BIOGRAPHICAL SKETCH

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NAME: **Jorge D. Miranda**

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

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 Puerto Rico, Rio Piedras Campus	**B.S.**	**05/88**	**Biology**
University of Puerto Rico, Rio Piedras Campus	**M.S.**	**05/90**	**Biology**
Baylor College of Medicine, Houston, TX	**Ph.D.**	**10/96**	**Neuroscience**
Univ. of Miami School of Medicine-Miami Project	**Postdoc**	**12/98**	**Regeneration**

A. Personal Statement → **website: https://md.rcm.upr.edu/physiology/dt_team/dr-jorge-d-miranda/**

The research experience and concepts obtained during my graduate and postdoctoral training support my qualification to accomplish the research project presented in this proposal. As a postdoctoral fellow at the Miami Project to Cure Paralysis, I was expose to the most recent issues related to spinal cord injury (SCI). Under the mentorship of Dr. Scott Whittemore, he introduced me to the topics, research models and controversial issues in the field of SCI. This research center was an excellent place to perform my postdoctoral training because the environment was suitable to ask questions and share information at all the levels (ions, molecules, proteins, cells, systems, behavior). After two years of postdoctoral training, I joined the Physiology Department at UPR-Medical Sciences Campus in 1999 with a lot of energy and enthusiasm to pass to others what I have learned. At the same time, I developed a collaboration with a group at the Kentucky Spinal Cord Injury Research Center in Louisville, KY. This experience gave me the opportunity to expand my knowledge and skills to answer specific questions related to spinal cord trauma. Initially, the main focus of my laboratory was on the role of repulsive molecules expressed after trauma (Eph receptors and ephrin ligands). However, several new projects were developed. For example, the role of purinergic receptors in the formation of the glial scar, the role of Flotilin-2 lipid raft protein in the clustering of repulsive proteins for axonal regeneration, the role of ephexin (a guanine exchange factor, activated by Eph receptors) in generating the cellular events for growth cone collapse after spinal cord injury and more recently, the neuroprotective role of estradiol and Tamoxifen after injury. Therefore, the technical skills that will be used to achieve the objectives of this proposal are routinely used in my laboratory (& published in several peer review journals). Therefore, no difficulties are expected. So far, I trained three postdoctoral fellows, eight PhD graduate students, and over 20 undergraduate students confirming my motivation and leadership to stimulate others to get involved in science. All my graduate students finished their degree with several publications in peer review journals. Also, my publication record demonstrates that I could work in collaboration with others, confirming my abilities to be a team player. Publications have been developed from collaborations with faculty from the Physiology Department (with Dr. Walter Silva, Dr. Annabell Segarra. Dr. Maria Crespo and Dr. Carlos Jimenez) and also with faculty from other institutions in the USA mainland (Dr. Scott Whittemore, Dr. David Magnuson, and Dr. Marino De Leon). The manuscripts mentioned below endorse our abilities to perform the experiments of interest in our laboratory.

1. Willson CA, Irizarry-Ramírez M, Gaskins HE, Cruz-Orengo L, Figueroa JD, Whittemore SR and Miranda JD (2002) Upregulation of EphA Receptor Expression in the Injured Adult spinal Cord. Cell Transplantation 11(3): p.229-239. PMID: 12075988

2. Rosas OR, Santiago JM, Torrado AI, Rodriguez AE, Salgado IK, Miranda JD (2014) Inhibition of Src kinase after spinal cord injury resulted in functional locomotor recovery and increased spared tissue. Neural Regeneration Research. 9 (24): 2164-2173. PMID: 25657738; PMC4316450
3. Santiago JM, Rosas O, Torrado AI, González MM, Kalyan-Masih PO, and Miranda JD (2009) Molecular, Anatomical, Physiological and Behavioral studies of rats treated with Buprenorphine. J. Neurotrauma. 26 (10), 1783-1793. PMID: 19653810; PMC2864459
4. Figueroa JD, Benton R, Willson CA, Velázquez I, Torrado A, Ortiz C, Whittemore SR and Miranda JD (2006) Inhibition of EphA7 Upregulation after spinal cord injury reduces Apoptosis and Promotes Locomotor Recovery. J. Neurosc. Res. 84(7), p. 1438-51. PMID: 16983667

