

## **1. Datos de Contacto:**

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**Anexos: 3833-3826**

## **2. Líneas de Investigación:**

Nos interesa estudiar los mecanismos moleculares y celulares implicados en el transporte de lípidos intracelulares, entre ellos colesterol y esfingolípidos, y las consecuencias de sus alteraciones. Particularmente, estamos enfocados en entender las alteraciones producidas en las enfermedades lisosomales de depósito de lípidos como Niemann-Pick A, B y C. Estamos enfocados en el hígado, estudiando como alteraciones en el transporte de lípidos impactan el estrés oxidativo y el metabolismo del cobre, daño, la fibrosis y la apoptosis. En el Sistema Nervioso Central, se está estudiando la conexión entre los defectos del transporte de lípidos y la respuesta al estrés y la apoptosis de las neuronas del cerebelo. Además, estamos interesados en explorar las bases celulares y moleculares de las enfermedades lisosomales de Niemann-Pick A, B y C y en la búsqueda de sus posibles blancos terapéuticos.

## **3. Proyectos de Investigación:**

- Proyecto apoyado por Genzyme "Assessment of the A359D acid sphingomyelinase gene mutation frequency in the Chilean population". Investigador responsable.

-Centro FONDAF 2010-2015: Genome Regulation. Investigador Asociado.

- FONDEF D10I1077, 2011-2015: Identification of c-Abl inhibitors for the potential treatment of Alzheimer Disease. Sub-director.

- FONDECYT 1110310, 2011-2015: Relevance of Oxidative damage due to mitochondrial dysfunction and/or decreased antioxidant defenses in the pathogenesis of Niemann Pick Type C disease. Investigador responsable.

- FONDECYT 1120512, 2012-2016: The synaptic c-Abl kinase regulates synaptic plasticity in adult brain. its dysregulation is involved in synaptic loss in Alzheimer disease. Co-investigador. Investigador responsable: Alejandra Alvarez.

-Proyecto Fondecyt Regular 1150327, 2015-2019: Liver injury in non-alcoholic fatty liver disease: exploring new modulators and biomarkers. Co-investigador. Investigador responsable: Marco Arrese.

-FONDECYT Regular 1150186, 2015-2019: Searching for Common Pathogenic Pathways leading to Neuronal and Hepatic Damage in Niemann-Pick Diseases. Investigador responsable.

#### **4. Publicaciones: (últimos 5 años; de preferencia formato J. Clinical Investigation o similar)**

1. Busso D, Oñate-Alvarado MJ, Balboa E, Zanlungo S, Moreno RD. Female infertility due to anovulation and defective steroidogenesis in mice deficient for lysosomal cholesterol transport protein NPC2. *Mol Cell Endocrinol.* 2010 ;315:299-307.
2. Morales MG, Amigo L, Balboa E, Acuña M, Castro J, Molina H, Miquel JF, Nervi F, Rigotti A, Zanlungo S. Deficiency of Niemann-Pick C1 protein protects against diet-induced gallstone formation in mice. *Liver Int.* 2010; 30:887-97.
3. Von Bernhardt R, Zanlungo S, Arrese M, Arteaga A, Rigotti A. The Metabolic Syndrome: from aggravating role to major risk factor of Chronic Diseases. *Rev. Med. Chil.* 2010;138:1012-9.
4. Rigotti A, Cohen DE, Zanlungo S. STARTing to understand MLN64 function in cholesterol transport. *J Lipid Res.* 2010;51:2015-7.
5. Klein A, Mosqueira M, Martinez G, Robledo F, González M, Caballero B, Cancino GI, Alvarez AR, Hetz C, Zanlungo S. Lack of activation of the Unfolded Protein Response (UPR) in mouse and cellular models of Niemann-Pick type C disease. *Neurodegener Dis.* 2011;8:124-8.
6. Klein A, Vargas LM, Robledo F, González M, Maldonado C, Muñoz F, Alvarez AR, Zanlungo S. Oxidative stress activates the c-Abl/p73 proapoptotic pathway in Niemann-Pick type C neurons. *Neurobiol. Dis Neurobiol Dis.* 2011;41:209-18.
7. Amigo L, Quiñones V, Leiva A, Busso D, Zanlungo S, Nervi F, Rigotti A. Apolipoprotein A-I deficiency does not affect biliary lipid secretion and gallstone formation in mice. *Liver Int.* 2011; 31:263-71.
8. Amigo L, Husche C, Zanlungo S, Lütjohann D, Arrese M, Miquel JF, Rigotti A, Nervi F. Cholecystectomy increases hepatic triglyceride content and very-low-density lipoproteins production in mice. *Liver Int.* 2011;31:52-64.
9. Estrada L, Zanlungo S, Alvarez AR. c-Abl tyrosine kinase signaling: a new player in AD tau pathology. *Curr Alzheimer Res.* 2011;8:643-51
10. Vázquez MC, del Pozo T, Robledo FA, Carrasco G, Pavez L, Olivares F, González M, Zanlungo S. Alteration of gene expression profile in Niemann-Pick type C mice correlates with tissue damage and oxidative stress. *PLoS One.* 2011;6:e28777.
11. Parra J, Klein AD, Castro J, Morales MG, Mosqueira M, Valencia I, Cortés V, Rigotti A, Zanlungo S. Npc1 deficiency in the C57BL/6J genetic background enhances Niemann-Pick disease type C spleen pathology. *Biochem Biophys Res Commun.* 2011; 413:400-6.
12. Balboa E, Morales G, Aylwin P, Carrasco G, Amigo L, Castro J, Rigotti A, Zanlungo S. Niemann-Pick C2 protein expression regulates

