BIOGRAPHICAL SKETCH

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NAME: Madeline Nieves-Cintron

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

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
University of Puerto Rico, San Juan	BS	1999	Biology
University of Puerto Rico, San Juan	PhD	2004	Biology
University of Washington, Seattle	Postdoc	2012	Vascular Physiology

A. Personal Statement

My work describes an essential link between scaffold proteins, anchored kinases, phosphatases, GPCRs, and vascular calcium and potassium channels regulating vascular reactivity. I have employed multi-scale approaches to provide a mechanistic understanding of vascular smooth muscle contraction regulation from single cells to organ-system levels. Through this vertically integrated approach, we have offered groundbreaking work on mechanisms regulating artery function in health and disease. We uncovered a signaling complex that includes the purinergic receptor $P2Y_{11}$, adenylyl cyclase 5 (AC5), PKA, and $Ca_V1.2$ subunit of the LTCC, allowing local regulation of LTCC by PKA in hyperglycemic conditions. We identify a critical role for AC5-generated cAMP in regulating vascular reactivity in diabetes. We provided a mechanistic framework for excitation-contraction coupling impacting the K_V channel's functional expression in disease states like diabetes and hypertension. I have over 20 years of research experience in cardiovascular physiology and pharmacology. Throughout my career, I have developed expertise in several cutting-edge approaches, including electrophysiology, cardiovascular physiology, molecular biology, animal model development, Ca^{2+} imaging, and biosensors. This experience and strong collaborations have led to an extensive and productive track record in molecular, cellular, electrophysiological, and imaging studies published in high-impact journals such as *PNAS*, *JCI*, *Scientific Reports*, *Science Signaling*, *JBC*, *JGP*, *EMBO J*, and *Circ Res among others*.

Ongoing Funding and projects include:
R01HL171014
12/15/2023 – 11/30/2027
Mechanisms of VSM dysfunction in diabetes and HFpEF
Role: MPI

SYNERGY
10/01/2023 – 9/30/2025
UC Davis School of Medicine Award
Effects of tobacco products and nicotine on autonomic control of cardiovascular function and cAMP signaling
Role: PI

1R01HL159304-01A1
04/01/22-03/31/27
Lipid regulation of Cardiac Excitation-Contraction coupling
Role: Co-investigator; Dixon (PI)

2R01HL121059

Navedo (PI)
07/16/22-04/30/25
Coupling of vascular $Ca_V1.2$ channels in health and disease
Role: Co-investigator; Navedo (PI)

Relevant Publications:

1. Singhrao N, Flores-Tamez VA, Moustafa YA, Reddy GR[1], Burns AB, Pinkerton KE, Chen CY, Navedo MF, **Madeline Nieves-Cintrón[1]*** Nicotine impairs smooth muscle cAMP signaling and vascular reactivity. Microcirculation. 2024 Aug;31(6):e12871. doi: 10.1111/micc.12871
2. EA Pereira da Silva, M Martín-Aragón, MF. Navedo, **M Nieves-Cintrón** (2022) Ion channel molecular complexes in vascular smooth muscle. *Front Physiol,* 26;13:999369 PMC9459047
3. M Martín-Aragón Baudel, VA Flores-Tamez, J Hong, GR Reddy, P Maillard, AE Burns, KNM Man, KC Sasse, SM Ward, WA Catterall, DM Bers, JW Hell, **M Nieves-Cintrón***, MF Navedo. Spatiotemporal Control of Vascular $Ca_V1.2$ by $\alpha1_C$ S1928 Phosphorylation. *Circ Res*. 2022 Dec 2;131(12):1018-1033. *co-corresponding author
4. MP Prada, AU Syed, GR Reddy, M Martin-Aragon Baudel, VA Flores-Tamez, KC Sasse, SM Ward, P Sirish, N Chiamvimonvat, P Bartels, EJ Dickson, JW Hell, JD Scott, LF Santana, YK Xiang, MF Navedo, **M Nieves-Cintrón** (2020) AKAP5 complex facilitates purinergic modulation of vascular L-type Ca^{2+} channel $Ca_V1.2$. *Nature Communications* 11: 5303. DOI: 10.1038/s41467-020-18947-y. PMC7575592

