Cutting Edge of the Recent TRPV1, TRPA1 Research and Drug Development

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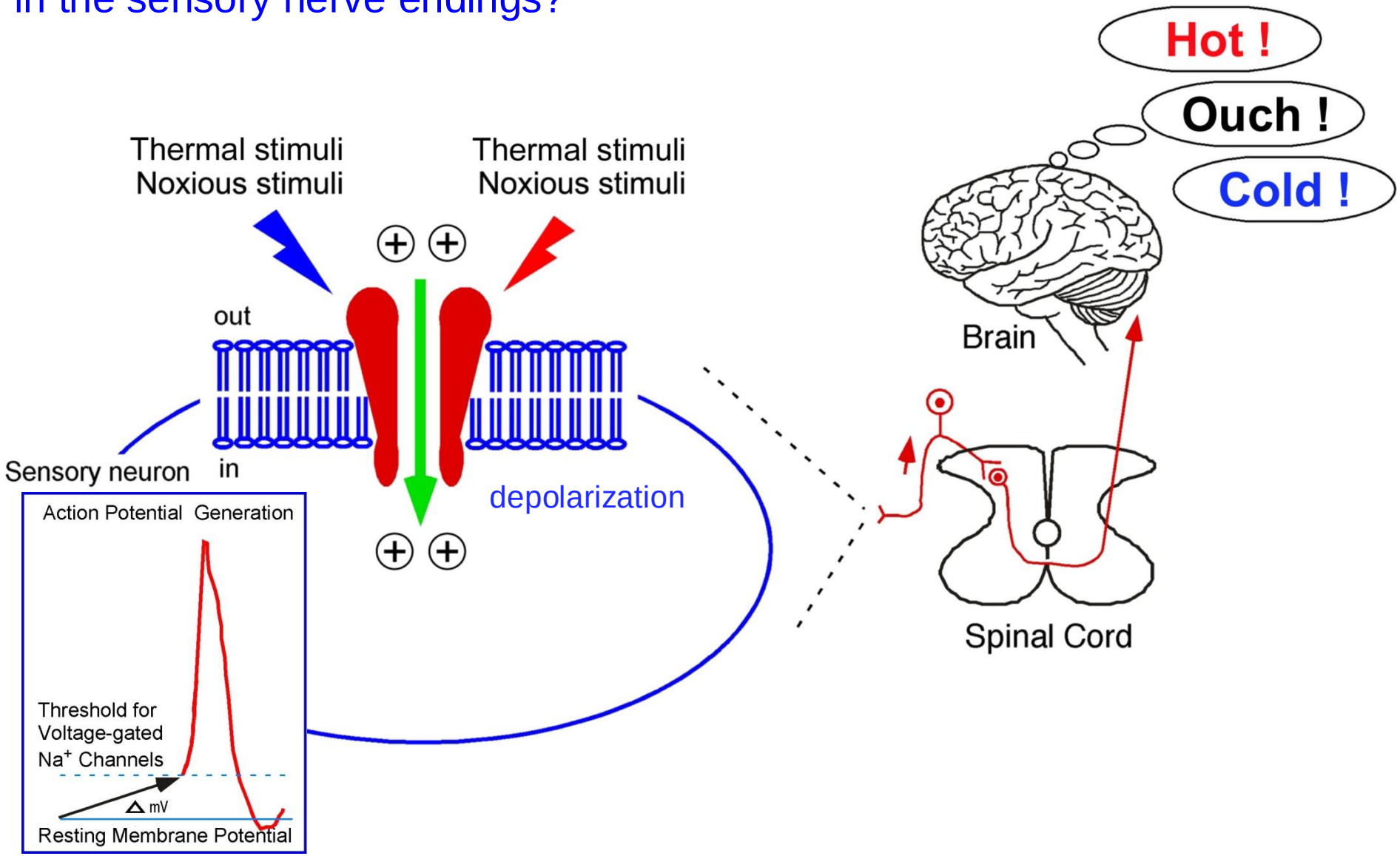
at Peter Hung Pain Research Institute (11.24.2024)

Conversion of Thermal Stimuli to Electrical Signals

How do we sense noxious stimuli
in the sensory nerve endings?



The Nobel Prize in Physiology or Medicine 2021

Ill. Niklas Elmehed © Nobel Prize Outreach

David Julius

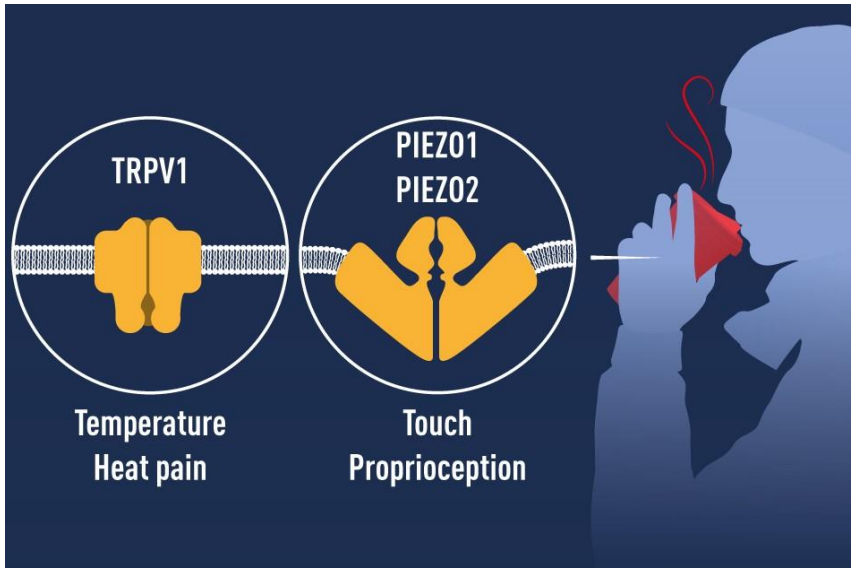
Prize share: 1/2

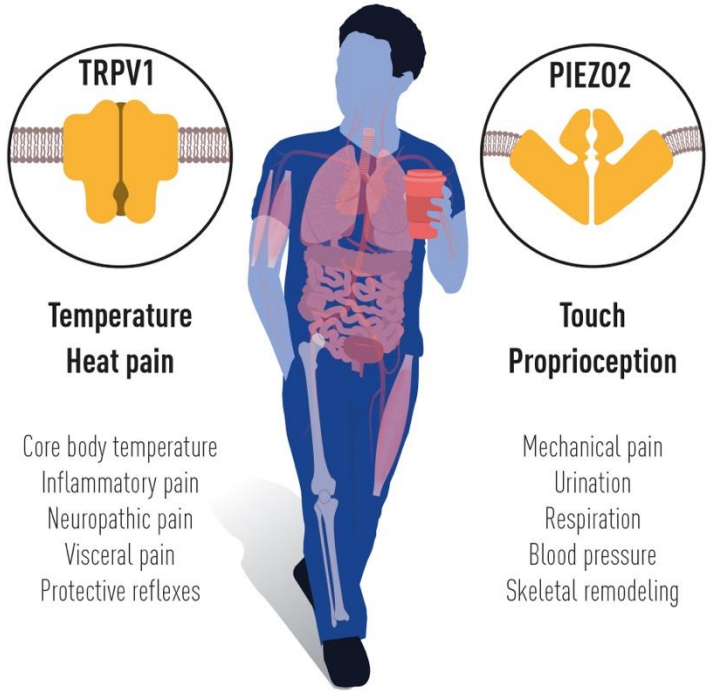
Ill. Niklas Elmehed © Nobel Prize Outreach

Ardem Patapoutian

Prize share: 1/2

The Nobel Prize in Physiology or Medicine 2021 was awarded jointly to David Julius and Ardem Patapoutian "for their discoveries of receptors for temperature and touch."





They are involved in various functions.

from HP of Nobel Foundation

Research about the mechanisms for detection of physical stimuli (thermal and mechanical stimuli) did not progress well because the sensors were not clarified.

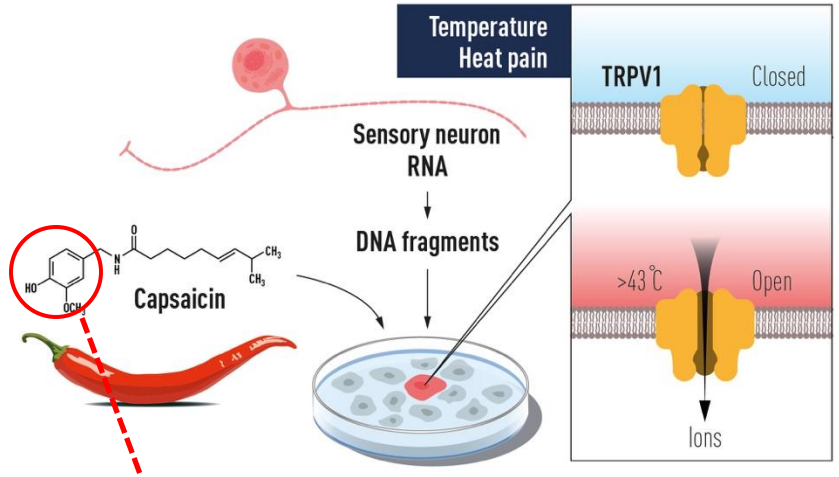
Pungent sensation is pain, but not taste.
It was not not known whether the receptors are membrane proteins.

A report was published showing that a capsaicin activates a non-selective cation channel in sensory neurons (Oh et al. J. Neurosci. 1996).

People thought that the gene coding the capsaicin receptor can be cloned and inhibitors of the receptor should be novel antinociceptive agents.

There was a fierce competition for the cloning of capsaicin receptor gene all over the world.

Julius lab succeeded in the cloning of capsaicin receptor gene using a Ca-imaging-based expression cloning method.



from HP of Nobel Foundation

We isolated a single clone in April, submitted the manuscript in July, and the paper was published in October, 1997.

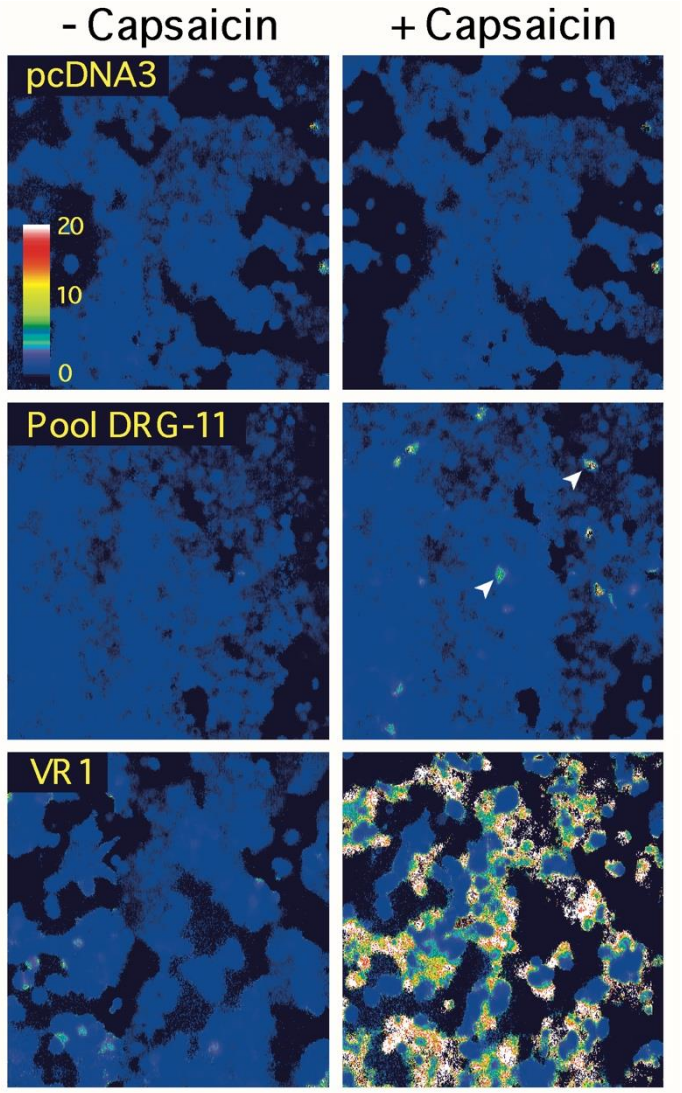
Red-hot receptor revealed

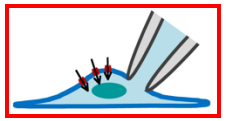
Because capsaicin has a vanillyl moiety in its structure, we initially named it Vanilloid Receptorsubtype 1 (VR1).

People did not imagine that heat stimulus opens ion channels at that time.

