

# Faculty

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## Rank/Discipline

Assistant Professor

## Education & Specialty Certification

Ph.D., Pharmacology, University of Minnesota, 2008. BS, Biology, University of Puerto Rico, 2003.

## José O. Colón Sáez, Ph.D.

### Research Areas and Active Projects

The research interests of my lab is focused towards understanding the role of nAChR's in the development of inflammation and subsequent neurodegeneration which has been shown to be involved in the development of many disease states such as Parkinson's and Alzheimer's disease as well as HIV associated neurocognitive disorders. Therefore, a better understanding on the factors associated in the modulation of nAChRs will allow us to target these receptors as a therapeutic approach.

Currently we are working on 3 different lines of research:

1. We are working on increasing our understanding of the role that nAChRs play on brain inflammation and subsequent development of dementia associated with obesity. Interestingly, it has been shown that a high fat diet on wild-type mice causes the activation of microglia resulting in impairments on working memory and in humans an elevated serum cholesterol is a risk factor for mild cognitive impairment and dementia. Suggesting that dietary fat content affects the function of the brain. Using electrophysiology and pharmacological manipulation of lipids, we demonstrated that changes in lipid levels in the plasma membrane causes dramatic changes in the function of the  $\alpha 7$  nAChRs. Therefore, we are working on dissecting the role that  $\alpha 7$  nAChR plays on the high fat diet mediated microglia activation and subsequent development of neuroinflammation.
2. In a collaborative effort, we are using a mouse model of HIV infection to understand the role that nAChR play in the development of HIV associated neurocognitive disorders. HIV-associated neurocognitive disorders (HAND) are a plethora of neurodegenerative diseases that can lead to severe cognitive, motor and behavioral disturbances of varying severity. The prevalence rates of HAND have been estimated to be as high as 50-60% of HIV positive patients despite the use of highly active antiretroviral therapy (HAART). HAND development has been associated with increased activation of the brain immunity, specifically there is an increased in microglial activation. This inflammatory response is thought to be responsible for neuronal damage, resulting in motor symptoms and the cognitive impairment associated with HAND. The molecular mechanism by which HIV infection leads to HAND, are not fully understood. Interestingly, data

from our lab shows that exposure of primary human monocyte derived macrophages (MDMs) to a HIV-1 glycoprotein (gp120) results in the up-regulation of the  $\alpha 7$ -nAChR, suggesting the possibility of modulating HIV neuroinvasion before it occurs. Furthermore, our group has shown that gp120 exposure results in the functional up-regulation of the  $\alpha 7$ -nAChR in a neuroblastoma cell line, leading to cell death through calcium overload. And preliminary data shows similar effects in primary cultures of striatal neurons from a transgenic mouse model of HAND that expresses gp120 in their brain (gp120-tgm). However, the role that  $\alpha 7$ -nAChRs may play in the development of HAND is unknown. Therefore, there is a need to improve our understanding on the pathogenesis of HAND to increase our chances of treating it successfully.

3. The recent legalization of medicinal and in some cases recreational use of marijuana by many states in the USA, has resulted in a significant increase in the comorbidity of both marijuana and tobacco use. Studies have implicated the use of marijuana with the addictive potential of tobacco and viceversa suggesting that the mechanism of action of the addictive substances in both, cannabinoids and nicotine, interact with each other in the brain. However little is known about the effects that the phytocannabinoids found on marijuana have on the function of nicotinic acetylcholine receptors (nAChRs). Interestingly, it has been shown that endogenous cannabinoids are able to modulate the function of the two most abundant nAChRs in the brain the  $\alpha 7$  nAChR and the  $\alpha 4\beta 2$  nAChR. Although there is a tremendous therapeutic potential of the two most abundant phytocannabinoids in marijuana  $\Delta^9$ -Tetrahydrocannabinol (THC) and cannabidiol (CBD), many of their effects have been shown to be independent of the cannabinoid system, and there is a critical need to increase our understanding of their molecular targets. Therefore, we are working on the functional effects that phytocannabinoids have on nAChRs of different subunit compositions.

