BIOGRAPHICAL SKETCH

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NAME: Jorge E. Contreras

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

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	Completion Date	FIELD OF STUDY
Catholic University of Chile, Santiago, Chile	BSc	07/1997	Biological Sciences
Catholic University of Chile, Santiago, Chile	PhD	12/2004	Physiology
NINDS NIH, Bethesda, MD	Fellow	03/2010	Biophysics

A. Personal Statement

The overall goal of my research is to discover the roles connexin channels play in health and disease. Our work has primarily focused on identifying the mechanisms involved in connexin channel gating, permeation, and regulation. We investigate molecular mechanisms of normal connexin channel function, as well as those affected by human mutations that produce channel dysfunction and disease. Our current interests include the role of connexin channels in cardiac disorders. We recently identified a novel role for remodeled connexin43 (Cx43) hemichannels in cardiac-stress induced arrhythmias and cardiomyopathy using a murine model of Duchenne muscular dystrophy (DMD). Funded by the NIH, we have identified a general mechanism by which extracellular Ca^{2+} controls connexin hemichannel opening and closing. Additionally, we have provided mechanistic insights as to how disease-linked connexin mutations affect hemichannel gating by Ca^{2+}. We also investigated whether and how Cx43 hemichannels are gated by nitric oxide. We recently identified the molecular mechanisms by which S-nitrosylated Cx43 hemichannels contribute to membrane depolarization and cardiac cell death, which consequently produces lethal arrhythmias.

Ongoing projects:

NIH/R01 GM099490 Contreras (PI) 09/01/22-06/30/26
Gating and Regulation of Connexin Hemichannels

NIH/R01 HL141170 Contreras, Fraidenraich (MPI) 01/9/18-06/30/23
Connexin 43: a new player in Duchenne muscular dystrophy associated cardiomyopathy

NIH/R21 HL163930 Contreras (PI) 04/01/22- 03/31/24
Role of S-nitrosylated Cx43 in normal cardiac contractility

1. Lopez W, Ramachandran J, Alsamarah A, Luo Y, Harris AL, and **Contreras JE** (2016). Mechanism of gating by calcium in connexin hemichannels. ***Proc. Natl. Acad. Sci. USA*** *113:*E7986-E7995. PMCID: PMC5150374.
2. Lillo MA, Himelman E, Shirokova N, Xie LH, Fraidenraich D, **Contreras JE**. S-nitrosylation of Connexin43 hemichannels elicits cardiac stress induced arrhythmias in Duchenne Muscular Dystrophy mice (2019). ***JCI Insight*** *Dec 19;4(24). pii: 130091.* PMCID: PMC6975272.
3. Himelman E, Lillo MA, Nouet J, Gonzalez PJ, Zhao Q, Xie LH, Li H, Liu T, Wehrens XHT, Lampe PD, Fishman GI, Shirokova N, **Contreras JE**, Fraidenraich D. Prevention of Connexin43 remodeling protects

against Duchene muscular dystrophy cardiomyopathy (2020). ***J Clin Invest.*** *128190. doi: 10.1172/JCI128190.* PMCID: PMC7108916

4. Gaete PS, Lillo MA, Lopez W, Luo Y, Harris AL, **Contreras JE** (2020). A novel voltage clamp/dye uptake assay reveals saturable transport of molecules through CALHM1 and connexin channels. ***J. Gen. Physiol.*** *152(11): e202012607.* PMCID: PMC7579738.