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

1999-2004 Predoctoral Fellow, Department of Biology, University of Puerto Rico.
2005-2012 Postdoctoral Fellow, Department of Physiology & Biophysics, University of Washington, Seattle.
2012-2016 Assistant Project Scientist, Department of Pharmacology, University of California, Davis.
2016-2018 Associate Project Scientist, Department of Pharmacology, University of California, Davis.
2018-2019 Assistant Professor In-residence, Department of Pharmacology, University of California, Davis.
2019-2022 Assistant Professor, tenure track, Department of Pharmacology, University of California, Davis.
2022-present Associate Professor with tenure, Department of Pharmacology, University of California, Davis.

Other Experience & Professional Membership

Member, SACNAS, Biophysical Society, American Heart Association, American Physiological Society
Review Editor for *Frontiers in Pharmacology*
Reviewer for multiple scientific journals (e.g., Molecular Metabolism, JAHA, Microcirculation)
Ad Hoc Reviewer NIH-NHLBI study sections (IVPP, BBHV)
Ad Hoc Reviewer for the American Heart Association- Pre & Postdoctoral Fellowship Signaling 2 Study Section
Section co-Chair APS 2022 Annual Meeting at Experimental Biology (EB). Symposium Intracellular Ca^{2+} in the Macro- and Microcirculation –Diversity of Function

Honors

2001 Minority Access to Research Career Travel Award
2002-2003 SACNAS Travel Award
2002-2004 National Institute of Health: Minority Biomedical Research Support: Research Initiative for Scientific Enhancement Research Fellowship (5R25GM61151)
2005-2007 NHBLI Minority Postdoctoral Supplement Program (5R01HL77115-4)
2019 UC Davis CAMPOS Faculty Scholar Award
2020 University of Valladolid, Spain, Visiting Scholar Fellowship
2023 UC Davis Graduate Studies Mentoring Award

C. Contributions to Science

1. Signal transduction and regulation of vascular reactivity during diabetes. Vascular dysfunction is a significant cause of morbidity and mortality among the diabetic population. We found that diabetic hyperglycemia engages a signaling complex that includes the purinergic receptor $P2Y_{11}$, adenylyl cyclase V, PKA, and $Ca_V1.2$ subunit of the LTCC. Activating this signaling module during diabetes leads to higher

LTCC $Ca_V1.2$ activation and myogenic tone that could contribute to vascular dysfunction in diabetes. Furthermore, some of the mechanisms regulating $Ca_V1.2$ in arterial myocytes are conserved in the modulation of the channel in neurons, thus highlighting the broad impact of our findings.

a. MP Prada, AU Syed, GR Reddy, M Martin-Aragon Baudel, VA Flores-Tamez, KC Sasse, SM Ward, P Sirish, N Chiamvimonvat, P Bartels, EJ Dickson, JW Hell, JD Scott, LF Santana, YK Xiang, MF Navedo, **M Nieves-Cintron*** (2020) AKAP5 complex facilitates purinergic modulation of vascular L-type Ca^{2+} channel $Ca_V1.2$. *Nature Communications* 11: 5303. DOI: 10.1038/s41467-020-18947-y. Recommended by Faculty Opinions (formerly Faculty 1000). PMC7575592
b. AU Syed, G Reddy, D Ghosh, MP Prada, MA Nystoriak, S Morotti, E Grandi, P Sirish, N Chiamvimonvat, JW Hell, LF Santana, YK Xiang, **M Nieves-Cintrón*,** MF Navedo (2019) Adenylyl cyclase 5-generated cAMP controls cerebral vascular reactivity during diabetic hyperglycemia. *Journal of Clinical Investigations* 129: 3140-3152. Highlighted by several news outlets and commentaries in the Journal of Diabetes Investigations and F1000. PMC6668679 *co-corresponding author
c. MP Prada, A Syed, OR Buonarati, RG Reddy, MA Nystoriak, D Ghosh, KC Sasse, SM Ward, LF Santana, YK Xiang, JW Hell, **M Nieves-Cintron***, MF Navedo (2019) A G_s-coupled purinergic receptor boost Ca^{2+} influx and vascular reactivity during diabetic hyperglycemia. *eLife* 8: e42214. PMC6397001 *co-corresponding author
d. H Qian, T Patriarchi, JL Price, L Matt, B Lee, **M Nieves-Cintron**, OR Buonarati, D Chowdhury, E Nanou, MA Nystoriak, WA Catterall, M Poomvanicha, F Hofmann, MF Navedo*, and JW Hell* (2017) Phosphorylation of serine 1928 mediates up-regulation of L-type $Ca_v1.2$ channel activity by β2 adrenergic receptor in neurons. *Science Signaling* 10, eaaf9659. *co-corresponding author. This article was highlighted on the cover and podcast of the journal and by the Faculty of 1000. PMC5310946

