

LÍNEA DE Investigación: Immunoregulation of Infectious, Inflammatory and Neurodegenerative Disorders

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LÍNEA DE INVESTIGACIÓN

The research goal of the Gonzalez-Rey laboratory consists of **knowing the relationship between the central nervous system (CNS) and the immune system, characterizing the connection between infectious diseases and their effects in neurodegenerative disorders, and in processes of pathological aging.** Our investigation focuses particularly on identifying endogenous mediators shared by both systems (neuropeptides) able to tune the immune system and to restore homeostasis under inflammation, autoimmunity and infection, with a therapeutic profile on these disorders and / or that have relevancy in the development and evolution of the above mentioned diseases. Specifically, **we are interested in characterizing the therapeutic effect of these neuropeptides in neuroinflammatory/neurodegenerative diseases** such as multiple sclerosis, Alzheimer's disease, and Parkinson's disease; in the study of their mechanisms of action; in the characterization of the neuroprotective and/or neuroregenerative effects of these molecules during the whole life of the individual, including the oldness. On the other hand, we have recently described that some of these neuropeptides have additional functions showing similar structural characteristics and functional behaviour that those exerted by antimicrobial peptides. In this respect, we are studying **the possible relationship that could exist between these antimicrobial neuropeptides and the potential protective effect in the development of aging-associated disorders.**

PUBLICACIONES RECIENTES (5 ÚLTIMOS AÑOS)

1. Rodriguez R, Rosu-Myles M, Aráuzo-Bravo M, Horrillo A, Pan Q, **Gonzalez-Rey E**, Delgado M, Menendez P. Human bone marrow stromal cells lose immunosuppressive and anti-inflammatory properties upon oncogenic transformation. **Stem Cell Reports**. 2014 Oct 14;3(4):606-19.
2. **Gonzalez-Rey E**, Delgado M. Therapeutic application of mesenchymal stromal cells in murine models of inflammatory bowel disease. **Methods Mol Biol**. 2014;1213:331-9.
3. Neubrand VE., Pedreño M., Caro M., Forte-Lago I., Delgado M., **Gonzalez-Rey E**. Mesenchymal stem cells induce the ramification of microglia via the small RhoGTPases Cdc42 and Rac1. **Glia**. 2014 Jul 3. doi: 10.1002/glia.22714