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2023-present	Professor, Dept. of Physiology and Membrane Biology, School of Medicine, University of California Davis
2021-2023	Associate Professor, Dept. of Physiology and Membrane Biology, School of Medicine, University of California Davis
2021-present	Adjunct Associate Professor Dept. of Pharmacology/Physiology/Neuroscience, New Jersey Medical School, Rutgers University
2020-2023	Council, Society of General Physiologists (SGP)
2019	Organizer, "Structural Basis of Electrical Signaling in the Heart and The Nervous System", SGP/SOBLA Conference
2018-2020	Associate Professor, Dept. of Pharmacology/Physiology/Neuroscience, New Jersey Medical School, Rutgers University
2016-2022	Reviewer for NIH, regular member of NTRC study section
2016-2019	President-Elect, Latin American Biophysical Society (SOBLA)
2015	Ad hoc reviewer for NIH: ZRG1 MDCN-Q (03) Special Emphasis Review Committee
2013-2018	Assistant Professor, Dept. of Pharmacology/Physiology/Neuroscience, New Jersey Medical School, Rutgers University
2013	Ad hoc reviewer for NIH: ZRG1 MDCN-G (40P) Special Emphasis Review Committee
2013	Ad hoc reviewer for NIH, NTRC study section
2010-2013	Assistant Professor, Dept. of Pharmacology/Physiology, New Jersey Medical School, UMDNJ
2009-2015	Council, Society of General Physiologists (SGP)
2004-present	Member, Biophysical Society
2004-present	Member, Latin American Biophysical Society (SOBLA)
2004-2010	Fellow, Division of Intramural Research, National Institute of Neurological Disorders and Stroke
2001-2004	Research scholar, Albert Einstein College of Medicine
1998-1999	Research Assistant, Catholic University of Chile
1998	Instructor in physiology, Catholic University of Chile

Honors

2022	Best Teacher Award from Inaugural Vanderbilt Basic Sciences' Hispanic and Latin Heritage Month.
2020	Top 100 Most Inspiring Hispanic/Latinx Scientists, Cell Press
2019	Excellence in Research Award, The New Jersey Health Foundation
2012-2014	Visiting Fellowship for Faculty, Mount Desert Island Biological Laboratory, Bar Harbor, ME
2009	Grass Fellowship for Neurophysiology, Marine Biological Laboratory, Woods Hole, MA
2008	Fellows Award for Research Excellence (FARE), NIH
2007	Ph.D. Dissertation Honor Recognition, The Chilean Academy of Sciences
2005-2008	Ruth L. Kirschstein National Research Service Award for individual postdoctoral Fellows
2001	Travel Award, CONICYT (Chile). Gap junctions Conference, HI

C. Contributions to Science

1. **Connexin hemichannels.** Connexin proteins assemble as hexamers to form hemichannels that are inserted into the plasma membrane. It was thought that two hemichannels from neighboring cells dock end-to-end to only form junctional or gap junction channels, which mediate intercellular exchange of nutrients, metabolites, ions and signaling molecules. As a graduate student, I found that hemichannels, without forming junctional channels, play pathological roles at the plasma membrane in ischemia models. As faculty, I have followed up on the pathological role of connexin hemichannels studying human connexin mutations that causes skin disorders.

a. **Contreras JE**, Sánchez H, Eugenín EA, Speidel D, Theis M, Willecke K, Bukauskas FF, Bennett MVL and Saez JC (2002) Metabolic inhibition induces opening of unapposed connexin43 gap junction hemichannels and reduces gap junctional communication in cortical rat astrocytes in culture. ***Proc. Natl. Acad. Sci. USA*** *99: 495-500.* PMID: 11756680. PMCID: PMC117588

b. **Contreras JE**, Sánchez HA, Veliz L, Bukauskas FF, Bennett MVL and Sáez JC (2004) Role of connexin-based gap junction channels and hemichannels in ischemia-induced cell death in nervous tissue. ***Brain Res. Rev.*** *47: 290-303.* PMID: 15572178. PMCID: PMC3651737

c. Garcia IE, Maripillan J, Jara O, Ceriani R, Palacios-Munoz A, Ramachandran J, Olivero P, Perez-Acle T, Gonzalez C, Saez JC, **Contreras JE**, Martinez AD (2015). Keratitis-Ichthyosis-Deafness syndrome-associated Cx26 mutants produce nonfunctional gap junctions but hyperactive hemichannels when co-expressed with wild type Cx43. ***J. Invest. Dermatol*****.** 135:1338-47. PMID: 25625422. PMCID: PMC4801018

d. Valdez Capuccino JM, Chatterjee P, Garcia IE, Botello-Smith WM, Zhang H, Harris AL, Luo Y, **Contreras JE** (2019). The connexin26 human mutation N14K disrupts cytosolic inter-subunit interactions and promotes channel opening. ***J. Gen. Physiol.*** *150: 328-341.* PMCID: PMC6400520 *(Co-corresponding authors)*