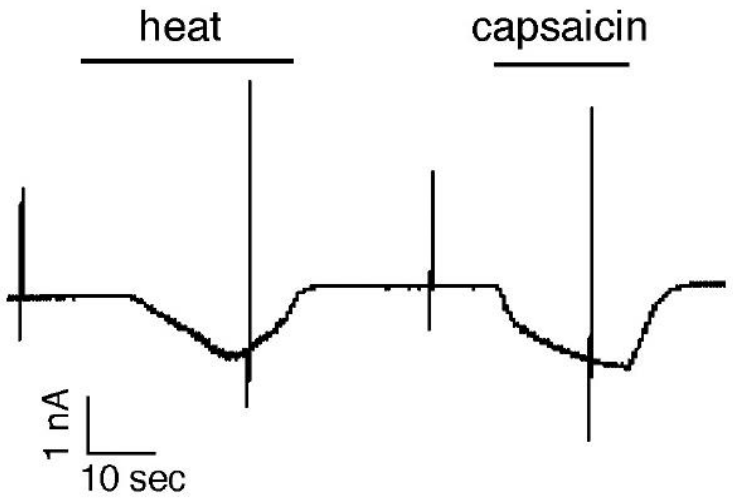
Because we feel hot in mouth upon eating pungent capsicums, we though that heat stimulus might activate TRPV1 and did experiments.
And it turned out to be the case.

Furthermore, when we tried to determine the temperature thresholds
for TRPV1 activation, they were temperatures causing pain in our body.

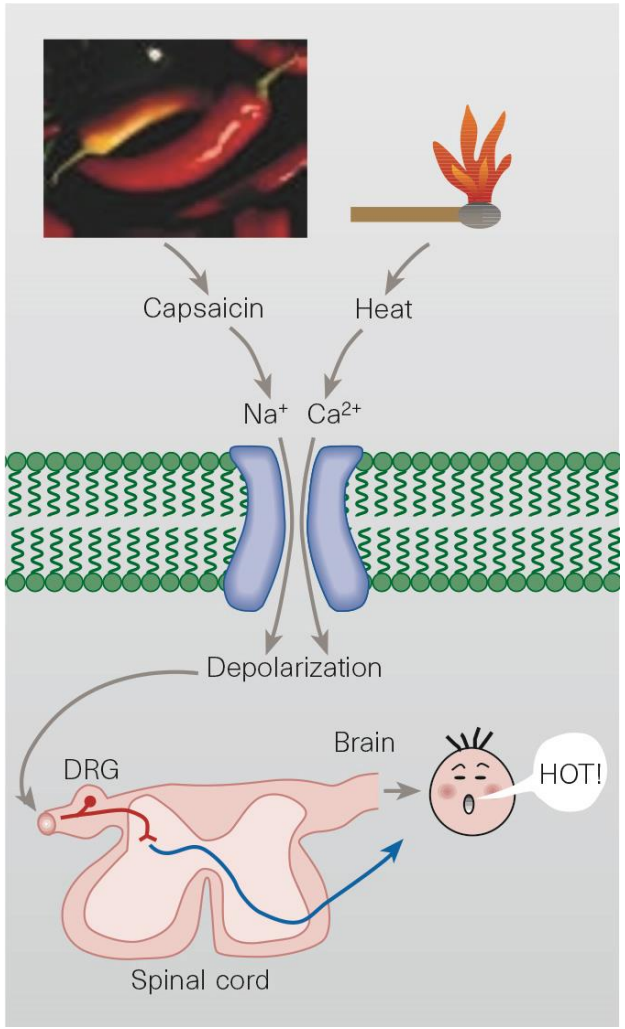




whole-cell recording



News & Views



Caterina et al. (Nature 1997)

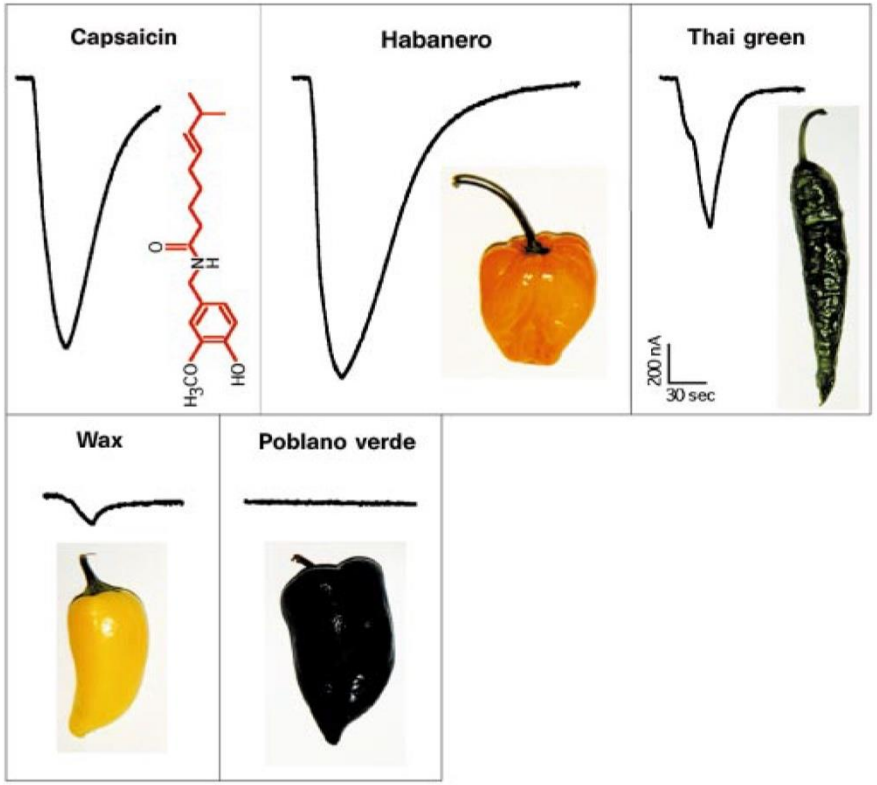
Key Publications (David Julius)

1. Caterina MJ, Schumacher MA, Tominaga M, Rosen TA, Levine JD, **Julius D**. The capsaicin receptor: a heat-activated ion channel in the pain pathway. Nature 1997:389:816-824.
2. Tominaga M, Caterina MJ, Malmberg AB, Rosen TA, Gilbert H, Skinner K, Raumann BE, Basbaum AI, **Julius D**. The cloned capsaicin receptor integrates multiple pain-producing stimuli. Neuron 1998:21:531-543.
3. Caterina MJ, Leffler A, Malmberg AB, Martin WJ, Trafton J, Petersen-Zeitz KR, Koltzenburg M, Basbaum AI, **Julius D**. Impaired nociception and pain sensation in mice lacking the capsaicin receptor. Science 2000:288:306-313.
4. McKemy DD, Neuhausser WM, **Julius D**. Identification of a cold receptor reveals a general role for TRP channels in thermosensation. Nature 2002:416:52-58.

from HP of Nobel Foundation

We went to a super-market to buy various capsicums.

Scoville units (how much dilution with sugar water is needed in order not to taste pungency) are still used.（Habanero; 300,000, Bell pepper; 0）



From Nature (1997)

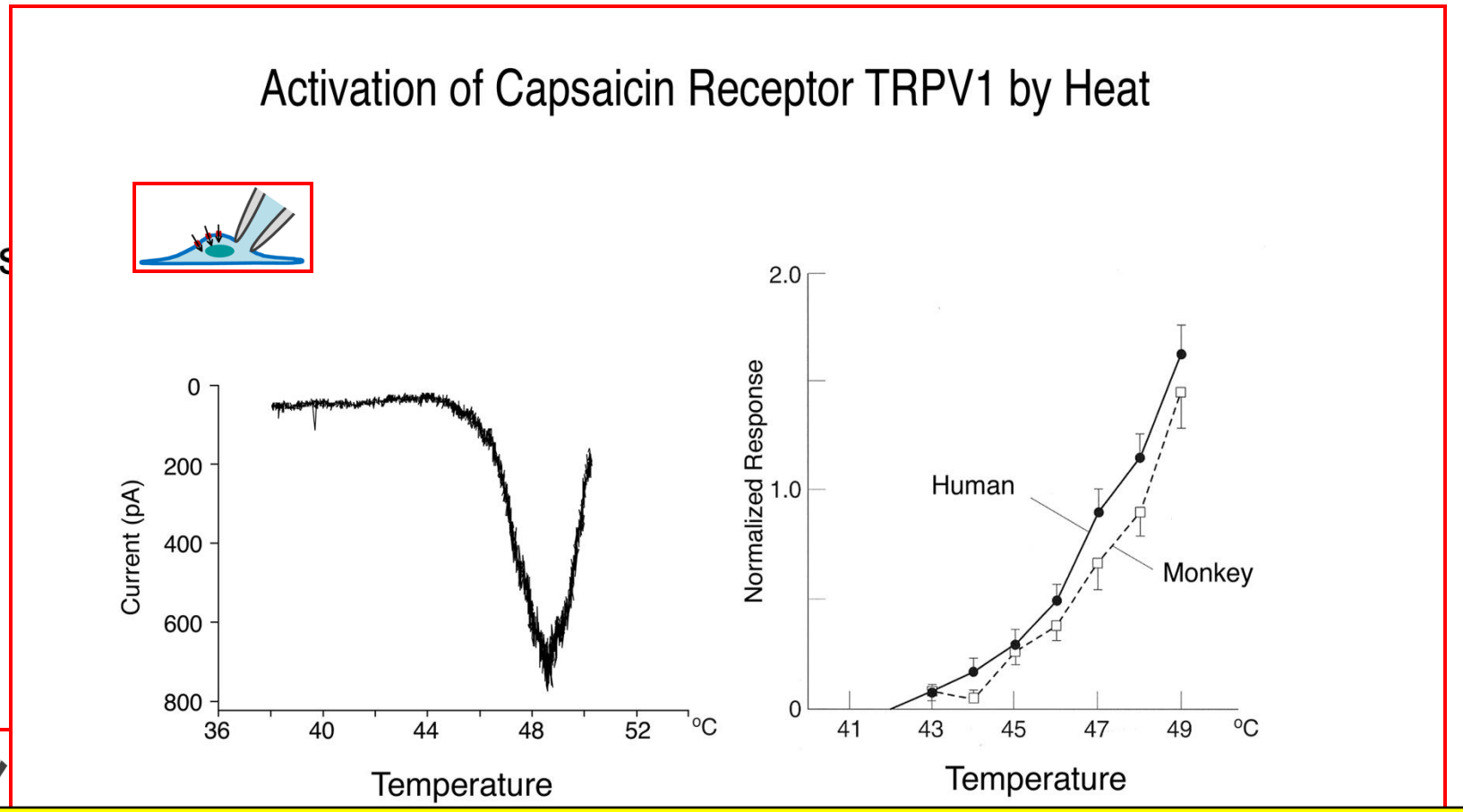
We can evaluate the pungency more precisely when comparing the ability to activate TRPV1.

Although we examined the effect of wasabi, it did not activate TRPV1.

A wasabi receptor TRPA1 was clarified later.

Single Channel Current of TRPV1

caps



TRPV1 is activated by temperatures causing pain in our body.

Tominaga et al. (1998)

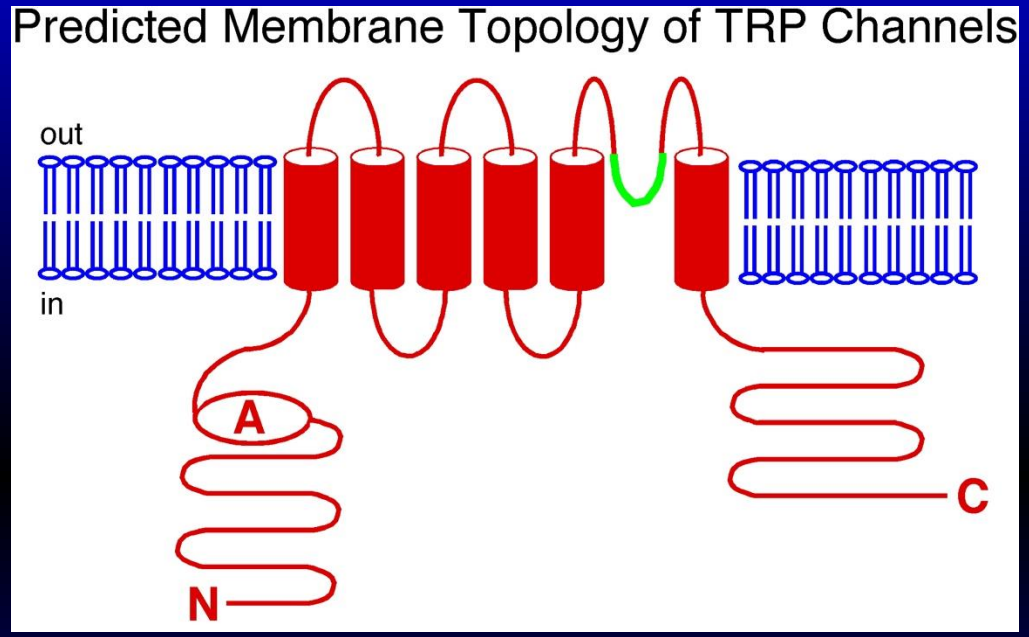

Julius lab (10.1997)

Science should progress in a curiosity-driven way.

“Most of the great advances in understanding mechanisms in medicine really start off by (scientists) following their curiosity without knowing in advance that they would be working on something that could be one day be useful in therapeutics,” Julius said on Oct. 4, 2021.

I really hope that the 2021 Nobel Prize would lead to the further progress of research regarding thermosensation and nociception in the future.