- lithogenic diet-induced gallstone formation and dietary cholesterol metabolism in mice. *Lipids* 2012;47:13-25.
13. Cabeza C, Figueroa A, Lazo OM, Galleguillos C, Pissani C, Klein A, Gonzalez-Billault C, Inestrosa NC, Alvarez AR, Zanlungo S, Bronfman FC. Cholinergic abnormalities, endosomal alterations and up-regulation of nerve growth factor signaling in Niemann-Pick type C disease. *Mol Neurodegener* 2012;7:11.
  14. Vazquez MC, Balboa E, Alvarez AR, Zanlungo S. Oxidative stress: a pathogenic mechanism for Niemann-Pick type C disease. *Oxid Med Cell Longev* 2012;2012:205713.
  15. Vazquez MC, Martinez P, Alvarez AR, Gonzalez M, Zanlungo S. Increased copper levels in in vitro and in vivo models of Niemann-Pick C disease. *Biometals* 2012;25:777-86.
  16. Vazquez MC, Rigotti A, Zanlungo S. Molecular Mechanisms Underlying the Link between Nuclear Receptor Function and Cholesterol Gallstone Formation. *J Lipids* 2012;2012:547643.
  17. Yevenes LF, Klein A, Castro JF, Marin T, Leal N, Leighton F, Alvarez AR, Zanlungo S. Lysosomal vitamin E accumulation in Niemann-Pick type C disease. *Biochim Biophys Acta* 2012;1822:150-60.
  18. Sáez PJ, Orellana JA, Vega-Riveros N, Figueroa VA, Hernández DE, Castro JF, Klein AD, Jiang JX, Zanlungo S, Sáez JC. Disruption in connexin-based communication is associated with intracellular Ca<sup>2+</sup> signal alterations in astrocytes from Niemann-Pick type C mice. *PLoS One*. 2013;8:e71361.
  19. Busso D, Oñate-Alvarado MJ, Balboa E, Castro J, Lizama C, Morales G, Vargas S, Härtel S, Moreno RD, Zanlungo S. Spermatozoa from mice deficient in Niemann-Pick disease type C2 (NPC2) protein have defective cholesterol content and reduced in vitro fertilising ability. *Reprod Fertil Dev*. 2014;26:609-21.
  20. Argüello G, Martinez P, Peña J, Chen O, Platt F, Zanlungo S, González M. Hepatic metabolic response to restricted copper intake in a Niemann-Pick C murine model. *Metallomics*. 2014;6:1527-39
  21. Marín T, Contreras P, Castro JF, Chamorro D, Balboa E, Bosch-Morató M, Muñoz FJ, Alvarez AR, Zanlungo S. Vitamin E dietary supplementation improves neurological symptoms and decreases c-Abl/p73 activation in Niemann-Pick C mice. *Nutrients*. 2014;6:3000-17.
  22. González-Zúñiga M, Contreras P; Estrada LD, Chamorro D, Villagra A, Zanlungo S, Seto E, Alvarez AR. c-Abl stabilizes HDAC2 levels by tyrosine phosphorylation repressing neuronal gene expression in Alzheimer Disease. *Molecular Cell* 2014;56:163-73.
  23. Klein AD, Alvarez A, Zanlungo S. The unique case of the Niemann-Pick type C cholesterol storage disorder. *Pediatr Endocrinol Rev*. 2014 Sep;12 Suppl 1:166-75.
  24. Cortés V, Amigo L, Zanlungo S, Galgani J, Robledo F, Arrese M, Bozinovic F, Nervi F. Metabolic effects of cholecystectomy: gallbladder ablation increases basal metabolic rate through G-protein coupled bile acid receptor Gpbar1-dependent mechanisms in mice. *PLoS One*. 2015;10:e0118478.
  25. Acuña M, Martínez P, Moraga C, He X, Moraga M, Hunter B, Nuernberg P, Gutiérrez RA, González M, Schuchman EH, Luis Santos

- J, Miquel JF, Mabe P, Zanlungo S. Epidemiological, clinical and biochemical characterization of the p.(Ala359Asp) SMPD1 variant causing Niemann-Pick disease type B. *Eur J Hum Genet.* 2015. doi: 10.1038/ejhg.2015.89 (en prensa).
26. Arguello G, Balboa E, Arrese M, Zanlungo S. Recent insights on the role of cholesterol in non-alcoholic fatty liver disease. *Biochim Biophys Acta.* 2015;1852:1765-78.
27. Acuña M, González-Hódar L, Amigo L, Castro J, Gabriela Morales M, Cancino GI, Groen AK, Young J, Miquel JF, Zanlungo S. Transgenic overexpression of Niemann-Pick C2 protein promotes cholesterol gallstone formation in mice. *J Hepatol.* 2015 (aceptado).
28. Contreras PS, Gonzalez-Zuñiga M, González-Hódar L, Yáñez MJ, Dulcey A; Marugan J, Seto E, Alvarez AR, Zanlungo S. Neuronal gene repression in Niemann-Pick type C models is mediated by the c-Abl/HDAC2 signaling pathway. *BBA - Gene Regulatory Mechanisms* (accepted).

### **5. Libros y patentes:**

Autores: Pontificia Universidad Católica de Chile; profesores Juan Francisco Miquel, Flavio Nervi, Attilio Rigotti y Silvana Zanlungo. "Methods of treating or preventing cholesterol gallstone disease with ezetimibe".

Países concedidos y fechas: USA: 8/361,999, Octubre 2, 2012; México: 289407, Agosto 17, 2011.