2. **Role of Cx43 hemichannels in cardiac arrhythmias and dysfunction.** Together with our collaborators at Rutgers, we published the first evidence that Cx43 hemichannels play key role in cardiomyopathy associate to Duchenne muscular dystrophy (DMD). My laboratory extended this research to evaluate the role of S-nitrosylated Cx43 hemichannels in cardiac arrhythmias. We demonstrated that beta-adrenergic stimulation promotes arrhythmias in DMD mice via opening of S-nitrosylated Cx43 hemichannels.

   a. *G*onzalez PJ, Ramachandran J, Xie LH, **Contreras JE**, Fraidenraich D (2015). Selective Connexin43 inhibition prevents isoproterenol-induced arrhythmias and lethality in muscular dystrophy mice. ***Scientific Reports***. 5: 134900. doi: 10.1038/srep13490. PMID: 26311238. PMCID: PMC4550874

   b. Gonzalez PJ, Ramachandran J, Himelman E, BadrMA, Kang C, Nouet J, Fefelova N, Xie LH, Shirokova N, **Contreras JE***, Fraidenraich D* (2018). Normalization of connexin 43 protein levels prevents cellular and functional signs of dystrophic cardiomyopathy in mice. ***Neuromuscular Disorders***. 28(4):361-372. **Corresponding author* PMID:29477453

   c. Lillo MA, Himelman E, Shirokova N, Xie LH, Fraidenraich D, **Contreras JE**. S-nitrosylation of Connexin43 hemichannels elicits cardiac stress induced arrhythmias in Duchenne Muscular Dystrophy mice (2019). ***JCI Insight*** *Dec 19;4(24). pii: 130091.* PMCID: PMC6975272

   d. Himelman E, Lillo MA, Nouet J, Gonzalez PJ, Zhao Q, Xie LH, Li H, Liu T, Wehrens XHT, Lampe PD, Fishman GI, Shirokova N, **Contreras JE**, Fraidenraich D. Prevention of Connexin43 remodeling protects against Duchene muscular dystrophy cardiomyopathy (2020). ***J Clin Invest.*** *128190. doi: 10.1172/ JCI128190.* PMCID: PMC7108916

3. **How connexin hemichannels work at the molecular level.** To further understand the roles of connexin hemichannels in physiology and pathology, it is critical to understand how they gate (open and close) and what stimuli trigger gating and the permeability properties of the channels. My laboratory has discovered novel molecular mechanisms that underlie gating by calcium and molecular permeability in hemichannels.

   a. **Contreras JE**, Sáez JC, Bukauskas FF and Bennett MVL (2003) Gating and regulation of connexin 43 (Cx43) hemichannels. ***Proc. Natl. Acad. Sci. USA*** *100: 11388-9.* PMID: 13130072. PMCID: PMC208767

   b. Lopez W, Gonzalez J, Liu Y, Harris AL, and **Contreras JE** (2013). Insights on the mechanisms of Ca^{2+} regulation of connexin26 hemichannels revealed by human pathogenic mutations (D50N/Y). ***J. Gen. Physiol.*** *142: 23-35.* PMID: 23797420. PMCID: PMC3691447

   c. Lopez W, Liu Y, Harris AL, and **Contreras JE** (2014). Divalent regulation and intersubunit interactions of human Connexin26 (Cx26) hemichannels. ***Channels*****.** 8(1): 1-4. doi: 10.4161/chan.26789. PMID: 24126106. PMCID: PMC4048337

d. Lopez W, Ramachandran J, Alsamarah A, Luo Y, Harris AL, and **Contreras JE** (2016). Mechanism of gating by calcium in connexin hemichannels. ***Proc. Natl. Acad. Sci. USA*** *113:*E7986-E7995. PMCID: PMC5150374