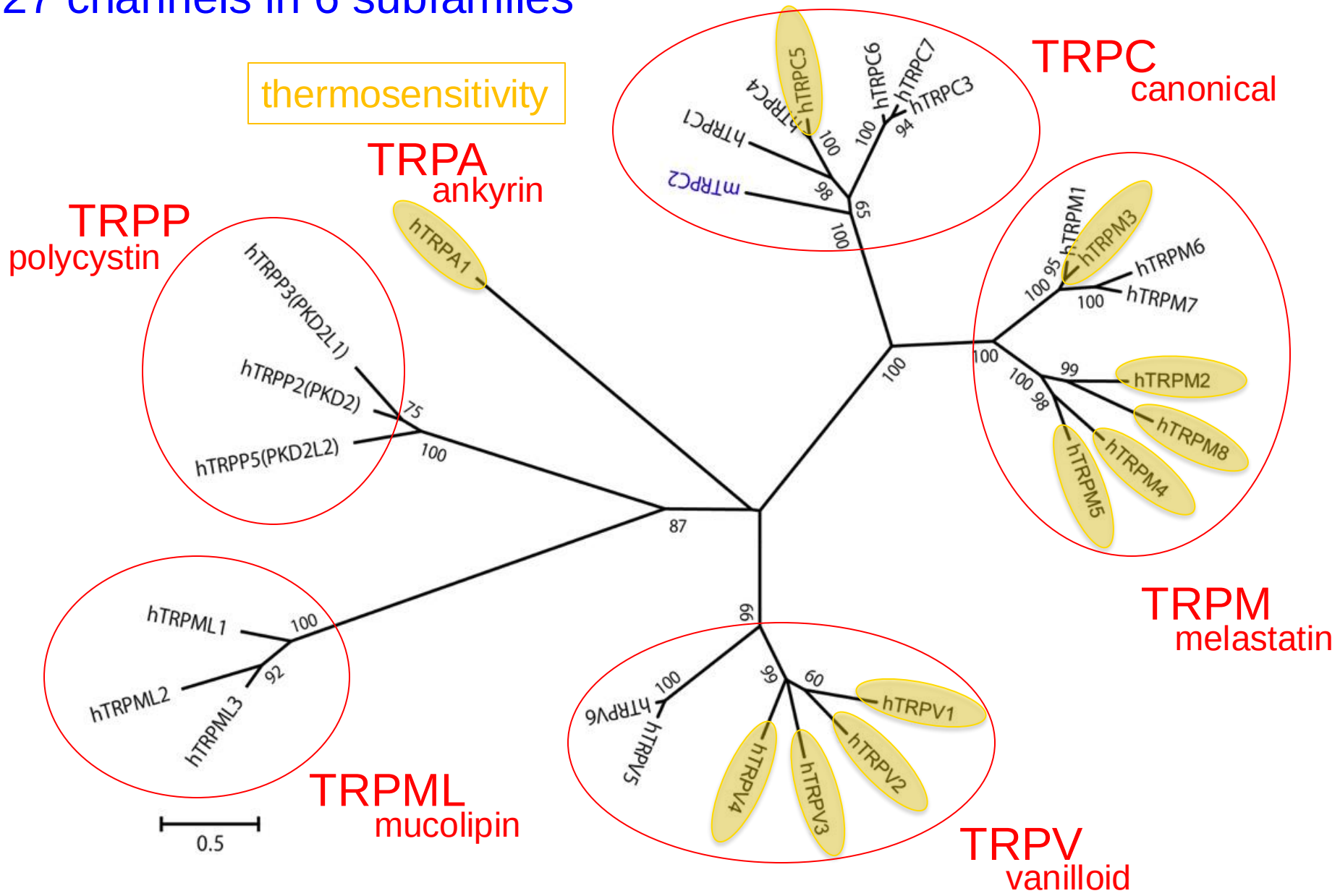
TRP (Transient Receptor Potential) Channels



- A prototypical member, TRP was deficient in *Drosophila* mutant exhibiting abnormal transient responsiveness to continuous light
- Have six transmembrane domains with a ankyrin repeat domain in N terminus
- Function as a tetramer
- Non-selective cation channels with high Ca^{2+} permeability