4. Campos-Salinas, J., Cavazzuti, A., O'Valle, F., Forte-Lago, I., Caro, M., Beverley, S., Delgado, M., **González-Rey, E.** Therapeutic effect of a stable analog of Vasoactive Intestinal Peptide in sepsis and leishmaniasis. **J Biol Chem.** 2014; 289: 14583-14599.
5. Pedreño, M., Morell, M., Robledo, G., Souza-Moreira, L., Forte-Lago, I., O'Valle, F., Ganea, D., **Gonzalez-Rey, E.** Adrenomedullin protects from experimental autoimmune encephalomyelitis at multiple levels: effects on neuroinflammation, autoimmunity and neurodegeneration. **Brain Behav Immun.** 2014, 37: 152-63
6. Parolini, O., Souza-Moreira, L., O'Valle, F., Hernandez-Cortes, P., **Gonzalez-Rey, E.**, Delgado, M. Therapeutic effect of human amniotic membrane-derived cells in experimental arthritis and other inflammatory disorders. **Arthritis Rheum.** 2014; 66: 327-339.
7. Campos-Salinas, J., Caro, M., Cavazzuti, A., Forte-Lago, I., Beverley, SM., O'Valle, F., **Gonzalez-Rey, E.** Protective role of the neuropeptide Urocortin II against experimental sepsis and leishmaniasis by direct killing of pathogens. **J Immunol.** 2013; 191 (12): 6040-51
8. Roodvelt, C., Labrador-Garrido, A., **Gonzalez-Rey, E.**, Lachaud, CC., Guilliams, T., Fernandez-Montesinos, R., Benitez-Rondan, A., Robledo, G., Hmadcha, A., Delgado, M., Dobson, CM., Pozo, D. Preconditioning of microglia by alpha-synucleina atrongly affects the response induced by Toll-like receptor (TLR) stimulation. **Plos One.** 2013; 8 (11): e79160
9. Souza-Moreira, L., Morell, M., Delgado-Maroto, V., Pedreño, M., Martinez-Escudero, L., Caro, M., O'Valle, F., Luque, R., Luis de Lecea., Gallo, M., Castaño, JP and **González-Rey, E.** Paradoxical effect of Cortistatin treatment and its deficiency on Experimental Autoimmune Encephalomyelitis. **J. Immunol.** 2013. 191 (5): 2144-54
10. Campos-Salinas, J., León-Guerrero, D., **González-Rey E.**, Delgado, M., Castanys, S., Pérez-Victoria, JM., Gamarro, F. LABCG2, a new ABC transporter implicated in phosphatidylserine exposure is involved in the infectivity and pathogenesis of Leishmania. **PLoS Negl Trop Dis.** 2013 Apr 25;7(4):e2179
11. Souza-Moreira, L., Delgado-Maroto, V., Morell, M., O'Valle, F., Del Moral, R.G., **González-Rey, E.** Therapeutic effect of ghrelin in experimental autoimmune encephalomyelitis by inhibiting antigen-specific Th1/Th17 responses and incuding regulatory T cells. **Brain Behav Immun.** 2013; 30: 54-60
12. Morell, M., Souza-Moreira, L., Caro, M., O'Valle, F., de Lecea, L., **González-Rey, E.** and Delgado, M. Analgesic effect of the neuropeptide cortistatin in arthritic inflammatory pain. **Arthritis Rheum.** 2013. Jan 31. doi: 10.1002/art.37877
13. Anderson P, Souza-Moreira L, Morell M, Caro M, O'Valle F, **Gonzalez-Rey E**, Delgado M. Adipose-derived mesenchymal stromal cells induce immunomodulatory macrophages which protect from experimental colitis and sepsis. **Gut.** 2013; 62 (8): 1131-41
14. Klionsky DJ et al. Guidelines for the use and interpretation of assays for monitoring autophagy. **Autophagy.** 2012; 8(4): 445-544.
15. Souza-Moreira L, Campos-Salinas J, Caro M, **Gonzalez-Rey E.** Neuropeptides as pleiotropic modulators of the immune response. **Neuroendocrinology.** 2011; 94(2): 89-100.
16. Pereira CA, Silber AM, **Gonzalez-Rey E.** New enzymes as potential therapeutic targets for trypanosomiasis and leishmaniasis. **Enzyme Res.** 2011; 2011:907423
17. Lüder CG, Campos-Salinas J, **Gonzalez-Rey E**, van Zanbergen G. Impacto f protozoan cell death on parasite-host interactions and patogénesis. **Parasit Vectors.** 2010; 2(3): 116
18. Bienvenu AL, **Gonzalez-Rey E**, Picot S. Apoptosis induced by parasitic diseases. **Parasit Vectors.** 2010; 17(3):106.
19. Roodveldt C, Labrador-Garrido A, **Gonzalez-Rey E**, Fernandez-Montesinos R, Caro M, Lachaud CC, Waudby CA, Delgado M, Dobson CM, Pozo D. Glial innate immunity generated by non-aggregated alpha-synuclein in mouse: differences between wild-type and Parkinson´s disease-linked mutants. **Plos One.** 2010; 5(10):e13481
20. **Gonzalez-Rey E**, Delgado-Maroto V, Souza Moreira L, Delgado M. Neuropeptides as Therapeutic Approach to Autoimmune Diseases. **Curr Pharm Des.** 2010 Aug 5.
21. Boscardin SB, Torrecilhas AC, Manarin R, Revelli S, **Rey EG**, Tonelli RR, Silber AM. Chagas' disease: an update on immune mechanisms and therapeutic strategies. **J Cell Mol Med.** 2010 Jun;14(6B):1373-84.
22. Prasse A, Zissel G, Lützen N, Schupp J, Schmiedlin R, **Gonzalez-Rey E**, Rensing-Ehl A, Bacher G, Cavalli V, Bevec D, Delgado M, Müller-Quernheim J. Inhaled vasoactive