2. <u>Regulation of vascular reactivity by local cAMP/PAK signaling</u>. cAMP/PKA signaling has long been associated with relaxation. Our group challenged this long-held view when we found that in diabetic mice and hyperglycemic conditions, cAMP/PKA potentiated the $Ca_V1.2$ subunit of the LTCC, leading to increased arterial tone. Using various approaches such as cAMP biosensor, live-cell FRET, electrophysiology, myography, and in vivo measurements of vascular reactivity and blood flow, we identified a signaling complex in vascular smooth muscle that depends on AKAP5. This complex includes the purinergic receptor P2Y11, adenylyl cyclase V, PKA, and the $Ca_V1.2$ subunit of the LTCC. When this signaling module is activated during diabetes, it leads to local activation of cAMP/PKA signaling near the LTCC $Ca_V1.2$ subunit, which allows cAMP/PKA mediated potentiation of $Ca_V1.2$ and myogenic tone, which may contribute to vascular dysfunction in diabetes.

a. MA Nystoriak, **M Nieves-Cintrón**, T Patriarchi, S Morotti, E Grandi, J Dos Santos Fernandes, K Forbush, F Hofmann, KC Sasse, JD Scott, SM Ward, JW Hell, MF Navedo (2017) Ser^{1928} phosphorylation by PKA stimulates L-type $Ca_v1.2$ channels and vasoconstriction during acute hyperglycemia and diabetes. *Science Signaling* 10, eaaf9647. This article was highlighted on the cover and podcast of the journal and by the *Faculty* of 1000. PMC529743

b. MP Prada, AU Syed, GR Reddy, M Martin-Aragon Baudel, VA Flores-Tamez, KC Sasse, SM Ward, P Sirish, N Chiamvimonvat, P Bartels, EJ Dickson, JW Hell, JD Scott, LF Santana, YK Xiang, MF Navedo, **M Nieves-Cintron*** (2020) AKAP5 complex facilitates purinergic modulation of vascular L-type Ca^{2+} channel $Ca_V1.2$. *Nature Communications* 11: 5303. DOI: 10.1038/s41467-020-18947-y. Recommended by Faculty Opinions (formerly Faculty 1000). PMC7575592
c. AU Syed, G Reddy, D Ghosh, MP Prada, MA Nystoriak, S Morotti, E Grandi, P Sirish, N Chiamvimonvat, JW Hell, LF Santana, YK Xiang, **M Nieves-Cintrón*,** MF Navedo (2019) Adenylyl cyclase 5-generated cAMP controls cerebral vascular reactivity during diabetic hyperglycemia. *Journal of Clinical Investigations* 129: 3140-3152. Highlighted by several news outlets and commentaries in the Journal of Diabetes Investigations and F1000. PMC6668679 *co-corresponding author
d. MP Prada, A Syed, OR Buonarati, RG Reddy, MA Nystoriak, D Ghosh, KC Sasse, SM Ward, LF Santana, YK Xiang, JW Hell, **M Nieves-Cintron***, MF Navedo (2019) A G_s-coupled purinergic

receptor boost Ca^{2+} influx and vascular reactivity during diabetic hyperglycemia. *eLife* 8: e42214. PMC6397001 *co-corresponding author