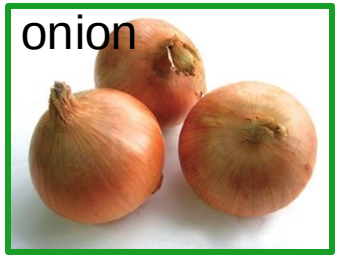
Phylogenetic Tree of Human TRP Channels

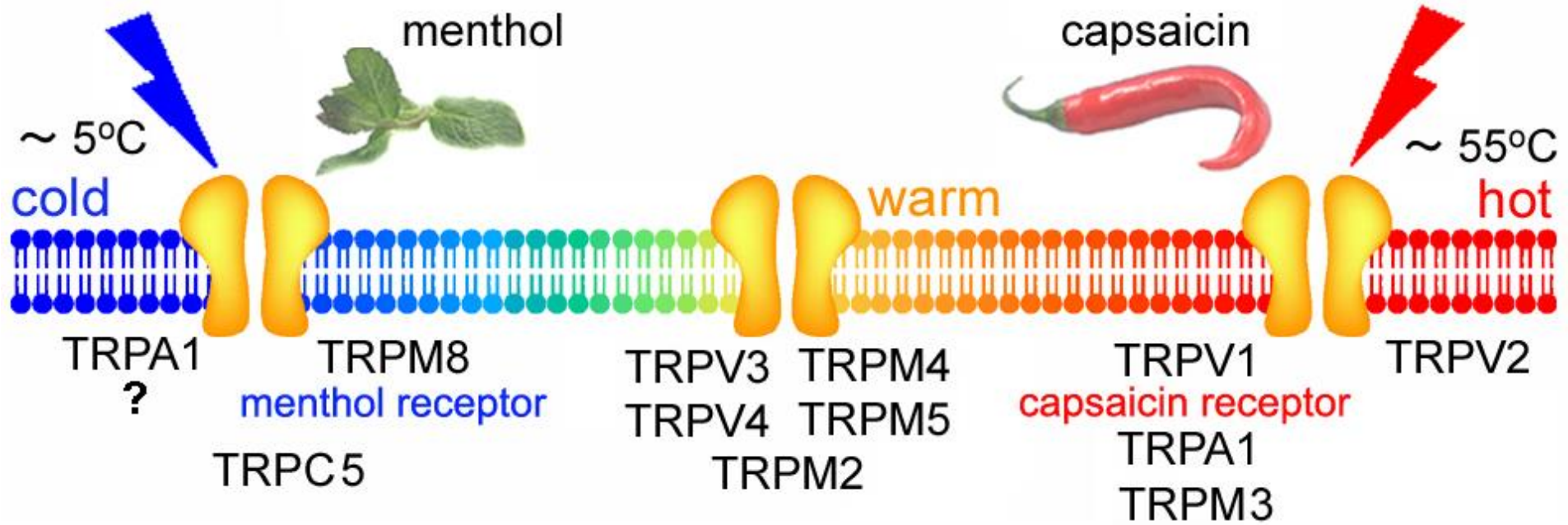
27 channels in 6 subfamiles



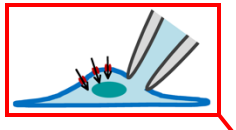
Thermosensitive TRP Channels

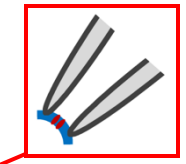
allicin



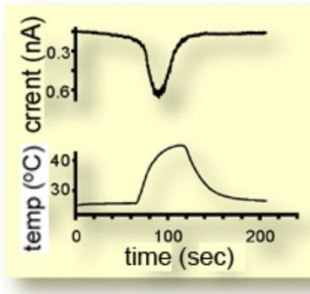


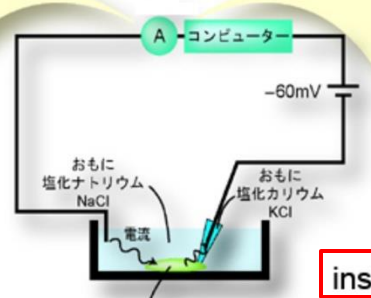
Patch-clamp Method



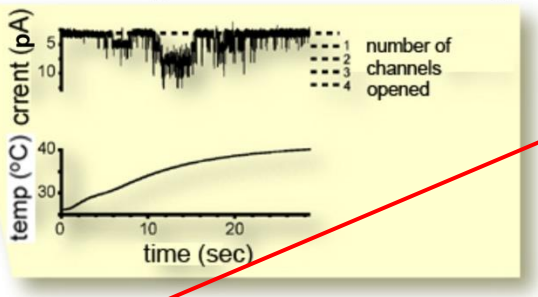


whole-cell recording

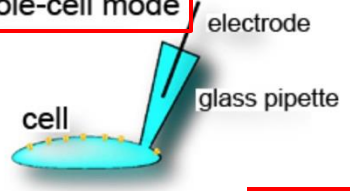




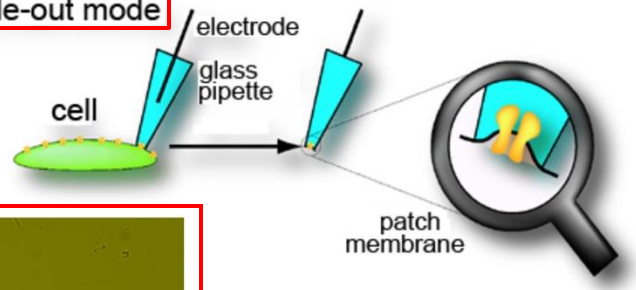
single-channel recording

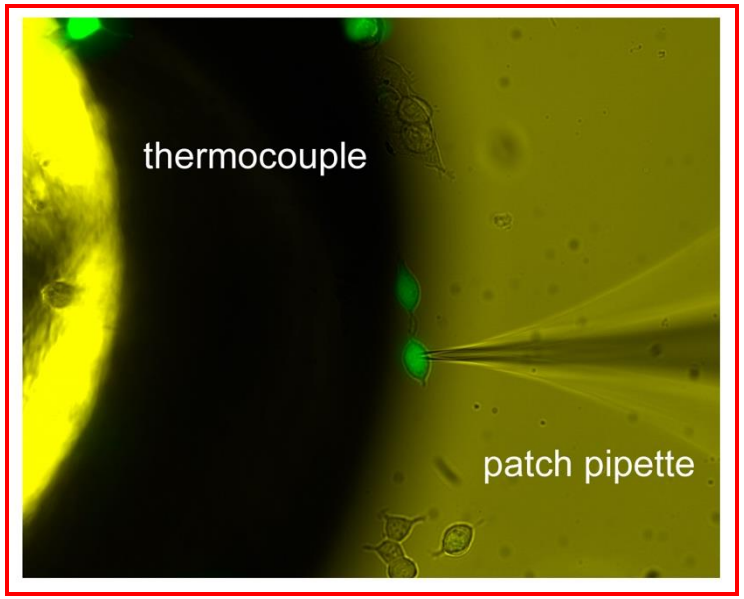


whole-cell mode

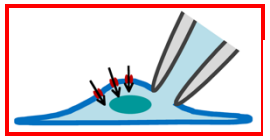


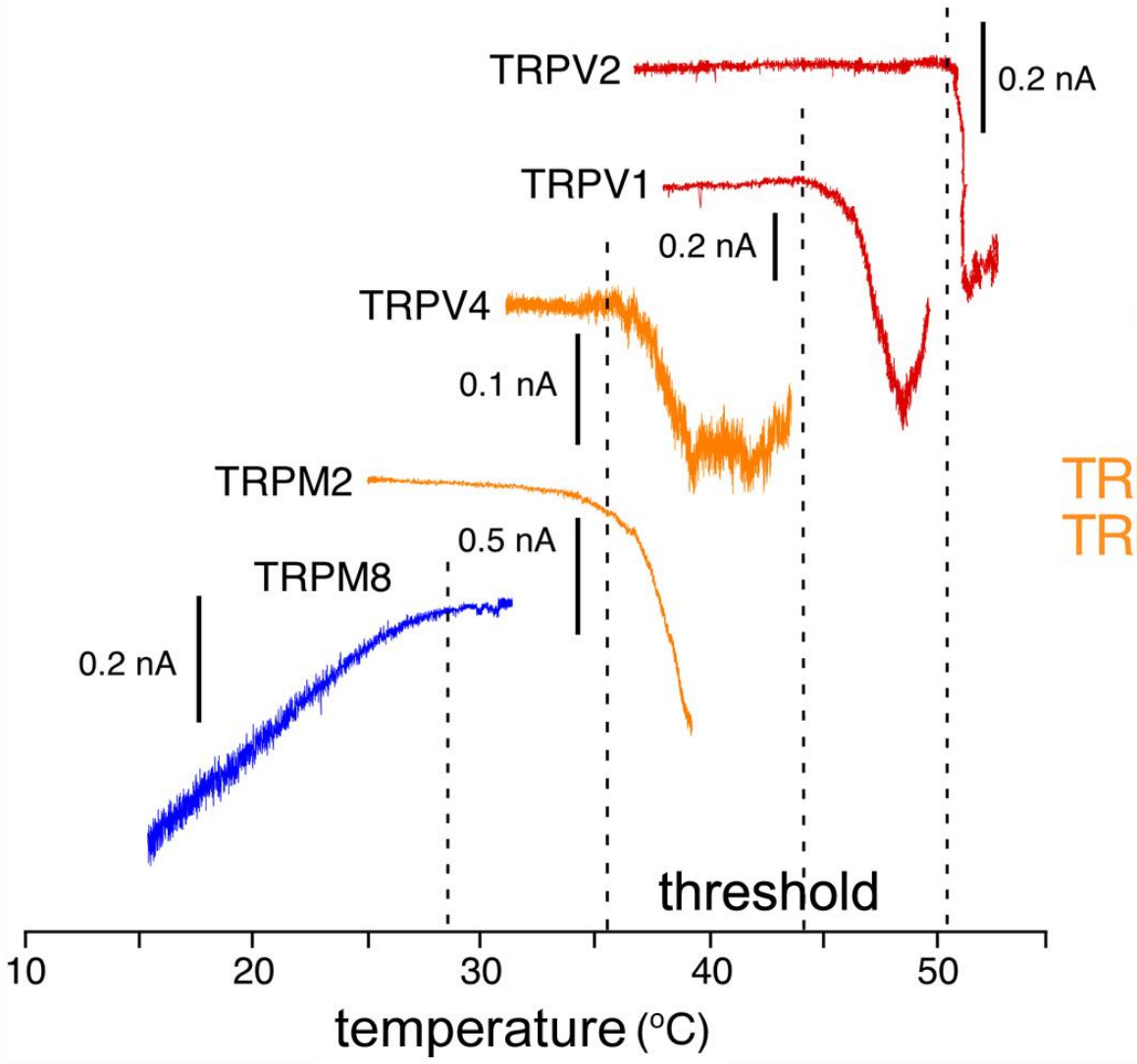
inside-out mode

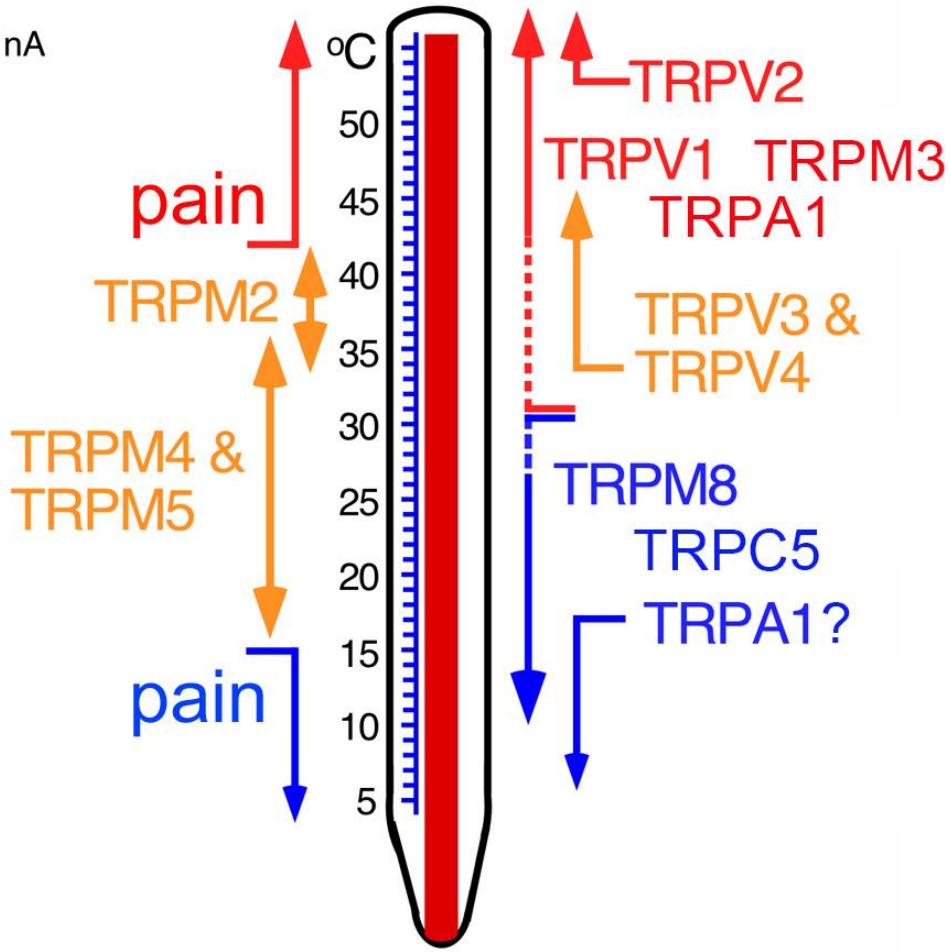




Temperature-evoked Activation of Thermosensitive TRP Channels



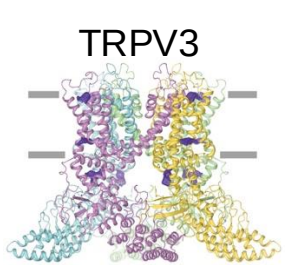


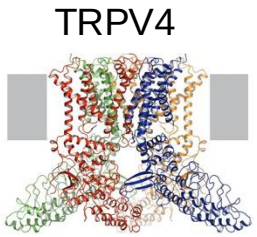


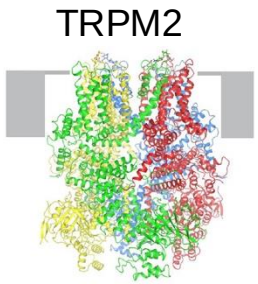
How about the structures？

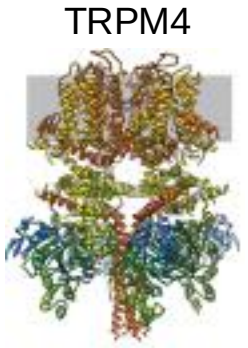
Structures of Thermosensitive TRP Channels

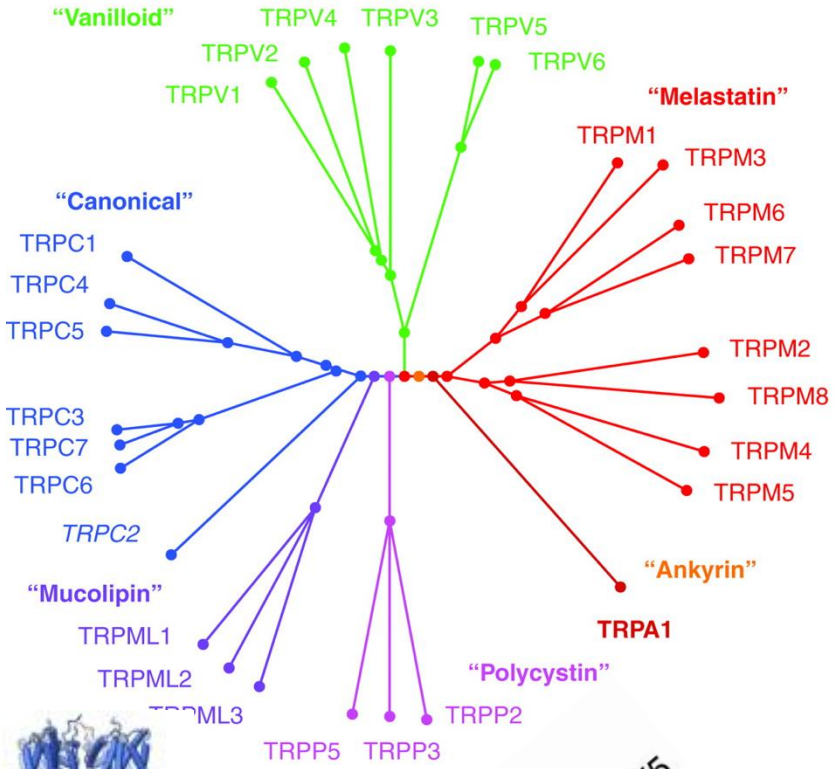
with Cryo-EM
（2017 Nobel Prize in Chemistry）

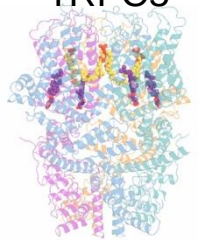


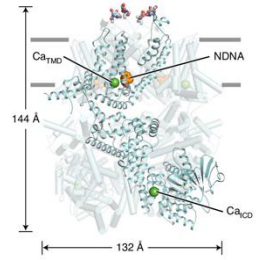


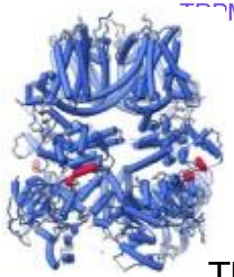


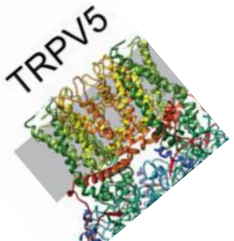


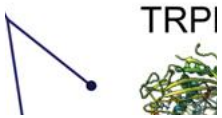




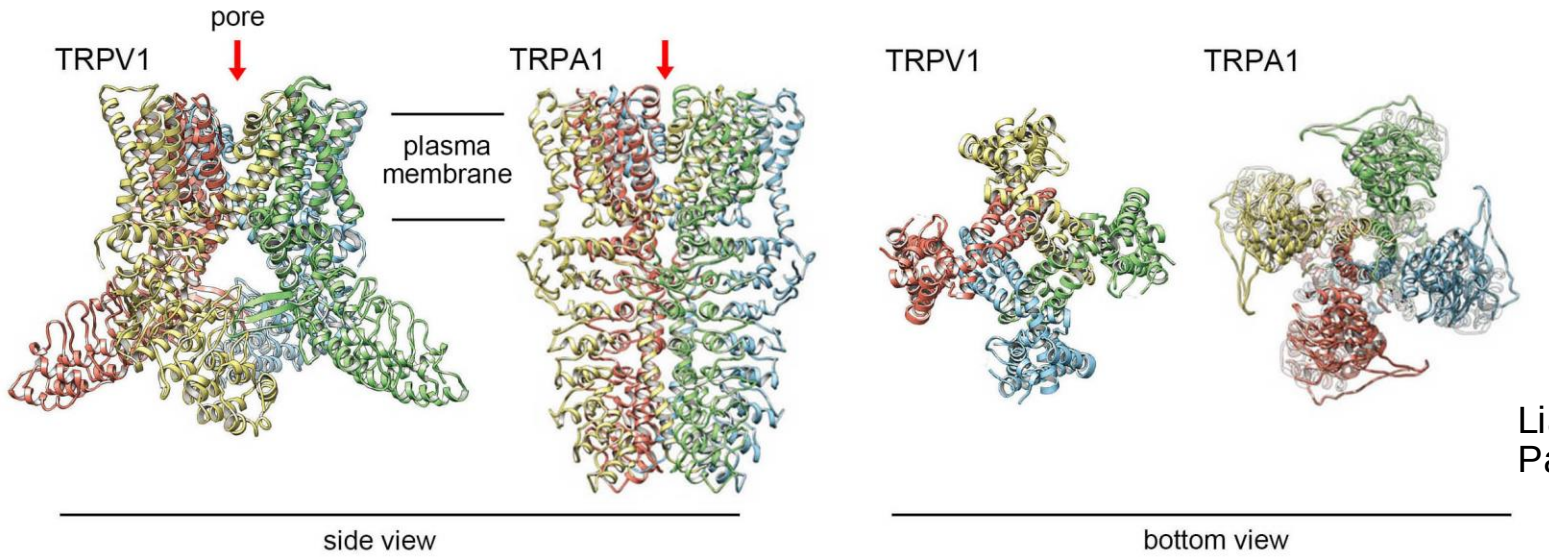




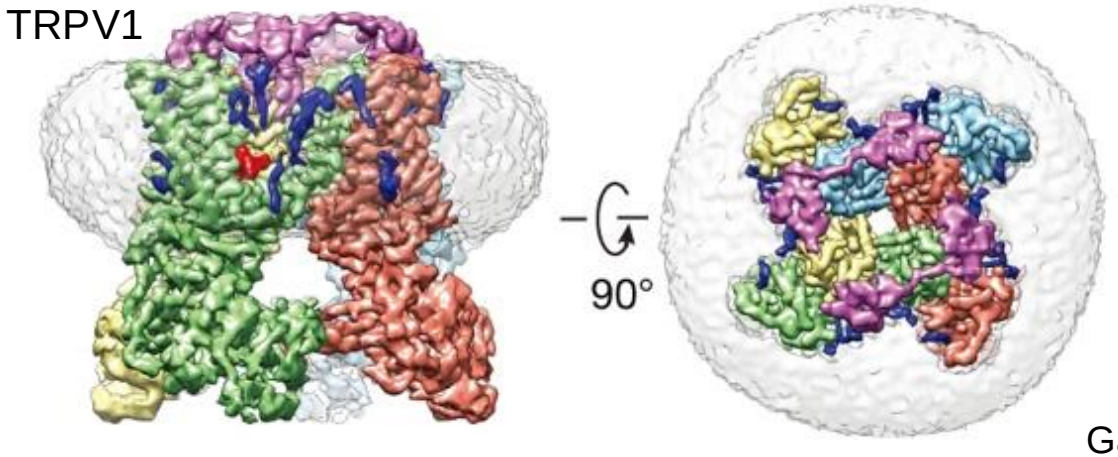




Structure of TRPV1 and TRPA1 by single particle analysis with Cryo-EM



Liao et al. Nature (2013)
Paulsen et al. Nature (2015)



ion channel embedded in lipids (nano disc)