- intestinal peptide exerts immunoregulatory effects in sarcoidosis. **Am J Respir Crit Care Med.** 2010 Aug 15;182(4):540-8.
23. **Gonzalez-Rey E**, Ganea D, Delgado M. Neuropeptides: keeping the balance between pathogen immunity and immune tolerance. **Curr Opin Pharmacol.** 2010 Aug;10(4):473-81.
 24. Anderson P, **Gonzalez-Rey E**. Vasoactive intestinal peptide induces cell cycle arrest and regulatory functions in human T cells at multiple levels. **Mol Cell Biol.** 2010 May;30(10):2537-51.
 25. Herrera JL, **Gonzalez-Rey E**, Fernandez-Montesinos R, Quintana FJ, Najmanovich R, Pozo D. Toll-like receptor stimulation differentially regulates vasoactive intestinal peptide type 2 receptor in macrophages. **J Cell Mol Med.** 2009 Sep;13(9B):3209-17.
 26. **Gonzalez-Rey E**. Keeping the balance between immune tolerance and pathogen immunity with endogenous neuropeptides. **Neuroimmunomodulation.** 2010;17(3):161-4.
 27. Fernandez-Montesinos R, Castillo PM, Klippstein R, **Gonzalez-Rey E**, Mejias JA, Zaderenko AP, Pozo D. Chemical synthesis and characterization of silver-protected vasoactive intestinal peptide nanoparticles. **Nanomedicine** (Lond). 2009 Dec;4(8):919-30.
 28. Pozo D, Anderson P, **Gonzalez-Rey E**. Induction of alloantigen-specific human T regulatory cells by vasoactive intestinal peptide. **J Immunol.** 2009 Oct 1;183(7):4346-59.
 29. Campos-Salinas J, **Gonzalez-Rey E**. Autophagy and neuropeptides at the crossroad for parasites: to survive or to die? **Autophagy.** 2009 May;5(4):551-4
 30. Gonzalez MA, **Gonzalez-Rey E**, Rico L, Büscher D, Delgado M. Treatment of experimental arthritis by inducing immune tolerance with human adipose-derived mesenchymal stem cells. **Arthritis Rheum.** 2009 Apr;60(4):1006-19
 31. Herrera JL, **Gonzalez-Rey E**, Fernandez-Montesinos R, Quintana FJ, Najmanovich R, Pozo D. Toll-like receptor stimulation differentially regulates vasoactive intestinal peptide type 2 receptor in macrophages. **J Cell Mol Med.** 2009 Jan 16.
 32. **Gonzalez-Rey E**, Anderson P, González MA, Rico L, Büscher D, Delgado M. Human adult stem cells derived from adipose tissue protect against experimental colitis and sepsis. **Gut.** 2009 Jul;58(7):929-39.
 33. Gonzalez MA, **Gonzalez-Rey E**, Rico L, Büscher D, Delgado M. Adipose-derived mesenchymal stem cells alleviate experimental colitis by inhibiting inflammatory and autoimmune responses. **Gastroenterology.** 2009 Mar;136(3):978-89.
 34. **Gonzalez-Rey E**, Gonzalez MA, varela N, O'Valle, F, Hernandez-Cortes P, Rico L, Büscher D, Delgado M. Human adipose-derived mesenchymal stem cells reduce inflammatory and T cell responses and induce regulatory T cells in vitro in rheumatoid arthritis. **Ann Rheum Dis.** 2010 Jan;69(1):241-8.
 35. Delgado M, Anderson P, Garcia-Salcedo JA, Caro M, **Gonzalez-Rey E**. Neuropeptides kill African trypanosomes by targeting intracellular compartments and inducing autophagic-like cell death. **Cell Death Differ.** 2009 Mar;16(3):406-16.

TESIS DIRIGIDAS RECIENTEMENTE (5 ÚLTIMOS AÑOS).

Characterization of the immunomodulatory and neuroprotective role of the adrenomedullin in neurodegenerative diseases. PhD student: Marta Pedreño. Institute of Parasitology and Biomedicine, IPBLN-CSIC. Granada 2011-2014 (Spain). In progress.