3. NFAT signaling & cardiovascular function: I combined electrophysiology with state-of-the-art imaging and molecular biology to study the role of the calcineurin/NFAT signaling pathway in regulating potassium channel expression and function in smooth muscle cells from murine models of AngII-induced hypertension. These studies showed that the calcineurin/NFTA-signaling pathway controls the functional expression of K_V and BK channels, thereby regulating cardiovascular function during different pathological conditions.
   a. **M Nieves-Cintrón**, GC Amberg, CB Nichols, JD Molkentin and LF Santana. (2007) Activation of NFATc3 Down-regulates the β1 Subunit of Large Conductance, Calcium-activated K^+ Channels in Arterial Smooth Muscle and Contributes to Hypertension. *J Biol Chemistry.* 282 (5): 3231-40. PMC17148444
   b. **M Nieves-Cintrón**, GC Amberg, MF Navedo, J Molkentin, and LF Santana. (2008). The control of Ca^{2+} influx and NFATc3 signaling in Arterial Smooth Muscle during Hypertension. *PNAS,* 105 (40): 15623-8. PMC2557027
   c. **M Nieves-Cintrón**, D Hirenallur-Shanthappa, Nygren PJ, Hinke SA, Dell'Acqua ML, Langeberg LK, Navedo MF, Santana LF, Scott JD. AKAP150 participates in calcineurin/NFAT activation during the downregulation of voltage-gated K^+ currents in ventricular myocytes following myocardial infarction. *Cellular Signalling* 28(7): 733-740. PMC4902329

4. Functional regulation of L-type calcium channels. Ca^{2+} influx through voltage-gated L-type $Ca_V1.2$ channels (LTCCs) is a crucial signal regulating gene expression, cell excitability, and muscle contraction. We demonstrated that the phosphorylation state of $Ca_V1.2$ S1928 tunes LTCC function in arterial myocytes and modulates vascular reactivity. Phosphorylation of S1928 promotes channel clustering, leading to an increase in channel couple gaiting during diabetes. Moreover, we have shown that the trafficking of LTCC and alpha-actinin1 regulate LTCC activity.

   1. MA Nystoriak, **M Nieves-Cintrón**, T Patriarchi, S Morotti, E Grandi, J Dos Santos Fernandes, K Forbush, F Hofmann, KC Sasse, JD Scott, SM Ward, JW Hell, MF Navedo (2017) Ser^{1928} phosphorylation by PKA stimulates L-type $Ca_v1.2$ channels and vasoconstriction during acute hyperglycemia and diabetes. *Science Signaling* 10, eaaf9647. This article was highlighted on the cover and podcast of the journal and by the *Faculty* of 1000. PMC5297430
   2. D Ghosh, **M Nieves-Cintrón**, S Tajada, I Brust-Mascher, MC Horne, JW Hell, RE Dixon, LF Santana, MF Navedo (2018) Dynamic L-type $Ca_V1.2$ channel trafficking facilitates $Ca_V1.2$ clustering and cooperative gating. *BBA Molecular Cellular Research* 1865: 1341-1355. PMC64407617
   3. M Turner[#], DE Anderson[#], P Bartels[#], **M Nieves-Cintrón[#]**, A Coleman, PB Henderson, KN Man, PY Tseng, V Yarov-Yarovoy, DM Bers, MF Navedo, MC Horne, JB Ames, JW Hell (2020) Alpha-actinin-1 promotes gating of L-type Ca^{2+} channel $Ca_V1.2$. *EMBO Journal* 39: e102622. PMC7049811 ([#]equally contributing authors)
   4. M Martín-Aragón Baudel, VA Flores-Tamez, J Hong, GR Reddy, P Maillard, AE Burns, KNM Man, KC Sasse, SM Ward, WA Catterall, DM Bers, JW Hell, **M Nieves-Cintrón***, MF Navedo. Spatiotemporal Control of Vascular $Ca_V1.2$ by $\alpha1_C$ S1928 Phosphorylation. *Circ Res*. 2022 Dec 2;131(12):1018-1033. *co-corresponding author
   5. Flores-Tamez VA, Martín-Aragón Baudel M, Hong J, Taylor JL, Ren L, Le T, Syed AU, Moustafa Y, Singhrao N, Lemus-Martinez WR, Reddy GR, Ramer V, Man KNM, Bartels P, Chen-Izu Y, Chen CY, Simo S, Dickson EJ, Morotti S, Grandi E, Santana LF, Hell JW, Horne MC, **Nieves-Cintrón M**, Navedo MF. A1C S1928 Phosphorylation of CaV1.2 Channel Control Vascular Reactivity and Blood Pressure. J Am Heart Assoc. 2024 Oct 15;13(20):e035375. doi: 10.1161/JAHA.124.035375. Epub 2024 Oct 8. PubMed PMID: 39377203.

