

Brown Deer High School SMART Team

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TRPA1 Makes You Feel The PAiN

PDB: 3J9P

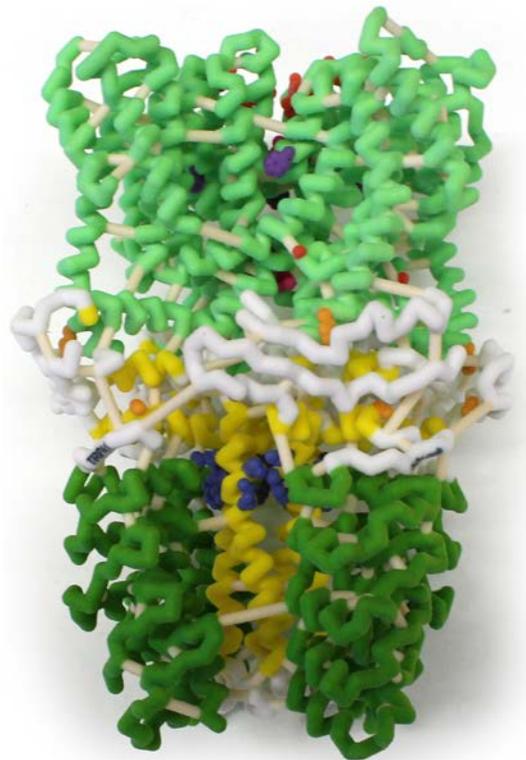
Primary Citation: Paulson, C.E., Armache, J., Gao, Y., Cheng, Y., Julius, D. (2015). Structure of the TRPA1 ion channel suggests regulatory mechanisms. *Nature* 520: 511-513.

Format: Alpha carbon backbone

RP: Zcorp with plaster

Description:

About 3-4% of people worldwide suffer from chronic pain. The United States spends \$60 billion annually treating pain. Current treatments are ineffective; opioids are addictive and lose efficacy while pregabalin, a non-opioid neuropathic pain drug, only works in 30% of patients. Pain receptors (nociceptors) are activated chemically or mechanically. The nociceptor transient receptor potential cation channel, subfamily A, member 1 (TRPA1) is an ion channel located in the membranes of free nerve endings in the skin. TRPA1 is activated by mechanical stretching, and has many active sites where ligands (e.g. tear gas, mustard gas, and wasabi) can bind to open the channel. Once opened, Ca^{2+} and Na^{2+} ions pass through, depolarizing the neuron. Structurally, TRPA1 is a tetramer, with each subunit containing several domains. In the pre-S1 domain, ligands bind covalently to the sulfurs at Cys621, Cys641, Cys665, and Lys710. The TRP-like domain opens for ion passage. The ankyrin repeat domain contains 16 recurring sequences of 33 residues, and may be involved with the stretch activation of TRPA1. In domains S1-S6, α helices hold the protein's shape and contain binding sites for agonists to open the channel and for antagonists, which prevent functioning. One antagonist, A-967079, binds in a pocket around Phe909, forming a wedge to prevent movement and function of TRPA1. Researchers aim to develop a TRPA1 antagonist that will help treat pain sufferers. The Brown Deer SMART (Students Modeling A Research Topic) Team constructed a model of TRPA1 using 3D printing technology to assist researchers in studying its structure and function.



Specific Model Information:

- The amino acids where agonists bind (Cys621, Cys641, Lys710) are orange.
- The amino acids that attract cations to the pore mouth (Glu920, Glu924, Glu930) are orangered.
- The amino acids forming the upper and lower restrictions of the pore channel (Asp915, Ile957, Val961) are magenta.
- A mutation site at amino acid Asn855, causing a familial episodic pain syndrome is red.
- The amino acid where antagonists bind (Phe909) is indigo.
- The Ankyrin repeat domain is green.
- The transmembrane alpha chains are springgreen.
- The amino acids in the coiled coil where polyphosphates bind (Lys1046, Arg1050, Lys1048, Lys1052) are mediumblue.
- Alpha chains are yellow.
- The alpha carbon backbone is white.
- Struts are colored papayawhip.

<http://cbm.msoe.edu/smartTeams/index.php>

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