

LINE

1

STRUCTURE AND
FUNCTION OF MOLECULAR
SENSORS

This line of research aims to reveal mechanisms that lead to ion channel opening in response to stimuli such as changes in electric potential, intracellular calcium concentration or environmental temperature. At present we are attempting to answer the following questions: (a) Is there a temperature sensor in transient receptor potential (TRP) channels? And if so, (b) what is its molecular nature? and (c) How the electrical, chemical or thermal energy is transformed into mechanical energy (the pore opening)? In order to answer these questions we are using electrophysiological (voltage clamp y patch clamp), fluorescence (lanthanide resonance energy transfer -LRET- and voltage-controlled fluorometry-VCF), and molecular modeling techniques (together with research line 5). Our researchers have carried out studies on the functioning of voltage sensors in proton channels (Hv), in voltage- and Ca^{2+} -activated K^{+} channels, in voltage-dependent Ca^{2+} channels, and in connexins. They have succeeded in detecting gating currents in Hv and movements of an extracellular domain in a connexin (Cx) by using VCF (together with research line 2). They have also found that the TRPM8 channel (a cold receptor) can be opened only by decreasing temperature through a temperature-independent pathways and we have identified the molecular nature of the phosphatidylinositol 4,5-bisphosphate binding site in TRPV1 channel (a heat receptor).

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SELECTED PUBLICATIONS

Qiu F, Rebolledo S, **González C**, Larsson HP (2013). Subunit interactions during cooperative opening of voltage-gated proton channels. *Neuron*. 77(2):288-98.

Pantazis A, Savalli N, Sigg D, **Neely A**, **Olcese R** (2014). Functional heterogeneity of the four voltage sensors of a human L-type calcium channel. *Proc. Natl. Acad. Sci. USA*. 111(51):18381-6.

Raddatz N, Castillo JP, **González C**, **Alvarez O**, **Latorre R** (2014). Temperature and voltage coupling to channel opening in transient receptor potential melastatin 8 (TRPM8). *J Biol Chem*. 289(51):35438-54. (Selected as JBC paper of the week).

Pupo A & **González C** (2014). In pursuit of an inhibitory drug for the proton channel (Hv1). *Proc. Natl. Acad. Sci. USA*. 111(27):9673-74.

Jabba S, Goyal R, Sosa-Pagán JO, Moldenhauer H, Wu J, Kalmeta B, Bandell M, **Latorre R**, Patapoutian A, Grandl J (2014). Directionality of Temperature Activation in Mouse TRPA1 Ion Channel Can Be Inverted by Single-Point Mutations in Ankyrin Repeat Six. *Neuron*. 82(5):1017-1031.

Castillo, JP, Rui H, BasilioD, Roux B, **Latorre R**, **Bezanilla F** and **Holmgren M** (2015). Mechanism of potassium ion uptake by $\text{Na}^{+}/\text{K}^{+}$ -ATPase. *Nature Comm*. July 24 6:7622

Diaz-Franulic I, Poblete H, Miño G, **González C** and **Latorre R** (2016). Allosterism and Structure in Thermally Activated Transient Receptor Potential Channels *Ann. Rev. Biophys.* 45:371-398

Pinto BI, García IE, Pupo A, Retamal MA, **Martinez AD**, **Latorre R** and **Gonzalez C** (2016). Charged residues at the first transmembrane region contribute to the voltage dependence of connexins slow gate. *J Biol Chem* 291:15740-52