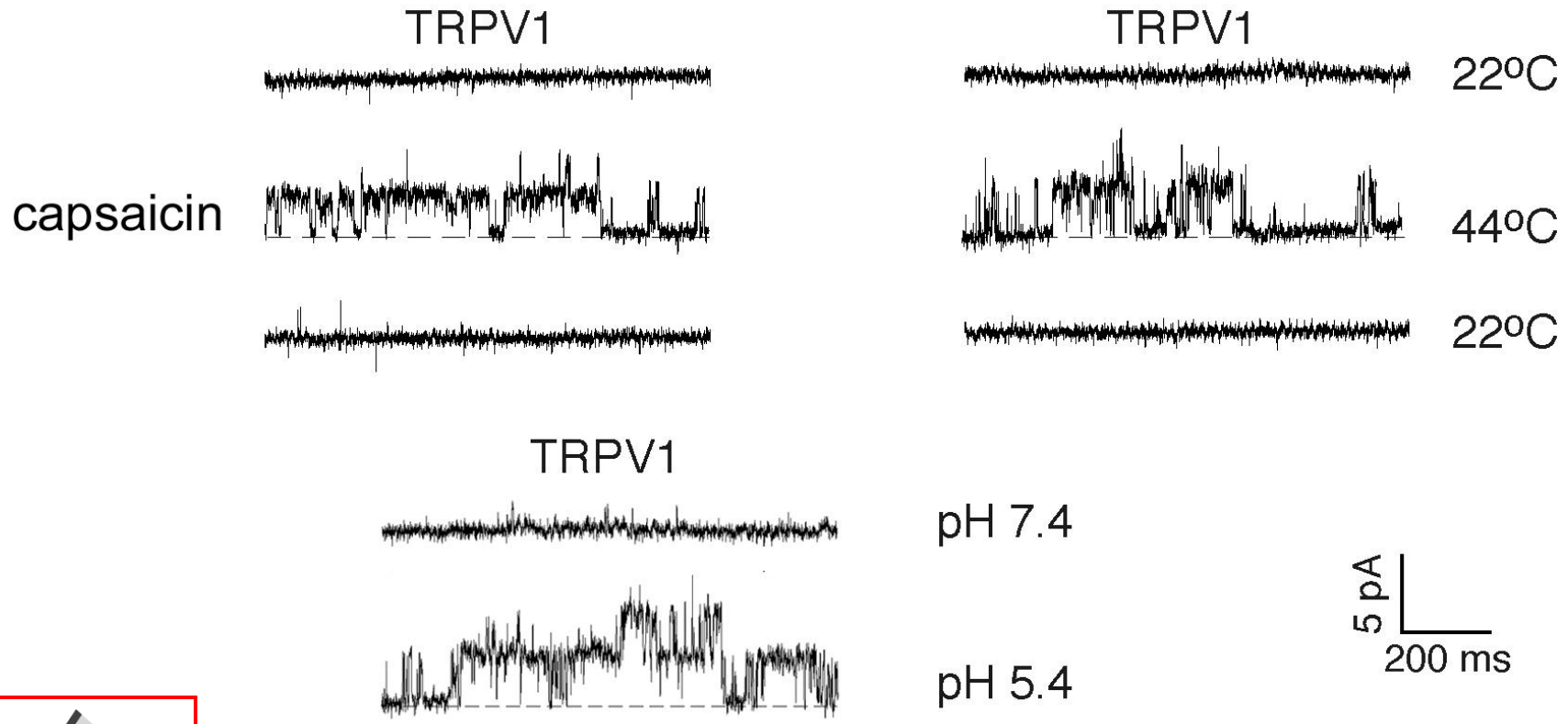
Gao et al. Nature (2016)

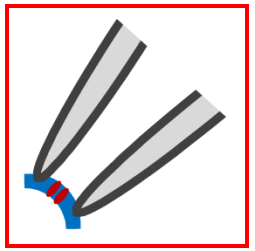
It is still not understood how temperature opens thermosensitive TRP channels.

Capsaicin Receptor TRPV1

TRPV1 gene was cloned in 1997, and its knock out phenotype was reported in 2000. TRPV1 is activated by different noxious stimuli including capsaicin, heat (over 43^{o}C) and protons. There is a synergism among stimuli, and the temperature threshold for heat-evoked activation is reduced upon various post-translational modifications such as phosphorylation, which could explain the inflammatory pain.

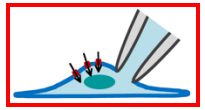
Single Channel Current of TRPV1

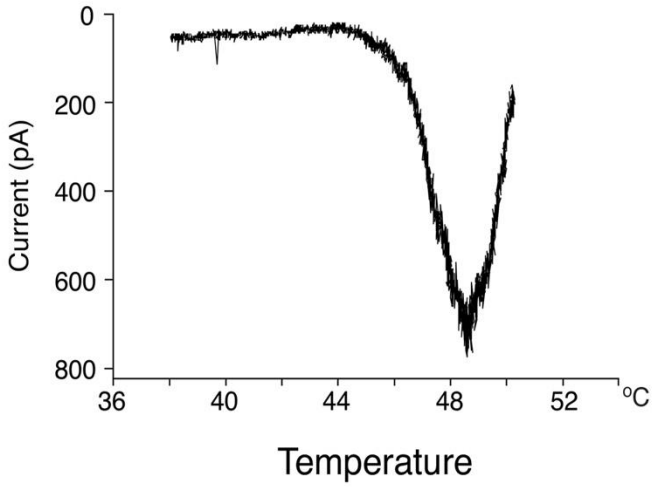


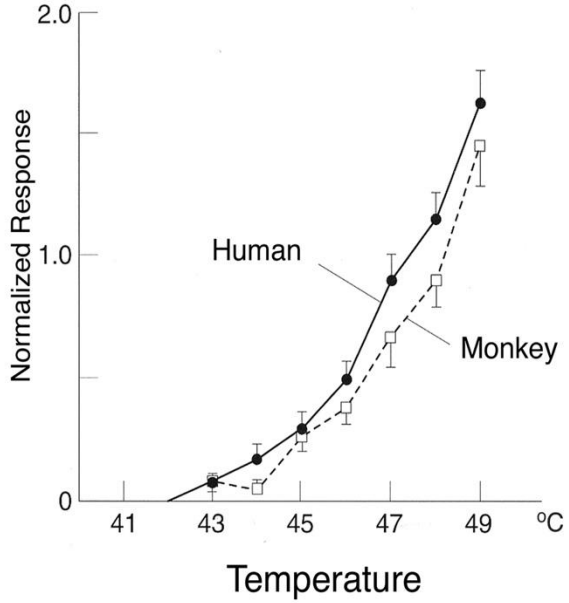


Tominaga et al. (Neuron 1998)

Activation of Capsaicin Receptor TRPV1 by Heat







From Meyer & Campbell (1981)

TRPV1 is activated by temperatures causing pain in our body.

Allyl isothiocyanate (main ingredient of wasabi) Receptor TRPA1

TRPA1 was isolated as a receptor for nociceptive cold stimulus (Cell, 2003), and its knock out phenotype was reported in 2006. Whether mammalian TRPA1 is activated directly by cold stimulus is still not clear although TRPA1 seemed to be involved in cold stimulus-evoked behavioral responses. There was a report showing that TRPA1 is involved in noxious　high temperature sensing in 2018.

The First Report of Involvement of TRPA1 in Noxious Cold Sensation

Cell, Vol. 112, 819–829, March 21, 2003, Copyright ©2003 by Cell Press

ANKTM1, a TRP-like Channel Expressed in Nociceptive Neurons, Is Activated by Cold Temperatures

Gina M. Story,[1] Andrea M. Peier,[2] Alison J. Reeve,[3] Samer R. Eid,[1] Johannes Mosbacher,[4] Todd R. Hricik,[1] Taryn J. Earley,[1] Anne C. Hergarden,[2] David A. Andersson,[3] Sun Wook Hwang,[1] Peter McIntyre,[3] Tim Jegla,[2] Stuart Bevan,[3] and Ardem Patapoutian[1,2,*]

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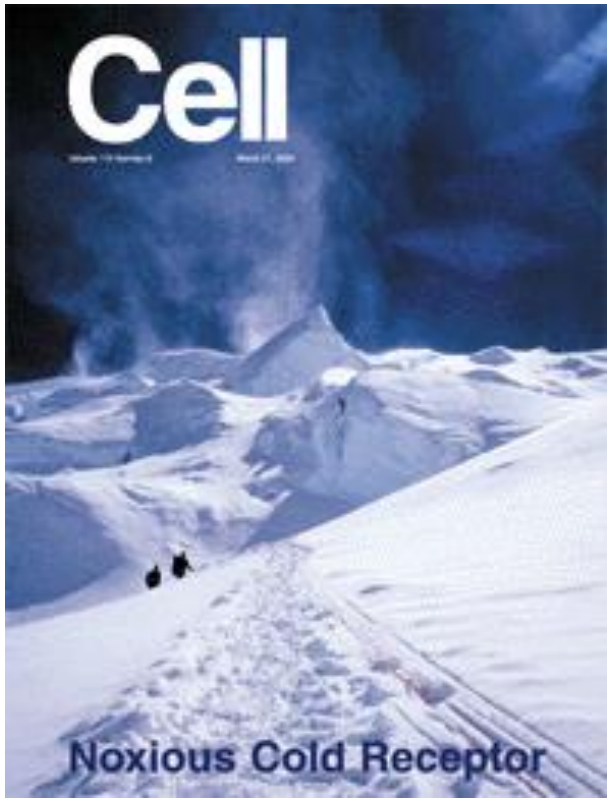
Summary

Mammals detect temperature with specialized neurons in the peripheral nervous system. Four TRPV-class channels have been implicated in sensing heat, and one TRPM-class channel in sensing cold. The combined range of temperatures that activate these channels covers a majority of the relevant physiological spectrum sensed by most mammals, with a significant gap in the noxious cold range. Here, we describe the characterization of ANKTM1, a cold-activated channel with a lower activation temperature compared to the cold and menthol receptor, TRPM8. ANKTM1 is a distant family member of TRP channels with very little amino acid similarity to TRPM8. It is found in a subset of nociceptive sensory neurons where it is coexpressed with TRPV1/VR1 (the capsaicin/heat receptor) but not TRPM8. Consistent with the expression of ANKTM1, we identify noxious cold-sensitive sensory neurons that also respond to capsaicin but not to menthol.



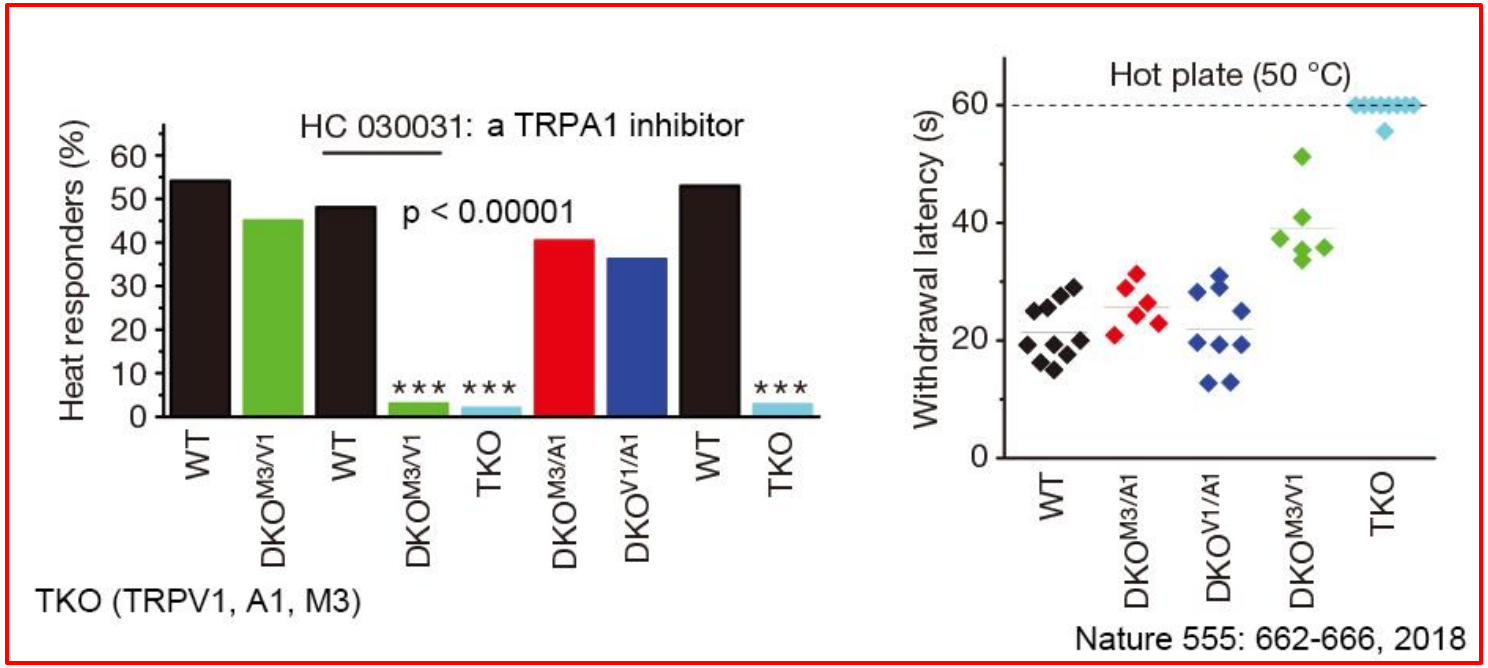
LETTER

doi:10.1038/nature26137

A TRP channel trio mediates acute noxious heat sensing

Ine Vandewauw[1,2], Katrien De Clercq[1,2,3], Marie Mulier[1,2], Katharina Held[1,2,3], Silvia Pinto[1,2], Nele Van Ranst[1,2], Andrei Segal[1,2], Thierry Voet[4], Rudi Vennekens[1,2], Katharina Zimmermann[5], Joris Vriens[3]§ & Thomas Voets[1,2]§

