Robert M Stroud, J Proteomics Bioinform 2016, 9:10(Suppl)
http://dx.doi.org/10.4172/0974-276X.C1.087

6th International Conference on

Structural Biology

August 22-23, 2016 New Orleans, USA

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How do voltage sensors in trans-membrane channels work?

The structure determination of an integral membrane protein complex of an ion regulated, voltage gated two-pore channel TPC-1 is reported at 2.9 Å resolution. The channel is gated by external Ca++ ions and by voltage such that at zero voltage the channel is closed, in its resting state. In other voltage gated channels the sensor is activated leading to a comparison of the two states that provides the first example of what kinds of transitions occur in an inactive-to-active state in a voltage sensitive channel. This leads to a proposal for the mechanism of voltage sensors that control channel activity. In addition the channel controls an intracellular organelle that controls viral entry into cells for membrane encapsulated filoviruses. An inhibitor NED19 is bound that shows how the channel is inhibited allosterically, at a distance from the channel. Inhibition of TPC1 by NED19 leads to a cure for Ebola infected mice.

Biography

Robert M Stroud is a Professor of Biochemistry and Biophysics at UCSF. He has obtained his BA, MA at Cambridge University and his PhD in J.D. Bernal's Laboratory at London University where he programmed non-centrosymmetric direct methods to determine structure of the nucleoside antibiotic tubercidin and vitamins. He did Post-doctoral studies with R. E. Dickerson where he determined the first structure of trypsin and trypsinogen. He became an Associate Professor of Chemistry at Caltech and moved to UCSF as the Founding Member of the Macromolecular Structure Group. He is a Member of the National Academy of Sciences USA, a Fellow of the American Academy of Arts and Sciences and a Fellow of the Royal Society of Medicine (UK). His research focuses on the mechanisms of trans-membrane transporters, receptors and channels and on the mechanisms of protein-RNA recognition and chemistry at the level of atomic structure, mechanisms, inhibition and structure-based drug discovery.

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