

BIOGRAPHICAL SKETCH

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NAME: Larre Perez, Maria Isabel

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

POSITION TITLE: Assistant Professor, Joan C. Edwards School of Medicine, Marshall University, WV.

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 Y	FIELD OF STUDY
Metropolitan Autonomous University of Mexico	B.S	2002	Experimental Biology
Center for Research and advanced Studies of National polytechnic Institute (CINVESTAV).	M. Sc.	2005	Cellular and Molecular Physiology
Center for Research and advanced Studies of National polytechnic Institute (CINVESTAV).	Ph.D	2012	Cellular and Molecular Physiology
Center for Research and advanced Studies of National polytechnic Institute (CINVESTAV).	Postdoctoral	2013	Cellular and Molecular Physiology

A. Personal Statement

I have the expertise, training and motivation necessary to successfully carry out the proposed research project. I have a specific training in epithelial physiology and one of the features of those cells is the presence of tight Junctions. Key technologies to study tight junctions were actually pioneered by the group who trained me as a Ph.D. student. My research includes the regulation of the function and the molecular composition of tight junctions by the Na/K-ATPase ligand ouabain, which is the foundation of this proposed research. In addition, I have had numerous fruitful collaborations with other researchers in the field of gap junctions. These accomplishments demonstrate my ability to participate in productive-collaborative teams requiring frequent communication among project members to define realistic research goals and to publish papers. I was invited to write book chapters detailing techniques for studying tight junction. As a junior investigator at MIIR and in Marshall University School of Medicine, my interest is to study how sodium pump regulates epithelial phenotype. With the newly developed technology that allows the expression of mutants of alpha 1 with defect in signaling function, it becomes possible to use this COBRE program as the first step for me to study how Na/K-ATPase signaling function regulates kidney function. Support and collaborative work with the Genomics core at Marshall for RNA-seq will allow us to screen the differential regulation of tight junction genes (feature of epithelial cells) and other genes that are important for the epithelial phenotype.

1. The emergence of the concept of tight junctions and physiological regulation by ouabain. **Larre I**, Ponce A, Franco M, Cerejido M. Semin Cell Dev Biol. doi: 10.1016.
2. Ouabain induces endocytosis and degradation of tight junction proteins through ERK1/2-dependent pathways. Rincon-Heredia R, Flores-Benitez D, Flores-Maldonado C, Bonilla-Delgado J, García-Hernández V, Verdejo-Torres O, Castillo AM, **Larré I**, Poot-Hernández AC, Franco M, Gariglio P, Reyes JL, Contreras RG. Exp Cell Res. 2013.

3. The Na⁺-K⁺-ATPase as self-adhesion molecule and hormone receptor. Cereijido M, Contreras RG, Shoshani L, **Larre I**. Am J Physiol Cell Physiol. 2012;302(3):C473-81. 3.
4. Ouabain modulates ciliogenesis in epithelial cells. **Larre I**, Castillo A, Flores-Maldonado C, Contreras RG, Galvan I, Muñoz-Estrada J, Cereijido M. Proc Natl Acad Sci U S A. 2011;108(51):20591-62.
5. Ouabain modulates cell contacts as well as functions that depend on cell adhesion. **Larre I**, Contreras RG, Cereijido M. Methods Mol Biol. 2011;763:155-68.
6. Na, K-ATPase is the putative membrane receptor of hormone ouabain. **Larre I** and Cereijido M. Commun Integr Biol. 2010 (6):625-8.
7. Ouabain modulates epithelial cell tight junction. **Larre I**, Lazaro A, Contreras RG, Balda MS, Matter K, Flores-Maldonado C, Ponce A, Flores-Benitez D, Rincon-Heredia R, Padilla-Benavides T, Castillo A, Shoshani L, Cereijido M. Proc Natl Acad Sci U S A. 2010;107(25):11387-92.
8. Tight junction and polarity interaction in the transporting epithelial phenotype. Cereijido M, Contreras RG, Shoshani L, Flores-Benitez D, **Larre I**. Biochim Biophys Acta. 2008;1778(3):770-93.
9. New diseases derived or associated with the tight junction. Cereijido M, Contreras RG, Flores-Benitez D, Flores-Maldonado C, **Larre I**, Ruiz A, Shoshani L. Arch Med Res. 2007;38(5):465-78

Book chapters

1. Book: Tight junctions in Cancer Metastasis. **Larre, I**, Flores-Maldonado C and Marcelino C. Methods to study tight junctions, (Martin, T.A. and Jiang W.G Eds). Chapter 3 (19), pp. 65-80, 2013.
2. Book: Permeability Barrier: Methods and Protocols, Methods in Molecular Biology. **Larre, I**, Contreras, R.G., Cereijido, M. Hormone ouabain modulates cell contacts as well as functions that depend on cell adhesion, (Kursad, Turksen Ed), Chapter 10 (763), pp.155-168, 2011

B. Positions and Honors

Positions and Employment

2012-13	Postdoctoral Fellow, Department of physiology Biophysics and Neurosciences, Center of research and Advanced Studies of National Polytechnic Institute, Mexico.
2013-14	Visiting Professor, Department of physiology Biophysics and Neurosciences, Center of research and Advanced Studies of National Polytechnic Institute, Mexico.
2014	Instructor of Neurophysiology, Metropolitan Autonomous University, Mexico.
2014-2015	Assistant Investigator or residence at MIIR. Marshall University, WV.
2015-	Assistant Investigator at MIIR, Marshall, University, WV.
2014- _____	Assistant Professor. Joan C. Edwards School of Medicine, Marshall University, WV.

Professional Memberships

2012- Member of American Society of Cell Biology, USA.