DRG responses



Behavioral analysis

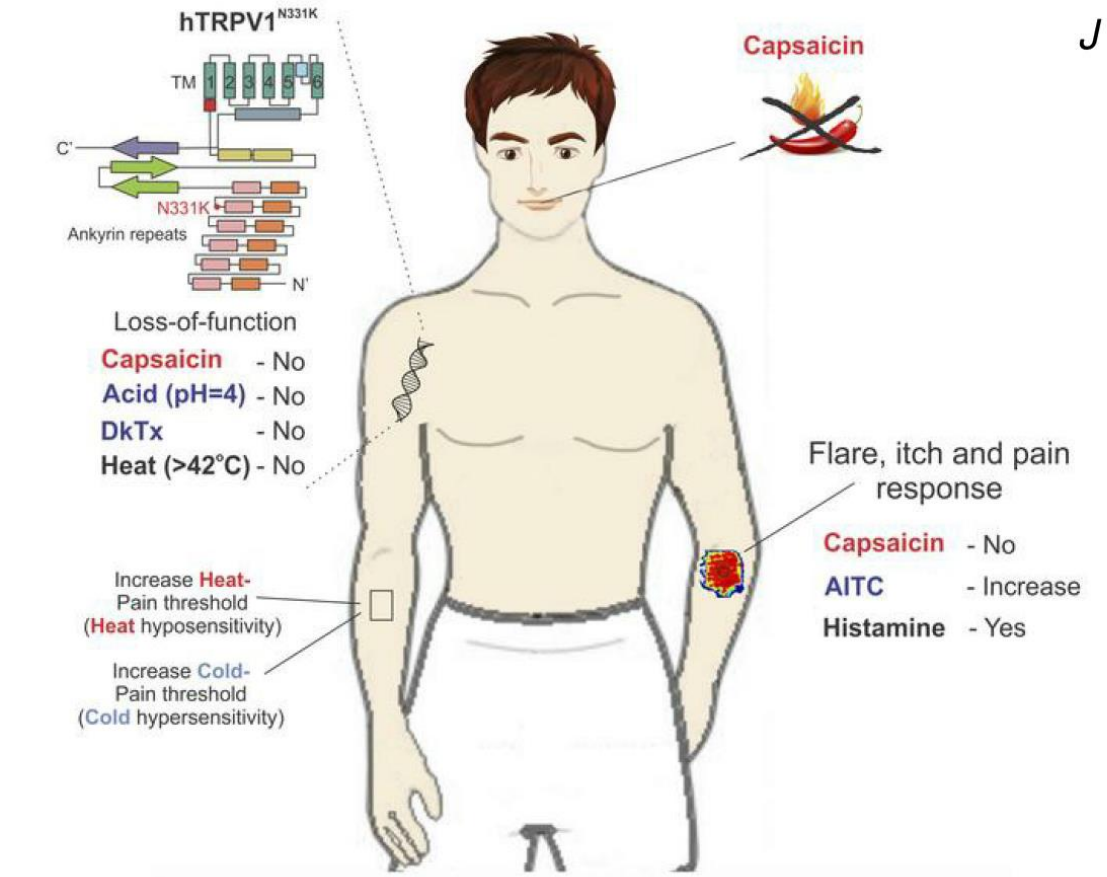
Now it is believed that TRPA1 is involved in the noxious heat sensation.

Mutations in human TRPV1 and human TRPA1

JCI The Journal of Clinical Investigation

Nociception and pain in humans lacking functional TRPV1 channel

Ben Katz, … , Alexander M. Binshtok, Baruch Minke



J Clin Invest. 2023 133 (3): e153558

Familial Episodic Pain Syndrome and TRPA1

Neuron
Clinical Study

Neuron *66*, 671–680, June 10, 2010 ©2010 Elsevier Inc.

A Gain-of-Function Mutation in TRPA1 Causes Familial Episodic Pain Syndrome

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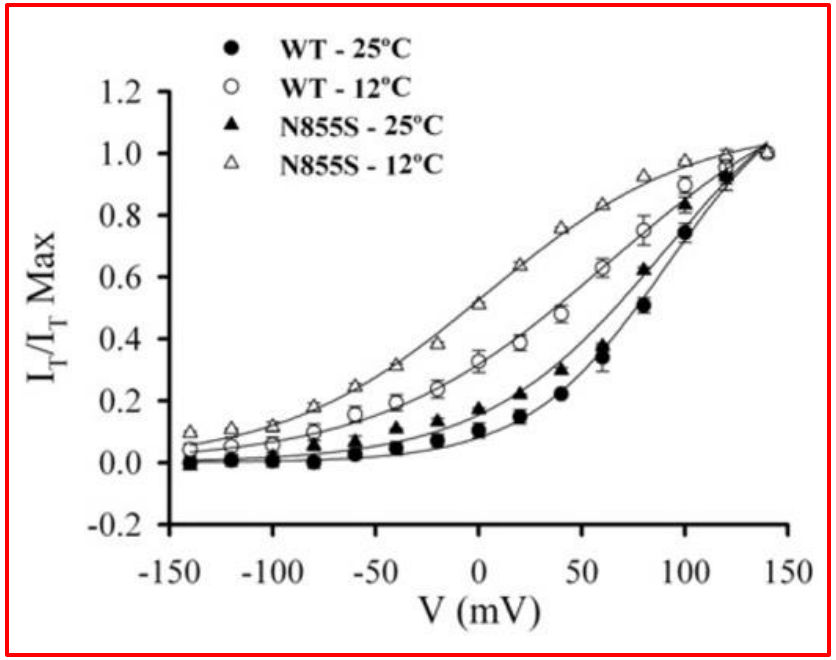
DOI 10.1016/j.neuron.2010.04.030



There are no medicines in the market targeting thermosensitive TRP channels.

in the case of TRPV1,

- TRPV1 agonists are used as analgesic.
- TRPV1 antagonists cause hyperthermia.
- TRPV1 is reported to be involved in the body temperature regulation.

Pain 136 (2008) 202–210

PAIN

www.elsevier.com/locate/pain

Pharmacological blockade of the vanilloid receptor TRPV1 elicits marked hyperthermia in humans

Narender R. Gavva [a,*], James J.S. Treanor [a], Andras Garami [b], Liang Fang [c], Sekhar Surapaneni [d], Anna Akrami [d], Francisco Alvarez [e], Annette Bak [e], Mary Darling [f], Anu Gore [e], Graham R. Jang [d], James P. Kesslak [f], Liyun Ni [c], Mark H. Norman [g], Gabrielle Palluconi [f], Mark J. Rose [d], Margaret Salfi [c], Edward Tan [f], Andrej A. Romanovsky [b], Christopher Banfield [f], Gudarz Davar [f]

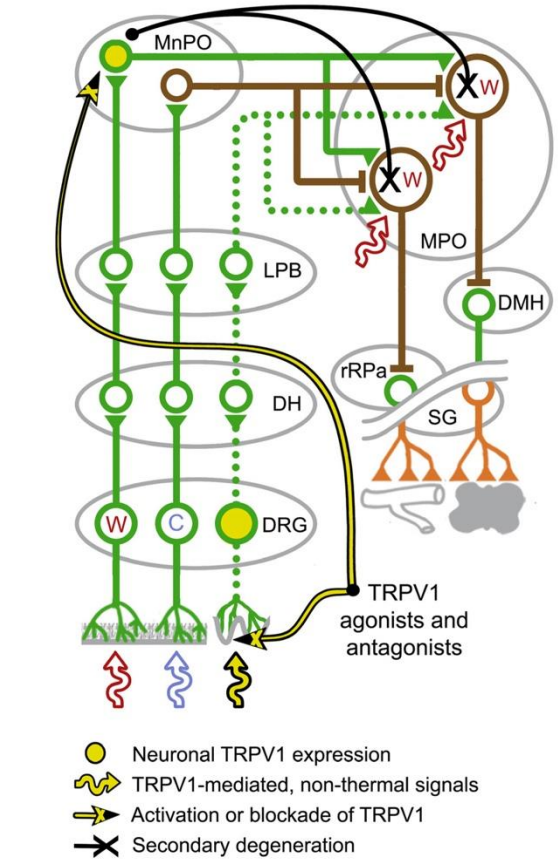
The Journal of Neuroscience, March 28, 2007 • 27(13):3366–3374

The Vanilloid Receptor TRPV1 Is Tonically Activated *In Vivo* and Involved in Body Temperature Regulation

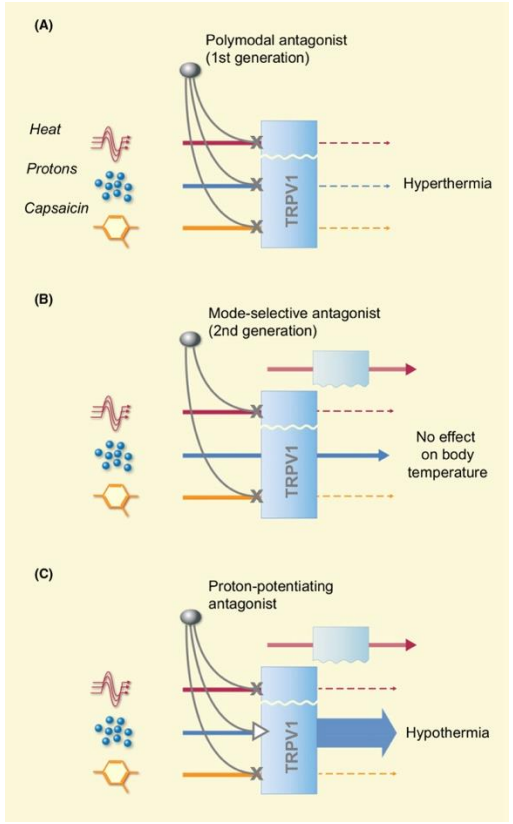
Narender R. Gavva,[1] Anthony W. Bannon,[1] Sekhar Surapaneni,[2] David N. Hovland Jr,[3] Sonya G. Lehto,[1] Anu Gore,[4] Todd Juan,[5] Hong Deng,[1] Bora Han,[3] Lana Klionsky,[1] Rongzhen Kuang,[1] April Le,[1] Rami Tamir,[1] Jue Wang,[1] Brad Youngblood,[1] Dawn Zhu,[1] Mark H. Norman,[6] Ella Magal,[1] James J. S. Treanor,[1] and Jean-Claude Louis[1]

Departments of [1]Neuroscience, [2]Pharmacokinetics and Drug Metabolism, [3]Toxicology, [4]Pharmaceutics, [5]Protein Sciences, and [6]Chemistry Research and Discovery, Amgen, Thousand Oaks, California 91320-1799

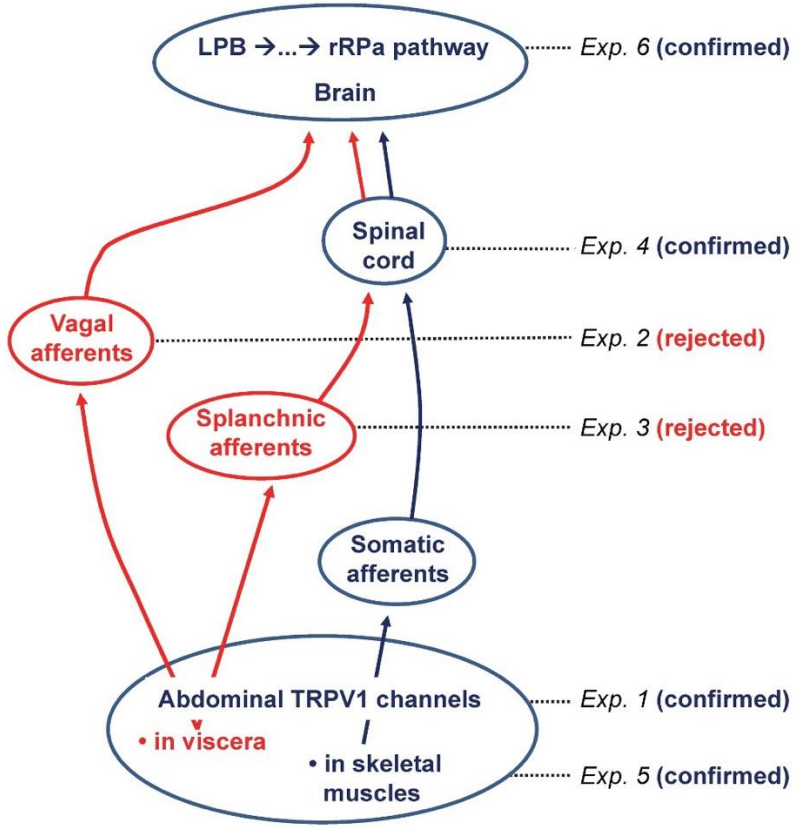
Current Understanding of the Mechanism for Hyperthermia by TRPV1 Antagonists



Pharmacol. Review
61: 228-261 (2009)



Acta Physiol.
223(3): e13038 (2018)



Temperature
10: 136-154 (2024)

It is currently thought that TRPV1 channels in trunk are tonically activated by protons and drive the reflectory inhibition of thermogenesis. And acute inhibition of the neural pathways by TRPV1 antagonists are believed to cause hyperthermia.