Regulation of the HPA axis by the neuropeptide cortistatin: involvement in behavior, memory and learning under basal and stress conditions. PhD student: Laura Martínez-Escudero. Institute of Parasitology and Biomedicine, IPBLN-CSIC. Granada 2013-2015 (Spain). In progress.

Therapeutic use of the neuropeptides cortistatin and ghrelin in an experimental model of multiple sclerosis. PhD student: Luciana de Souza-Moreira. Institute of Parasitology and Biomedicine, IPBLN-CSIC. Granada 2008-2012 (Spain). Sobresaliente cum laude

Effect of neuropeptides restoring homeostasis in inflammation and autoimmunity. PhD student: Alejo Chorny. Institute of Parasitology and Biomedicine, IPBLN-CSIC. Granada 2006-2009 (Spain). Sobresaliente cum laude

TRABAJOS FIN DE MÁSTER REALIZADOS

- Maxime Guyetant (France, predoctoral). Master Thesis: "Characterization of the action of cortistatin under hypoxic conditions induced by brain trauma". (2012)
- Lorena Carballo-Lago (Spain). Master Thesis: "Immunomodulatory effect of cortistatin in de- and remyelination". (2015).
- Jose María Villaescusa-González (Spain). Master Thesis: "Role of cortistatin as a neuroprotective agent in a dopaminergic cellular model". (2015).

PROYECTOS Y AYUDAS DE INVESTIGACIÓN

Ongoing Research Projects

CTS-2939

Delgado M (PI)

2014-2016. Science and Innovation Dept., Junta Andalucía, Spain

"Characterization of the role of cortistatin in inflammatory and neuropathic pain"

Role: Collaborator

Finished Research Projects

SAF2010-16923

Gonzalez-Rey (PI)

2010-2014. Science and Innovation Minister, Spain

"Therapeutic effect of cortistatin and adrenomedullin in degenerative processes on the nervous system induced by inflammation"

Role: PI

P09-CTS-4705

Gonzalez-Rey E (PI)

2010-2013. Science and Innovation Dept., Junta Andalucía, Spain

"New antiparasitic therapies: use of endogenous neuropeptides"

Role: PI

PETRI- Education and Science Minister,

Delgado M (PI)

2009-2011. PETRI- Education and Science Minister, Spain

"Converting stem cells in medicine: ASCs and biotechnological applications in clinic"

Role: Collaborator

Fundation Alicia Koplowitz ,

Delgado M (PI), Gonzalez-Rey E (Co-PI)

2009-2011. Fundation Alicia Koplowitz, Spain

"Therapeutic effect of adipose-derived stem cells in the animal model of multiple sclerosis. Tolerance induction and regeneration"

Role: Co-IP

SAF2007-60101.

Gonzalez- Rey E (PI)

2007-2010. Education and Science Minister. Spain

"Therapeutic application of the neuropeptides Cortistatin and Ghrelin in an experimental model of multiple sclerosis".

Role: PI

RO1 AI052306

Ganea D (PI)

2006-2011. National Institute of Health (NIH).

"Role of PGE2 in CNS and peripheral autoimmune disorders".

Role: Collaborator

PETRI- Education and Science Minister,

Delgado M (PI)

2007-2009. PETRI- Education and Science Minister, Spain

" Investigation of the immunoregulatory activity of adult stem cells in animal models of inflammatory diseases"

Role: Collaborator

CTS-980

Delgado (PI); Gonzalez-Rey (Co-PI)

1/1/06-12/31/08 Science and Innovation Dept., Junta Andalucia, Spain

"NFkB inhibitors in the treatment of rheumatoid arthritis"

Role: Co-IP

FA04-007

Delgado (PI); Gonzalez-Rey (Co-PI)

11/1/04-10/31/07 Areces Foundation, Spain

"Use of regulatory peptides for the treatment of inflammatory and autoimmune diseases"

Role: Co-IP

RO1 AI047325

Ganea D (PI)

2004-2008. National Institute of Health (NIH).

"Neuropeptides and Regulatory T cells".

Role: Collaborator