4. **Novel methods for the study of connexin hemichannels.** Connexin hemichannels have distinctive biophysical properties; they are permeable to ions and molecules, such as ATP and glutamate. My laboratory has provided more comprehensive protocols to study and analyze heterologous expressed connexin hemichannels in Xenopus oocytes. We also found that cysteine scanning mutagenesis using methanesulfonate reagents are critically affected by permeation of glutathione through the connexin pore. Thus, we modified this methodology to apply it in connexin channels. Using atomic force microscopy, in collaboration with another group, we demonstrated for the first time the stoichiometry and molecular rearrangements of heteromeric connexin hemichannels. More recently, we developed a simple and powerful methodology that reveals saturable transport to molecules by CALHM1 and connexin hemichannels, that can be described by Michaelis-Menten kinetics.

   a. Tong X, Lopez W, Ramachandran J, Ayad WA, Liu Y, Lopez-Rodriguez A, Harris AL, **Contreras JE** (2015). Glutathione release through connexin hemichannels: Implications on chemical modification for pores permeable to large molecules. ***J. Gen. Physiol.*** *146: 245-54.* PMID: 26324677. PMCID: PMC4555470

   b. Naulin PA, Lozano B, Fuentes C, Liu Y, Schmidt C, **Contreras JE**, Barrera NP (2020). Polydisperse molecular architecture of connexin 26/30 heteromeric hemichannels revealed by AFM imaging. ***J. Biol. Chem.*** *295(49):16499-16509*. PMID: 32887797

   c. Gaete PS, Lillo MA, Lopez W, Liu Y, Harris AL, **Contreras JE** (2020). A novel voltage clamp/dye uptake assay reveals saturable transport of molecules through CALHM1 and connexin channels. ***J. Gen. Physiol.*** *152(11): e202012607.* PMCID: PMC7579738

   d. Gaete PS and **Contreras JE** (2021). A method for assessing ionic and molecular permeation in connexin hemichannels. ***Methods in Enzymology***. Ion Channels, Part C Volume 653. PMID: 34120717

5. **Functional architecture of cyclic nucleotide gated (CNG) channels.** It was thought that the gate of voltage-gated potassium channels was located at the intracellular side of the pore. When this gate is closed, it substantially reduces K^+ ion permeation, as well as prevents the access of channel blocking agents, such as quaternary ammonium, to an inner cavity located between the selectivity filter and the gate. Because CNG channels are structurally similar to K^+ channels, it was hypothesized that they should share similar gating mechanism. As a postdoctoral fellow at the NIH, I discovered that CNG channel gate is at the middle of the selectivity filter, which is in stark contrast to what had been established, at the time, for potassium channels. Our observations indicate that the gating mechanisms differ among cation channels, even though they are homologous and share similar structural features.

   a. **Contreras JE** and Holmgren M (2006). Access of quaternary ammonium blockers to the internal pore of cyclic nucleotide-gated channels: Implications for the location of the gate. ***J. Gen. Physiol.*** *127: 481-494.* PMID: 23479636. PMCID: PMC2151523

   b. **Contreras JE**, Srikumar D and Holmgren M (2008). Gating at the selectivity filter of cyclic nucleotide-gated channels. ***Proc. Natl. Acad. Sci. USA*** *105: 3310-14.* PMID: 16606688. PMCID: PMC2265121

   c. **Contreras JE**, Chen J, Lau AY, Roux B, Holmgren M (2010). Voltage profile along the permeation pathway of an open channel. ***Biophysical J.*** *99: 2863-9.* PMID: 21044583. PMCID: PMC2965955

   d. Miranda P*, **Contreras JE***, Wesch D, Sigworth FJ, Holmgren M, Giraldez T (2013). State-dependent FRET reports calcium- and voltage-dependent gating-ring motions in BK channels. ***Proc. Natl. Acad. Sci. USA*** *110: 5217-22* PMID: 23479636. PMCID: PMC3612663. *(*Equal contribution)*

Complete List of Published Work in MyBibliography:
https://www.ncbi.nlm.nih.gov/sites/myncbi/jorge.contreras.1/bibliography/43924598/public/?sort=date&direction=descending