Honors

2014-16	Fellowship for National Researcher from National Research System (SNI), (http://www.conacyt.mx/index.php/el-conacyt/sistema-nacional-de-investigadores), Mexico
2012	Postdoctoral Fellowship from Institute of Science and Technology of D.F. (ICyTDF) for women, Rosalind Franklin, 2012, Mexico.
2006	Research fellowship from National Council for Science and Technology, "Becas Mixtas en el Extranjero", to stay in the University College of London, U.K. Mentor:

- 2003-9 María Susana Balda.
Research fellowship from National Council for Science and Technology (CONACYT) Mexico.
- 2002 Fellowship from the Mexican Academy of Science, "Summer of Scientific Research" (http://www.amc.edu.mx/p5/index.php?option=com_content&id=139).
- 2002 Degree in Experimental Biology with Honors, Metropolitan Autonomous University (UAM-Iztapala).

C. Contribution to Science

My early publications showed that ouabain could regulate cell adhesion. The binding of ouabain to Na-K-ATPase could disable different cell-cell adhesion and cell-substrate adhesion. Also, cells that are sensitive to ouabain became resistant to ouabain by establishing gap junctions. We used high concentrations of ouabain that inhibited and affected both pumping and signaling function, but this was the first evidence of the existence of a relationship between Na/KATPase and cell-cell adhesion.

1. Ouabain binding to Na⁺,K⁺-ATPase relaxes cell attachment and sends a specific signal (NACos) to the nucleus. Contreras RG, Flores-Maldonado C, Lázaro A, Shoshani L, Flores-Benitez D, **Larré I**, Cereijido M. *J Membr Biol.* 2004;198(3):147-58.
2. Contacts and cooperation between cells depend on the hormone ouabain. **Larre I**, Ponce A, Fiorentino R, Shoshani L, Contreras RG, Cereijido M. *Proc Natl Acad Sci U S A.* 2006 ;103(29):10911-6.

In 1991, Hamlyn et al. and Mathews et al. demonstrated the presence of a substance in plasma that they could not distinguish it from ouabain of vegetal origin, a finding confirmed with more advanced methods such as 1H-NMR and mass ionization spectrometry. Now endogenous ouabain is well accepted and recognized as a hormone. Using physiological concentrations of ouabain, we showed that it was able to regulate the two features of a transporting epithelium: Tight Junction and Polarity. Specifically, the binding of ouabain to Na/K-ATPase triggers c-Src/ERK signaling, which in turn regulates paracellular permeability (Tight Junction) and ciliogenesis (polarity). Those results suggested for first time that the signaling function of Na/K-ATPase could be involved in the regulation of Tight Junction.

1. Ouabain modulates ciliogenesis in epithelial cells. **Larre I**, Castillo A, Flores-Maldonado C, Contreras RG, Galvan I, Muñoz-Estrada J, Cereijido M. *Proc Natl Acad Sci U S A.* 2011;108(51):20591-62.
2. Ouabain modulates cell contacts as well as functions that depend on cell adhesion. **Larre I**, Contreras RG, Cereijido M. *Methods Mol Biol.* 2011;763:155-68.
3. Na, K-ATPase is the putative membrane receptor of hormone ouabain. **Larre I** and Cereijido M. *Commun Integr Biol.* 2010 (6):625-8.
4. Ouabain modulates epithelial cell tight junction. **Larre I**, Lazaro A, Contreras RG, Balda MS, Matter K, Flores-Maldonado C, Ponce A, Flores-Benitez D, Rincon-Heredia R, Padilla-Benavides T, Castillo A, Shoshani L, Cereijido M. *Proc Natl Acad Sci U S A.* 2010;107(25):11387-92.

In addition to the contribution described above, with a team of collaborators, I investigated the effect of ouabain on gap junctions. This type of cell communication is important in tissue morphogenesis, not only in epithelial but also in the heart, liver, etc. Finally, I was invited to collaborate in studying the effect of Epidermal Growth Factor on Tight Junction.

1. Ouabain increases gap junctional communication in epithelial cells. Ponce A, **Larre I**, Castillo A, García-Villegas R, Romero A, Flores-Maldonado C, Martínez-Rendón J, Contreras RG, Cereijido M. *Cell Physiol Biochem.* 2014;34(6):2081-90.
2. The polarized distribution of Na⁺,K⁺-ATPase: role of the interaction between {beta} subunits. Padilla-Benavides T, Roldán ML, **Larre I**, Flores-Benitez D, Villegas-Sepúlveda N, Contreras RG, Cereijido M, Shoshani L. *Mol Biol Cell.* 2010;21(13):2217-25.

3. Control of tight junctional sealing: roles of epidermal growth factor and prostaglandin E2. Flores-Benitez D, Rincon-Heredia R, Razgado LF, **Larre I**, Cereijido M, Contreras RG. Am J Physiol Cell Physiol. 2009;297(3):C611-20.
4. Tight junction and polarity interaction in the transporting epithelial phenotype. Cereijido M, Contreras RG, Shoshani L, Flores-Benitez D, **Larre I**. Biochim Biophys Acta. 2008;1778(3):770-93.

Complete List of Published Work in My Bibliography

<http://www.ncbi.nlm.nih.gov/sites/myncbi/1bEO8ejAe9v5N/bibliography/49260018/public/?sort=date&direction=ascending>

C. Research Support

Completed Research Support

2014-2015 CINVESTAV, Mexico

Larre (Co-Investigator)

Substance isolation from Urine that regulates TJ

The goal of this project was isolated substance from human urine that regulates Tight Junction.

PI:Marcelino Cereijido, Co-Investigator:Maria Isabel Larre.