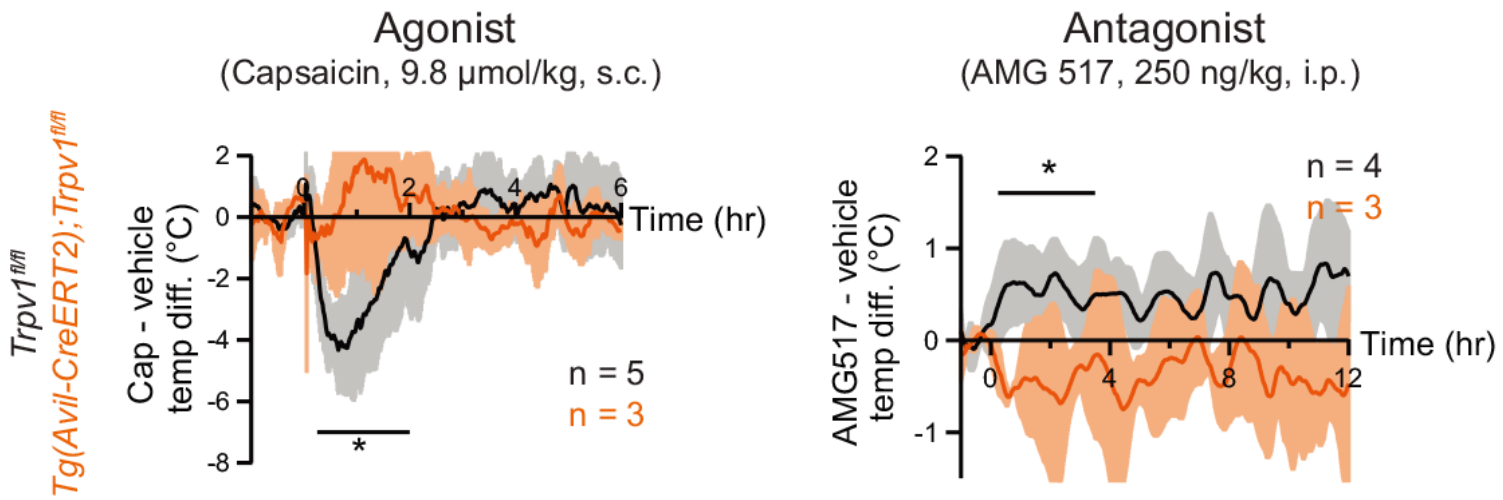
eLife

Yue *et al*. eLife 2022;11:e80139.

TRPV1 drugs alter core body temperature via central projections of primary afferent sensory neurons

Wendy Wing Sze Yue[1], Lin Yuan[1], Joao M Braz[2], Allan I Basbaum[2], David Julius[1]*

[1]Department of Physiology, University of California, San Francisco, United States;
[2]Department of Anatomy, University of California, San Francisco, United States



A TRPV1$^{fl/fl}$ mice study supports the involvement of peripheral TRPV1 in the TRPV1 antagonist-induced hyperthermia.

It would be better to treat local pain sensation with TRPV1 antagonists before clarification of the mechanisms for TRPV1 involvement in body temperature regulation.

There are several hundreds more sensory nerve innervation in cornea than in skin.

tvst 2023;12(3):7,

Cornea and External Disease

Topical Ocular TRPV1 Antagonist SAF312 (Libvatrep) for Postoperative Pain After Photorefractive Keratectomy

Vance Thompson[1,2], Majid Moshirfar[3], Thomas Clinch[4], Stephen Scoper[5], Steven H. Linn[3], Avery McIntosh[6], Yifang Li[6], Matt Eaton[7], Michael Ferriere[7], and Kalliopi Stasi[7]

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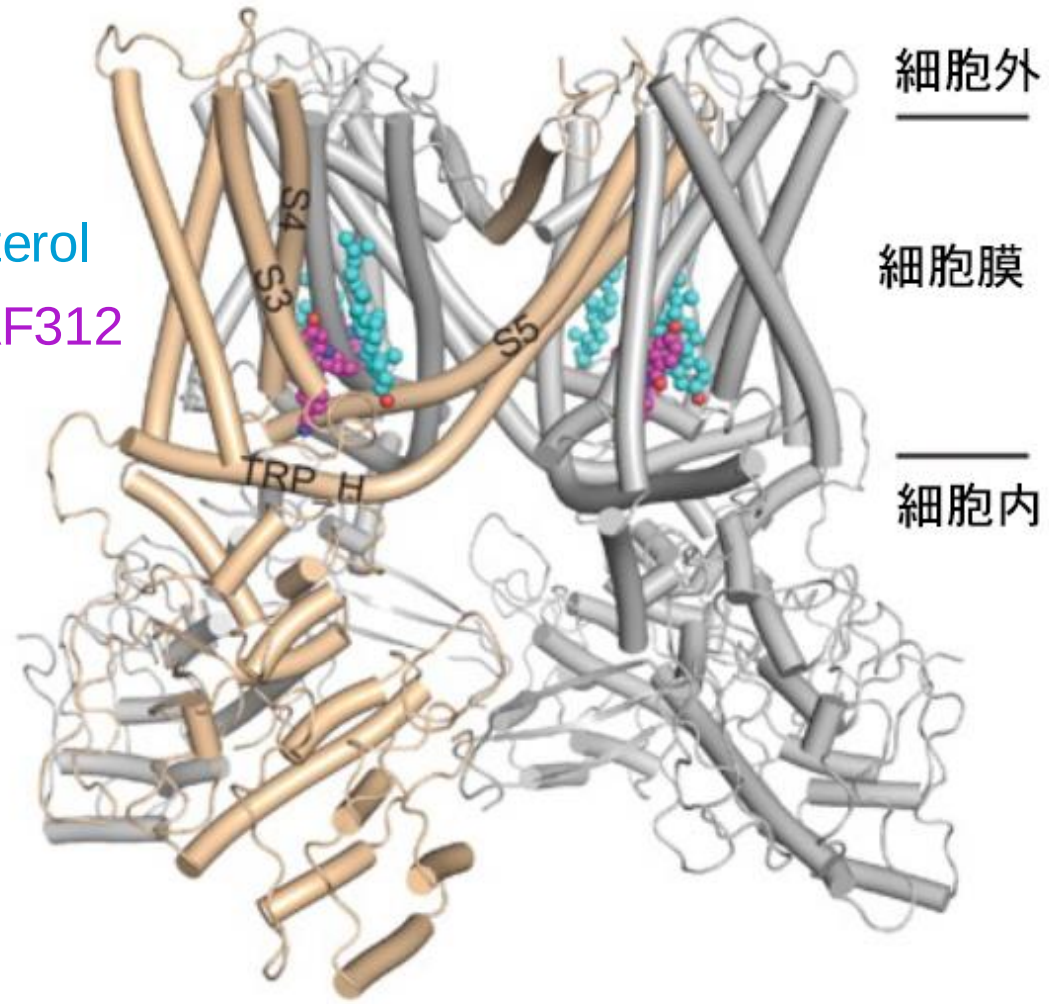
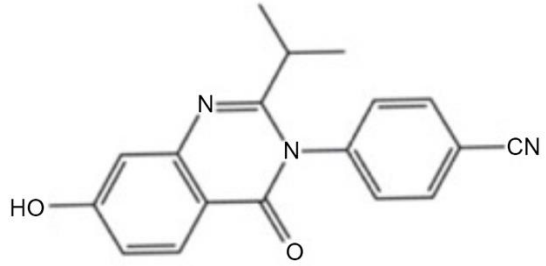
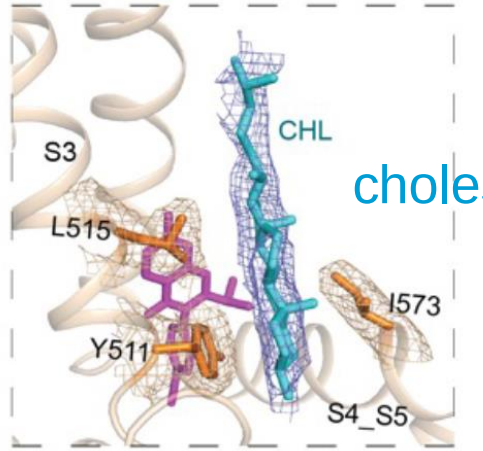
[2] University of South Dakota, Sanford School of Medicine, Sioux Falls, SD, USA
[3] Hoopes, Durrie, Rivera Research, Hoopes Vision, Draper, UT, USA
[4] Eye Doctors of Washington, Washington, DC, USA
[5] Virginia Eye Consultants, Norfolk, VA, USA
[6] Novartis Pharmaceuticals Corp., East Hanover, NJ, USA
[7] Novartis Institute of Biomedical Research, Cambridge, MA, USA

An Atomic-level Structure of TRPV1 with SAF312





SAF312

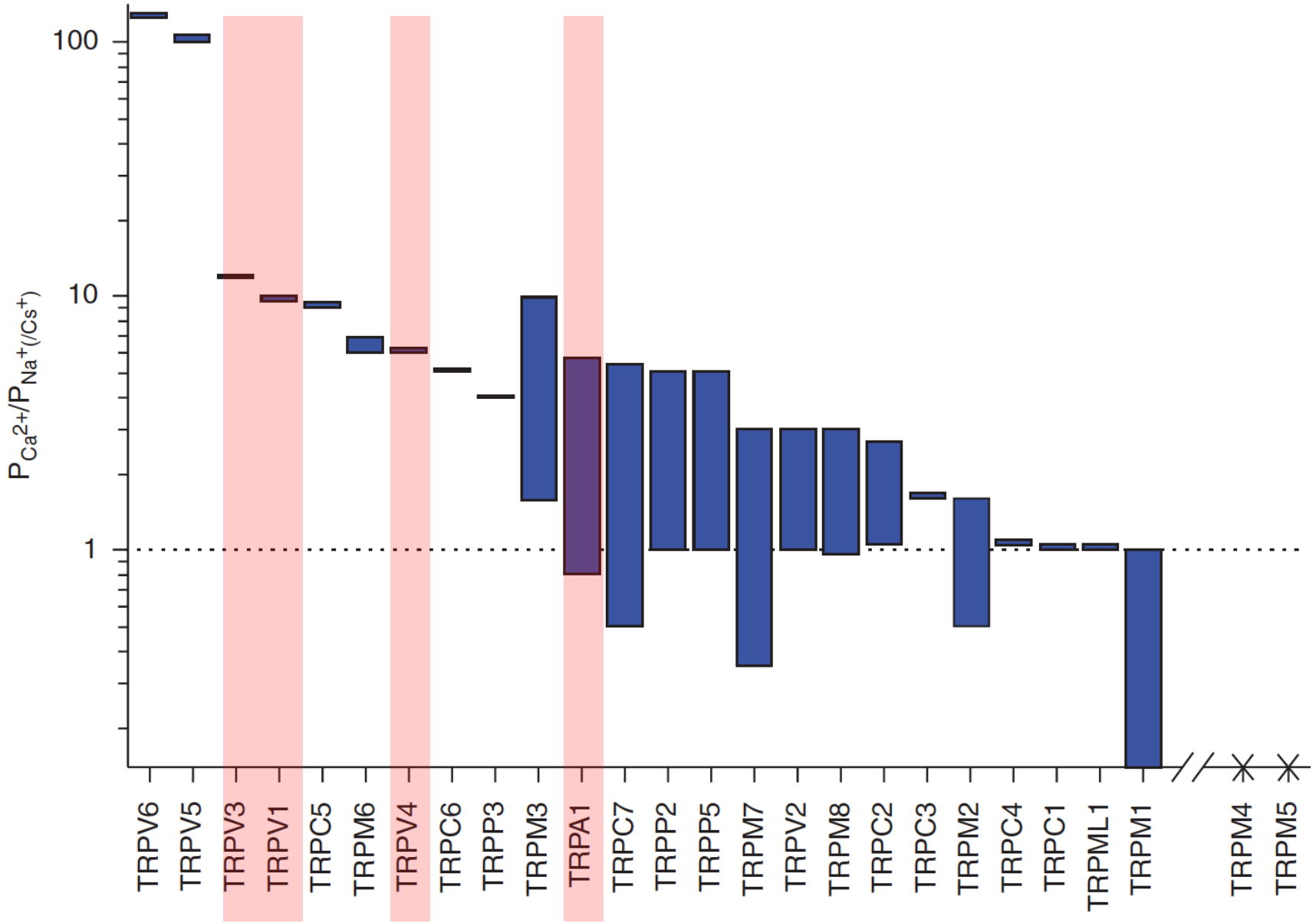


cholesterol

in the collaboration with Drs. Lei and Fan（Pekin University）

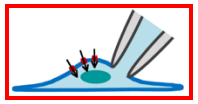
Fan et al. (Nat. Commun. 2024)

