase Fbw8. **Molecular Cell 2012** 48, 875-887**.** PMCID: PMC3534931. *(cited 99)*

***Recent work in my lab focuses on how mTORC2 can couple signals from nutrients and growth factors to control metabolic pathways.**

Using T cell specific rictor vs raptor knockout mice and in collaboration with Guy Werlen (Rutgers) and Michael Hall (Univ. of Basel), we have surprisingly found that disruption of either mTOR complexes can lead to very similar early T cell development phenotype. Furthermore, the developmental defects are due to impaired expression of critical cell surface receptors. Using proteomics, genomics and metabolomics approaches to elucidate how mTOR complexes respond to nutrients, our most recent work uncovers how mTORC2 responds to intracellular fluctuations in glutamine catabolites to restore metabolic homeostasis.

8. Moloughney, J.G., Kim, P.K., Vega-Cotto, N.M., Wu, C.C., Zhang, S., Adlam,M., Lynch, T., Chou, P.C., Rabinowitz, J.D., Werlen, G. and Jacinto, E. mTORC2 responds to glutamine catabolite levels to modulate the hexosamine biosynthesis enzyme GFAT1., **Molecular Cell 2016,** 63, 811-826. PMCID: PMC5006067 *(cited 85)*
   Highlighted in Mol Cell 63:723

9. Moloughney, J.G., Vega-Cotto, N.M., Liu, S., Patel, C., Kim, P.K., Wu, C., Albaciete, D., Magaway,C., Chang,A., Rajput,S., Su, X., Werlen, G., and Jacinto, E. mTORC2 modulates the amplitude and duration of GFAT1 Ser-243 phosphorylation to maintain flux through the hexosamine pathway during starvation., **J. Biol. Chem 2018**, 293(42):16464-16478 PMCID: PMC6200946. *(cited 26)*
   Selected as one of highlights of research on Cancer (Tumor Metabolism), JBC virtual issue: Cancer, Dec. 2020

10. Li, ML., Ragupathi, A., Patel, N., Hernandez, T., Magaway, J., Werlen, G., Brewer, G*. and Jacinto, E.* The RNA-binding protein AUF1 facilitates Akt phosphorylation at the membrane. **J.Biol.Chem. 2022**, 298(10):102437, PMID: 36041631 * co-corresponding authors
    Editor's Pick, JBC

11. Werlen, G*. Li, ML., Tottone, L., da Silva-Diz, V., Su, X., Herranz, D., and Jacinto, E.* Dietary glucosamine overcomes the defects in alpha/beta T cell ontogeny caused by the loss of de novo hexosamine biosynthesis **Nature Commun. 2022**, 13(1): 7404, PMID: 36456551 * co-corresponding authors

Our goal is to develop more effective therapeutic strategies to treat metabolism-related disorders. In addition to our own studies, our collaborative efforts have led to promising therapeutic applications of mTOR signaling inhibition in breast and prostate cancer, autism and cardiovascular disease. We have written several review articles to highlight the recent developments in our field and to serve as a useful resource for the community.

12. Oh, W.J. and Jacinto, E. mTOR complex 2 signaling and functions, **Cell Cycle 2011**, 10(14), 2305-2316, PMID: 21670596 *(cited 609)*

13. Magaway, C., Kim, E., and Jacinto, E. Targeting mTOR and metabolism in cancer: lessons and innovations, **Cells 2019,** 8, 1-51, PMID: 31817676 (*cited 117*)

14. Szwed, A., Kim, E. and Jacinto, E. Regulation and metabolic functions of mTORC1 and mTORC2., **Physiol. Rev. 2021**, 101(3), 1371-1426, PMID: 33599151 (*cited 89*)

15. Werlen, G., Jain, R. and Jacinto, E. mTOR signaling and metabolism in early T cell development. **Genes 2021**, 12, 728, PMID: 34068092 (*cited 6*)

Complete list of published work in MyNCBI:
https://www.ncbi.nlm.nih.gov/myncbi/estela.jacinto.1/bibliography/public/