5. Tobacco-induced cardiovascular dysfunction: Our studies in this area demonstrate that even secondhand smoke exposure at environmentally relevant levels (3 mg/m3 total suspended particles) can significantly impair cardiovascular function. Specifically, 12 weeks of secondhand smoke exposure led to alterations in ion channels, increased L-type calcium channel functional expression, and decreased large conductance calcium-activated potassium channels, contributing to impaired vascular reactivity. Tobacco

exposure activates the calcineurin/NFAT signaling pathway in vascular smooth muscle, leading to transcriptional changes that may contribute to long-term vascular remodeling. We found that secondhand smoke exposure reduced heart rate variability, baroreflex sensitivity, and pulse pressure - all indicators of altered autonomic function and cardiovascular regulation. These changes were associated with decreased excitability of cardiac vagal neurons, suggesting a neuronal mechanism for autonomic dysfunction. Additionally, our research revealed that nicotine alone, even without combustion products, can impair β-adrenergic receptor-mediated cAMP signaling and vasodilation in vascular smooth muscle. This suggests nicotine itself contributes to vascular dysfunction, which has implications for newer nicotine delivery products. This research provides a comprehensive view of how tobacco products affect the cardiovascular system at multiple levels - from individual cell ion channels and second messenger systems to autonomic regulation of the heart and blood vessels to systemic inflammatory pathways. By identifying these specific mechanisms, the work not only advances our understanding of tobacco-related cardiovascular risk but also points to potential therapeutic targets for mitigating these risks.

a. Singhrao N, Flores-Tamez VA, Moustafa YA, Reddy GR[1], Burns AB, Pinkerton KE, Chen CY, Navedo MF, **Madeline Nieves-Cintrón[1]*** Nicotine impairs smooth muscle cAMP signaling and vascular reactivity. Microcirculation. 2024 Aug;31(6):e12871. doi: 10.1111/micc.12871
b. Pan S, Karey E, **Nieves-Cintron M**, Chen YJ, Hwang SH, Hammock BD, Pinkerton KE, Chen CY. Effects of chronic secondhand smoke exposure on cardiovascular regulation and the role of soluble epoxide hydrolase in mice. Front Physiol. 2023 Jun8;14:1185744. doi: 10.3389/fphys. 2023.1185744.
c. T Le, M Martín-Aragón Baudel, A Syed, N Singhrao, S Pan, VA Flores-Tamez, AE Burns, KNM Man, E Karey, J Hong, JW Hell, KE. Pinkerton, CY Chen, **M Nieves-Cintrón** (2021) Secondhand Smoke impairs ion channel function and contractility of mesenteric arteries. *Function*, Volume 2, Issue 5, 2021, zqab041

Complete list of published work in MyBibliography:
https://www.ncbi.nlm.nih.gov/myncbi/m.nieves.1/bibliography/public/