B. Positions and Honors

Positions

1986-1988	Undergraduate Research Assistant (Cel. & Mol. Biol. Lab.), University of Puerto Rico
1988-1989	Teaching Assistant (General Biology Course), University of Puerto Rico
1989-1990	Graduate Research Assistant (Cel. & Mol. Biol. Lab.), University of Puerto Rico
1990	Microbiology Teacher, Technological College of San Juan
1992-1996	Graduate Research Assistant (Biochemistry Depart.), Baylor College of Medicine
1996-1998	Senior Research Associate (Miami Project), University of Miami School of Medicine
1999-2004	Assistant Professor, Physiology Department, UPR - School of Medicine
2004-2011	Associate Professor, Physiology Department, UPR- School of Medicine (Tenure 2006)
2012	Professor, Physiology Department, UPR- School of Medicine
2010-2013	Associate Dean and Director of Biomedical Sciences Graduate Program, UPR-Sch. of Medicine
2001-2004	Coordinator of the Graduate Program in the Physiology Department
2006-2010	Coordinator of the Graduate Program in the Associate Deanship of Biomedical Sciences
2006	Vice-President of the Puerto Rico Neuroscience Chapter
2007	President of the Puerto Rico Neuroscience Chapter
2008-2010	Coordinator of the Human Physiology Course for Medical Students (UPR-Medical Campus)
2010-2012	Coordinator of the Human Physiology Course for Dental Students (UPR-Medical Campus)
2011	Vice-President of the Puerto Rico Physiological Society Chapter
2012	President of the Puerto Rico Physiological Society Chapter
2012-2015	Coordinator of the Vertebrate Physiology Course for Graduate Students (UPR-Medical Campus)
2017-2023	Co-coordinator of the Human Physiology Course for Medical Students

Honors and Professional Memberships

1990-1995	MARC Predoctoral Fellowship (NIGMS)
1992-1996	Dean's Award for Excellence, Baylor College of Medicine
1995-1996	American Psychological Association Fellowship
1996-	Member, Society for Neuroscience
1996-1997	Research Supplement for Minorities (NIH-NINDS: #NS26887)
1997-1998	F32 Postdoctoral Fellowship (NIH-NINDS: #NS10304)
1999-2009	Organizing Committee, Puerto Rico Annual Neuroscience Meeting
2000-2003	Member, International Society for Developmental Neuroscience
2000-	Member, Society for Neurotrauma
2002	Distinguished Faculty, UPR - School of Medicine (Betances Award)
2003-2006	Outstanding Professor, Physiology Department, UPR - School of Medicine
2006	Alumni Achievement Award for Research, American Psychological Association (Atlanta,GA)
2008-2015	Outstanding Professor, Physiology Department, UPR - School of Medicine
2008-2014	Member, American Physiological Society (APS)
2009-	Member, Puerto Rico Physiological Society (PRPS)
2012	Distinguished Faculty, UPR-School of Medicine – Class of Medicine 2012 and 2013
2012	Distinguished Faculty, UPR-School of Medicine – Class of Graduate Students 2012
2015-	Reviewer: Neural Regeneration Research Adhoc Reviewer: 1) Neurological Research; 2) Neuroscience; 3) Brain Research; 4) Molecular and Cellular Endocrinology; 5) Journal of Neurotrauma; 6) J. Neurochemistry
2019 & 21	Outstanding Professor, Physiology Department, UPR - School of Medicine