Ca^{2+}-permeability of TRP Channels



(Gees et al, CSH Perspect Biol, 2010)

Ca^{2+}-activated Cl^- Channels, Anoctamin (TMEM16)

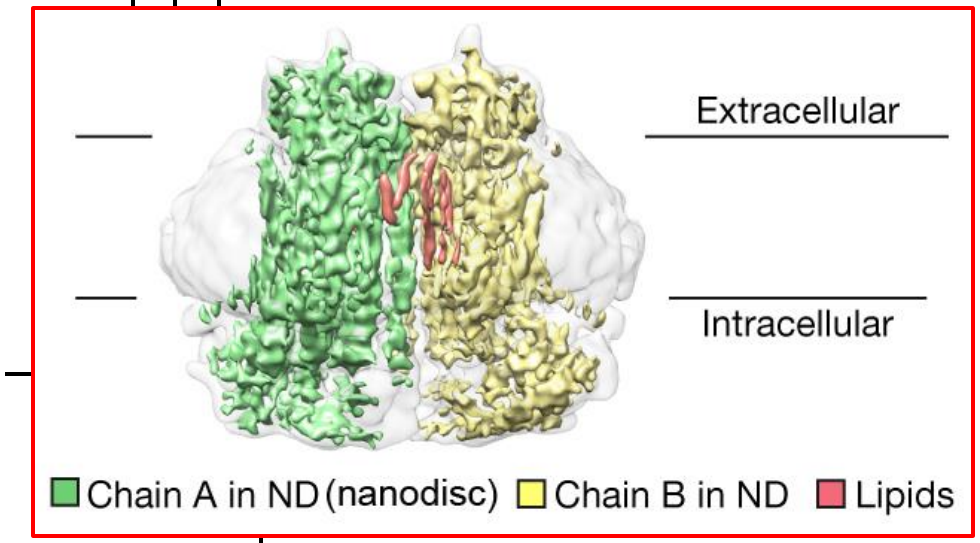


ANO1 **the most Ca^{2+} sensitive**

ANO2

ANO3

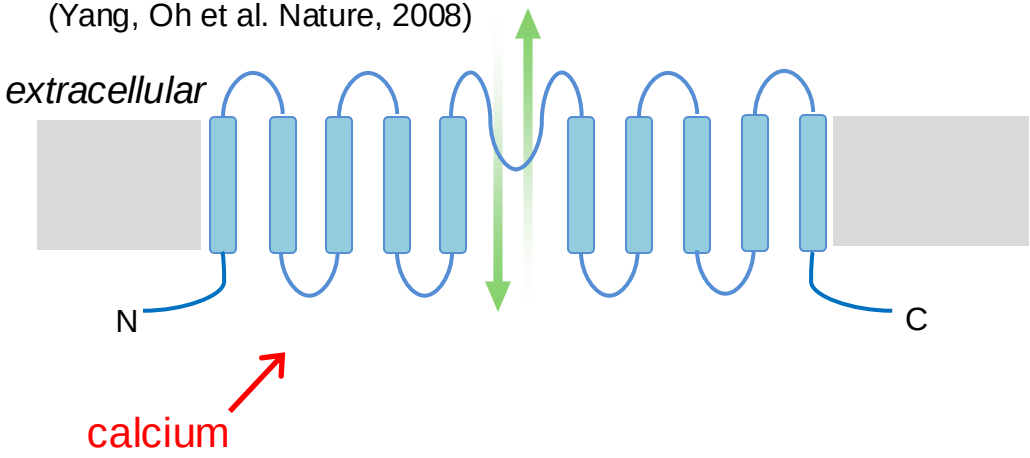
ANO4

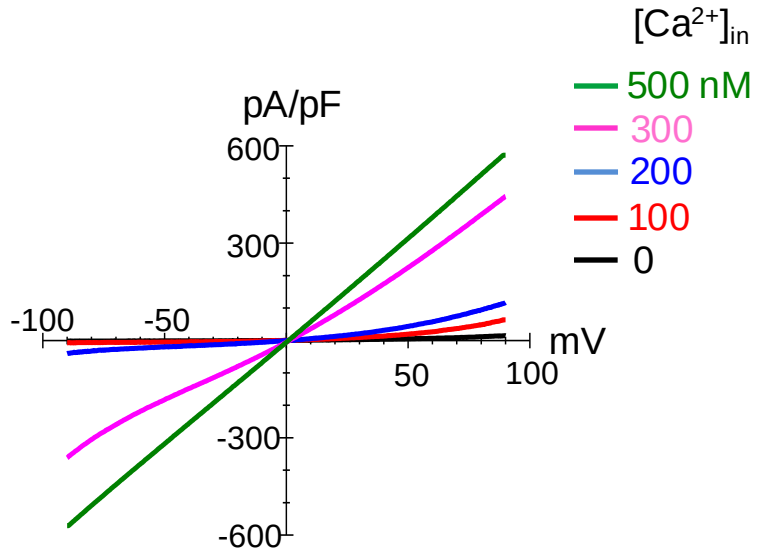


(Dang S et al, Nature, 2017)

ANO10

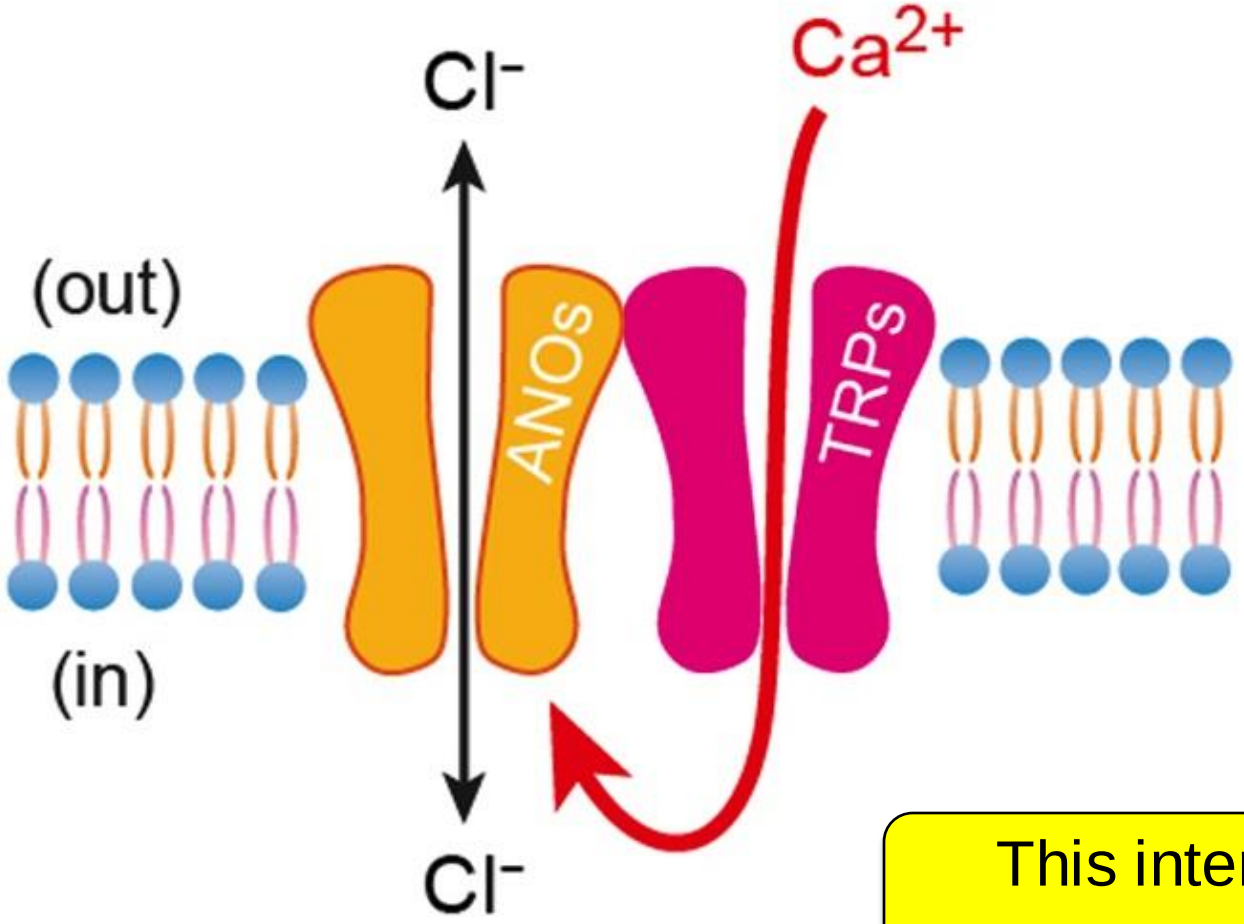
(Yang, Oh et al. Nature, 2008)





Takayama et al. (FASEB J. 2014)

An Interaction Model between TRP Channels (TRPs) and ANO1



TRPV4

- Secretion of cerebrospinal fluid from choroid plexus (Takayama et al. FASEB J. 2014)
- Saliva and tear secretion (Derouiche et al. FASEB J. 2018)
- Sweating (Kashio et al. eLife 2024)

TRPV3

- Skin keratinocyte movements (Yamanoi et al. Commun. Biol. 2023)

TRPV1, TRPA1

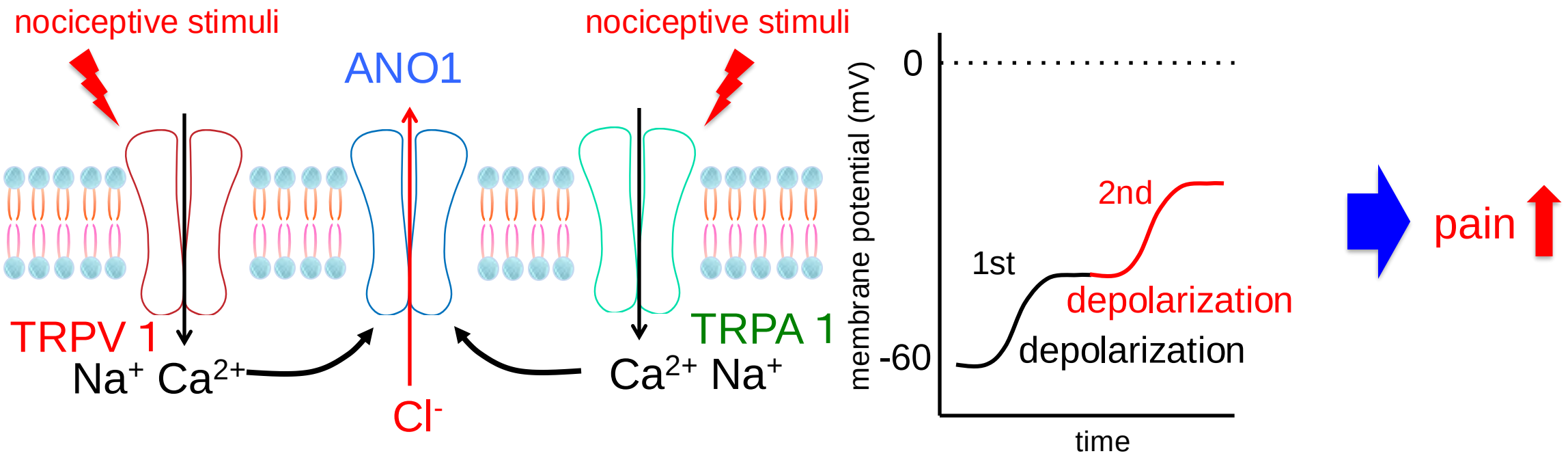
- Increase in nociceptive signal (Takayama et al. PNAS 2015)

This interaction looks occurring in many cells expressing both TRP channels and ANO1.

Direction of Cl^- movement is simply determined by the equilibrium potentials of Cl^- in the cells.

Takayama et al. (2019)

Functional Interaction between TRPV1 and ANO1 in Sensory Neurons



E_{Cl^-}= ~ -40 mV

Resting membrane potential: ~ -60 mV

A complex of TRP channels and ANO1 would be a novel target.

Takayama et al. (PNAS 2015)

I really hope that TRPV1- or TRPA1-antagonists would be available for the treatment of pain in the near future.