## Publications

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- Marker CL, Luján R, **Colón J**, Wickman K. Distinct populations of spinal cord lamina II interneurons expressing G-protein-gated potassium channels. *J Neurosci*. 2006 Nov 22;26(47):12251-9
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- Fernández-Alacid L, Aguado C, Ciruela F, Martín R, **Colón J**, Cabañero MJ, Gassmann M, Watanabe M, Shigemoto R, Wickman

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- McCormack TJ, Melis C, **Colon J**, Gay EA, Mike A, Karoly R, Lamb PW, Molteni C, Yakel JL. Rapid Desensitization of the Rat alpha7 nAChR is Facilitated by the Presence of a Proline Residue in the Outer {beta}-Sheet. *J Physiol.* 2010 Nov 15;588(Pt 22):4415-29.
- Brams M, Gay EA, **Sáez JC**, Guskov A, van Elk R, van der Schors RC, Peigneur S, Tytgat J, Strelkov SV, Smit AB, Yakel JL, Ulens C. Crystal structures of a cysteine-modified mutant in loop D of acetylcholine binding protein. *J Biol Chem.* 2011 Feb 11;286(6):4420-8.
- **Colón-Sáez JO**, Yakel JL. The alpha 7 nicotinic acetylcholine receptor function in hippocampal neurons is regulated by the lipid composition of the plasma membrane. *J Physiol.* 2011 Jul 1;589(Pt 13):3163-74.
- **Colón-Sáez JO**, Yakel JL. A mutation in the Extracellular domain of alpha 7 nicotinic acetylcholine receptor suppresses calcium permeability. *Pflugers Arch.* 2014 Aug;466(8):1571-9.
- Hernandez CM, Cortez I, Gu Z, **Colón-Sáez JO**, Lamb PW, Wakamiya M, Yakel JL, Dineley KT. Validation of Floxed  $\alpha$ 7 Nicotinic Acetylcholine Receptor Conditional Knockout Mice Using In Vitro and In Vivo Approaches. *J Physiol.* 2014 Aug 1;592(Pt 15):3201-14.
- Padilla-Morales LF, **Colón-Sáez JO**, González-Nieves JE, Quesada-González O, Lasalde-Dominicci JA. Assessment of the functionality and stability of detergent purified nAChR from Torpedo using lipidic matrixes and macroscopic electrophysiology. *Biochim Biophys Acta.* 2016 Jan;1858(1):47-56. doi: 10.1016/j.bbamem.2015.10.002. Epub 2015 Oct 8.
- Padilla-Morales LF, **Colón-Sáez JO**, González-Nieves JE, Quesada-González O, Lasalde-Dominicci JA. Functionality and Stability Data of Detergent Purified nAChR from Torpedo using Lipidic Matrixes and Macroscopic Electrophysiology. *Data Brief.* 2015 Dec 25;6:433-7. doi: 10.1016/j.dib.2015.12.010. eCollection 2016.
- Orestes Quesada-González, Carol Gonzalez, Emily Fernández, María Carla Ferrer, **José Colón**, Reginald Morales and José A.

Lasalde-Dominicci. Torpedo Electric Organ Lipid Composition: Nicotinic Acetylcholine Receptor Annular Lipids Composition and Activity Requirements. Accepted Manuscript, Scientific Reports.

## Presentations

- Doctors Medcannbiz:
  - Ritz Carlton Hotel. San Juan PR. October 2016.
  - Wvndham Garden at Palmas del Mar, Humacao PR, September 2016.
  - Hyatt Place Manati, Manati PR, September 2016.
  - Hilton Ponce Golf & Casino Resort, Ponce PR, August 2016.
  - Mayagüez Resort & Casino, Mayagüez PR, August 2016.
  - Ritz Carlton Hotel, San Juan PR, June 2016.
- University of Puerto Rico, Medical Science Campus, San Juan PR, June 2016. Pharmacology of Cannabis: drug-drug interactions and physiological effects of cannabinoids.
- Asociación de Farmacias de Comunidad, Yauco PR, October 2016. Pharmacology of Cannabis: drug-drug interactions and physiological effects of cannabinoids.
- University of Puerto Rico, Medical Science Campus, School of Pharmacy Continuous Education and Professional Studies (DECEP), San Juan PR, August 2016. Pharmacology of Cannabis: drug-drug interactions and physiological effects of cannabinoids.
- University of Puerto Rico at Rio Piedras, Department of Biology, Fall 2013. Alpha 7 nAChR function is dependent on the lipid composition at the plasma membrane.
- Society for Neuroscience Meeting 2012. A mutation in the Extracellular domain of alpha 7 nicotinic acetylcholine receptor suppresses calcium permeability.
- Society for Neuroscience Meeting 2011. The alpha 7 nicotinic acetylcholine receptor function in hippocampal neurons is regulated by the lipid composition of the plasma membrane.
- University of Puerto Rico at Cayey, Department of Biology, Fall 2006. Study of G protein-gated K<sup>+</sup> channel function in transgenic animals.