C. Contribution to Science

1. Spinal cord injury triggers a cascade of molecular and cellular events that generates a non-favorable environment for axonal outgrowth and cell survival. Therefore, the need to develop a multi-active drug or agent that tackle many of the events associated with the physical trauma is extremely important to obtain functional locomotor recovery. Initially, we studied the neuroprotective effects of estradiol after SCI in ovariectomized rats. However, long-term treatment with estradiol may produce some adverse effects that may overcome the neuroprotective effects that may create. Therefore, we analyzed the effect of a selective estrogen receptor modulator (Tamoxifen) that activates estrogen receptors without the adverse effects of estradiol. The rationale of the proposed project is to consider Tamoxifen as a neuroprotective agent that could produce a permissive environment for cell survival and axonal elongation, by either transcriptional or non-genomic pathways (like ROS scavengers). We have been able to demonstrate that Tamoxifen confers neuroprotection to the injured spinal cord in a sex-specific manner and with a particular therapeutic window (being longer in females than in male animals). Therefore, with the published data from my laboratory (and others) we need to identify the receptors and intracellular mechanisms activated by Tamoxifen to confers neuroprotection and how this drug affect specifically glial cells at the injury site. Moreover, since we observed a reduction in mechanical allodynia with Tamoxifen, there is a need to recognize the mechanisms activated by this drug to reduce pain after spinal cord injury. The publications produced, as a PI, in this project are:

a) Colón JM, González PA, Cajigas A, Maldonado WI, Torrado AI, Santiago JM, Salgado IK and Miranda JD (2018) Continuous Tamoxifen delivery improves locomotor recovery 6 hours after spinal cord injury by neuronal and glial mechanisms in male rats. Experimental Neurology. 299: 109-121 PMID: 29037533; PMC5723542
b) Colón JM, Torrado AI, Cajigas A, Santiago JM, Salgado IK, Arroyo Y and Miranda JD (2016) Tamoxifen administration immediately or 24 hours after spinal cord injury improves locomotor recovery and reduces secondary damage in female rats. J. of Neurotrauma. 33(18): 1696-708. PMID: 26896212; PMC5035917
c) Mosquera L, Colón JM, Santiago JM, Torrado AI, Melendez M, Segarra AC, Rodriguez-Orengo, JF, Miranda JD (2014) Tamoxifen and estradiol improved locomotor function and increased spared tissue in rats after spinal cord injury: their antioxidant effect and role of estrogen receptor alpha. Brain Research. 1561: 11-22. PMID: 24637260; PMC4046634
d) Colon JM and Miranda JD (2016) Tamoxifen: an FDA approved drug with neuroprotective effects for spinal cord injury recovery. Neural Regeneration Research. 11(8): 1208-1211. PMID: 27651756; PMC5020807

2. The studies performed in the laboratory during my early career were in the area of Eph receptors after spinal cord injury (SCI). The rationale was that trauma to the spinal cord triggers the expression of Eph receptors and ephrin ligands at the injury site, generating a repulsive environment for axonal regeneration and cell survival. We look at the spatio-temporal profile of several Eph receptors and ligands, at the mRNA and protein level. Moreover, when the expression of EphA7 was blocked with antisense technology after SCI we observed an improvement in locomotor recovery and return of nerve conduction. Other study demonstrated that blockaded of the EphA4 produced an increase in mechanical nociception. In addition, we observed an increase in the expression and activation of ephexin, an intracellular mediator of Eph receptor activation, after SCI. Blockade of the ephexin activation produced an increase in locomotor recovery and white matter spared tissue. The publication of my research project was the first article about Eph receptors after spinal cord injury, and for several years we were the group with most publications of this topic in the field. These findings support the idea that Eph receptors should be considered repellent signals that are activated after SCI and studies in this area should contemplate that some repulsive proteins are necessary to avoid sprouting of nociceptive fibers. I served as the primary investigator in most publications in this area. Some publications are:

a) Miranda JD, White LA, Willson CA, Marcillo A, Jaggid J and Whittemore SR. (1999) Induction of Eph B3 after spinal cord injury. *Exp.Neurol*. 156, p.218. PMID: 10192794
b) Irizarry-Ramírez M, Willson CA, Cruz L, Figueroa JD, Velázquez I, Jones H, Foster R, Whittemore SR and Miranda JD (2005) Upregulation of EphA3 Receptors After Spinal Cord Injry. J. of Neurotrauma 22(8), p.929-935. PMID: 16083359

c) Cruz-Orengo L, Velázaquez I, Torrado A, Ortiz C, Hernández C, Puig A, Segarra A, Whittemore SR and Miranda JD (2006) Blocking EphA4 upregulation after spinal cord injury results in enhanced chronic pain. Experimental Neurology. 202, p.421-433. PMID: 16959251

d) Rosas O, Figueroa JD, Torrado A, Rivera M, Konig-Toro F and Miranda JD (2011) Expression and activation of Ephexin Expression is altered after spinal cord injury. Developmental Neurobiology. 71(7): 595-607. PMID: 20949525; PMC3514508

3. In addition to the studies mentioned above, we also analyzed the role of purinergic receptors in the astrogliotic response after SCI. Specifically, we analyzed the spatio-temporal expression of P2Y2 after trauma and the role that this protein has in the development of the gliotic scar. The rationale behind this project was that release of ATP after injury activates purinergic receptors in astrocytes, which initiates the gliotic response and this event may generates a non-permissive environment for axonal regeneration. We observed that blockade of the P2Y2 activation reduced the gliotic response but also induced an increase in the cavity size. These results support the concept that the scar formation by reactive astrocytes is necessary to encapsulate the cyst formed after the injury. To improve locomotor recovery the expression of repellent molecules by reactive astrocytes should be blocked but not the gliotic response that surrounds the debris, dead cells and the fluid filled cavity. As PI of this project, some publications in this area were:

a) Rodríguez-Zayas A, Torrado A, Miranda JD (2010) $P2Y_2$ Receptor Expression is Altered in Rats after Spinal Cord Injury. International J. of Devel. Neurosci. Int. Journal of Developmental Neurosc. 28(6), 413-21. PMID: 20619335; PMC3225399

b) Rodriguez-Zayas AE, Torrado AI, Rosas OR, Santiago JM, Figueroa JD and Miranda JD (2011) Blockade of P2 Nucleotide Receptors After Spinal Cord Injury Reduced the Gliotic Response and Spared Tissue. J. Mol. Neurosci. 46(1), 167-176. PMID: 21647706; PMC3522077

4. Most membrane receptors that are activated after SCI and block axonal regeneration are located in lipid rafts. The rationale of this project was to analyze the spatio-temporal profile of Flotillin-2, a lipid raft protein that cluster receptors in domains of the plasma membrane, after SCI and determine the role that this protein has in the non-permissive environment for locomotor recovery. In addition, we investigated the expression pattern of caveolin proteins during differentiation of an astrocytoma cell line.

a) Martinez NA, Ayala AM, Martinez M, Martinez-Rivera FJ, Miranda JD and Silva WI (2016) Caveolin-1 Regulates the P2Y2 Receptor Signaling in Human 1321N1 Astrocytoma Cells. J. Biol. Chem. 291(3), p.12208-22. PMID: 27129210; PMC4933270

b) Santiago JM, Torrado AI, Arocho LC, Rosas OR, Rodríguez AE, Toro FK, Salgado IK, Torres YA, Silva WI, Miranda JD. (2013) Expression Profile of Flotillin-2 and Its Pathophysiological Role After Spinal Cord Injury. J. Mol. Neurosci. 49(2): 347-59. PMID: 22878913; PMC3545048

c) Silva WI, Maldonado HM, Velázquez G, Rubio-Dávila M, Miranda JD, Aquino E, Mayol N, Cruz-Torres A and Salgado-Villanueva IK (2005) Caveolin isoforms expression during differentiation of C6 glioma cells. Internat. J. of Develpmental Neuroscience 23, p. 599-612. PMID: 16135403

d) Martinez M, Martinez N, Miranda JD, Maldonado HM and Silva WI (2019) Caveolin-1 Regulates $P2Y_2$ Receptor Signaling During Mechanical Injury in Human 1321N1 Astrocytoma. *Biomolecules*. Oct. 18 9(10). PMID: 31635212

Complete List of Published Work in MyBibliography:
https://www.ncbi.nlm.nih.gov/sites/myncbi/1xKTwoumz7mA8/bibliography/47946842/public/?sort=date&direction=ascending

D. Additional Information: Research Support and/or Scholastic Performance

Active

SC1	Jorge D. Miranda (PI)	04/01/2022-03/31/2026
NIH/NIGMS	Role: Principal Investigator	30% Effort (Total Direct Cost:$1M)

The major goal of this grant is to study the effect of Tamoxifen after spinal cord injury in the contractile properties of single muscle fibers in skeletal muscles. Also to evaluate the effect of Tamoxifen on myogenic factors and proliferative proteins from skeletal muscles after spinal cord injury.

COBRE/NIEF José Lasalde (PI) 07/01/23-06/30/28
NIH/NIGMS Role: Director of NIEF 25% Effort (Total NIEF Cost: $4.5M)
The major goal of this activity is to develop microscopy and electrophysiological core facilities for the use of investigators in the University of Puerto Rico and other institutions in the island, as well as pharmaceutical companies. Technical and state-of-the-art equipment will be available for those users interested to look at high resolution cellular level and functional activity of ion channels in oocytes, cultured neurons, brain slices or anesthetized animals.

NIH/NIMH- MBRS/RISE (T32 G-RISE) Carmen Cadilla (PI) 06/01/23 – 05/31/28
Role: Coordinator Activity #2 4% Effort (Total Direct Cost: $75K)
Interdepartmental Seminar Series (Activity #2)
The major goal of this activity is to coordinate a monthly seminar series and an annual departamental mini-symposium. This involves the invitation of well-known investigators from the US mainland (different fields of research), and the coordination of seminars (and round table discussions) with the invited speaker and students/faculty.
OVERLAP: There is no scientific overlap between any research proposal and the T32 G-RISE grant.

Completed Support

PR Research, Science & Technology Trust Miranda (PI) 11/2021-09/2022
The major goal of this proposal is to identify the mechanisms used by Tamoxifen to improve locomotor recovery after spinal cord injury in male and female rats.

NIH/NIMH- MBRS/RISE Cadilla (PI) 09/01/04 – 08/31/22
Role: Coordinator Activity #2
The major goal of this activity was to coordinate a monthly seminar series. This involves the invitation of well-known investigators from the US mainland (different fields of research), and the coordination of seminars (and round table discussions) with the invited speaker and students/faculty.

NIH COBRE (1P20GM103642) Miller (PI) 07/01/13 – 12/31/16
Subproject 1: Estradiol and Tamoxifen as neuroprotective/neuroregenerative agents after spinal cord injury
Role: PI of Subproject #1
The major goal of this activity was to determine the neuroprotective and neuroregenerative role of the selective estrogen receptor modulator, tamoxifen, after spinal cord (SCI). Behavioral, anatomical, cellular and molecular analyses were performed to analyze the effect of these agents in the injured spinal cord and establish the therapeutic window of effectiveness.

R24-MH048190 07/01/05 – 06/30/09
NIH/NIMH
M-RISP (Expression Profile and role of Purinergic Receptors After spinal cord injury)
Role: PI of subproject #2

S06-GM08224 08/01/04-07/31/08
NIH/NIGMS
MBRS/SCORE (Role of Eph Receptors during Regeneration of the Nervous system)
Role: PI of subproject #9

U54NS39405-03 09/01/99-08/31/04
NIH/NINDS
The major goal of this subproject was to analyze the spatio-temporal expression of Eph A receptors at the mRNA and protein level after spinal cord injury (SCI) in adult rats.
Role: PI of subproject 2