# Structure and functioning of TRPV channels: insights from molecular modeling

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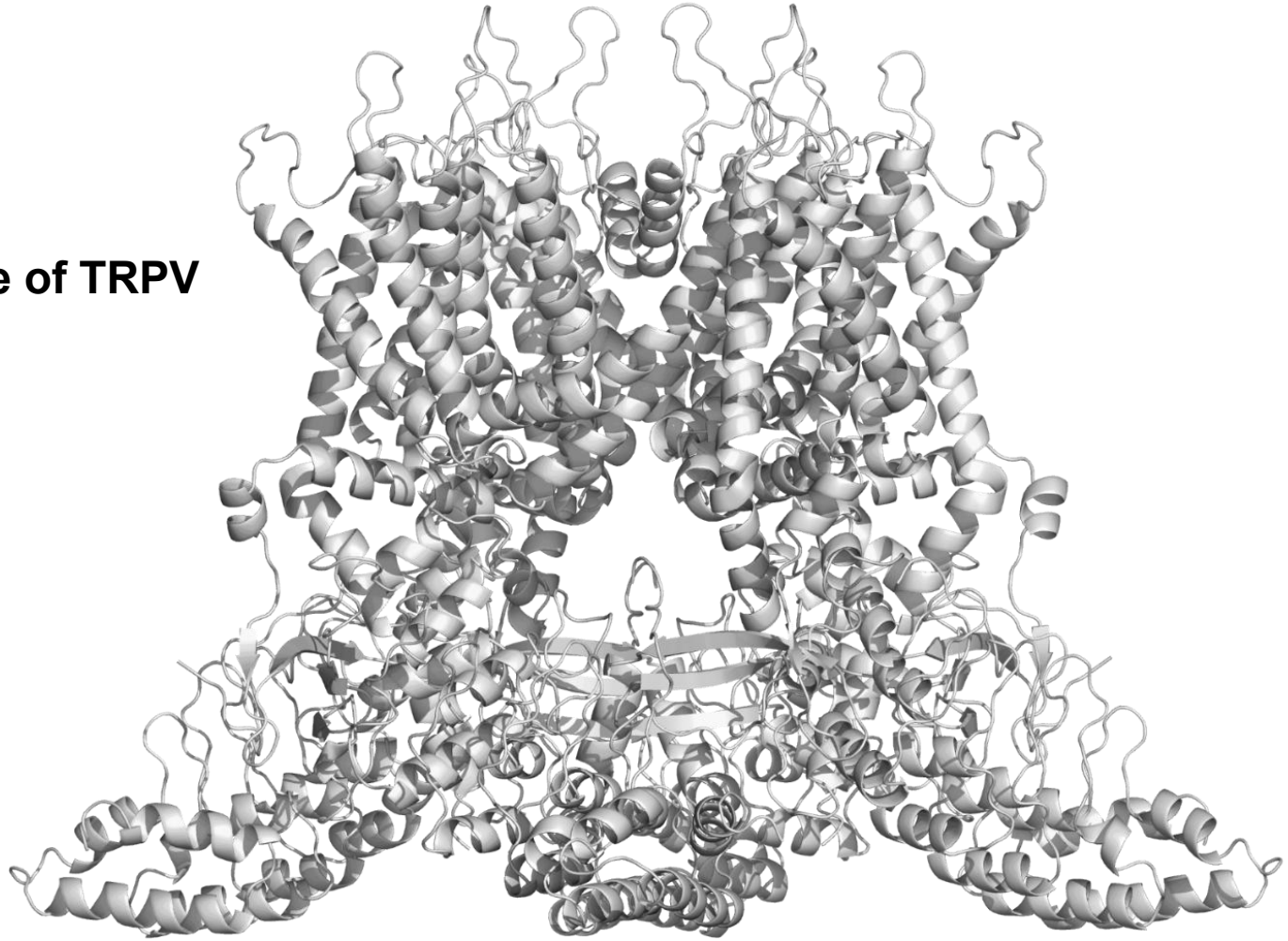
BCADD-2025, 21 September 2025

# In this talk:

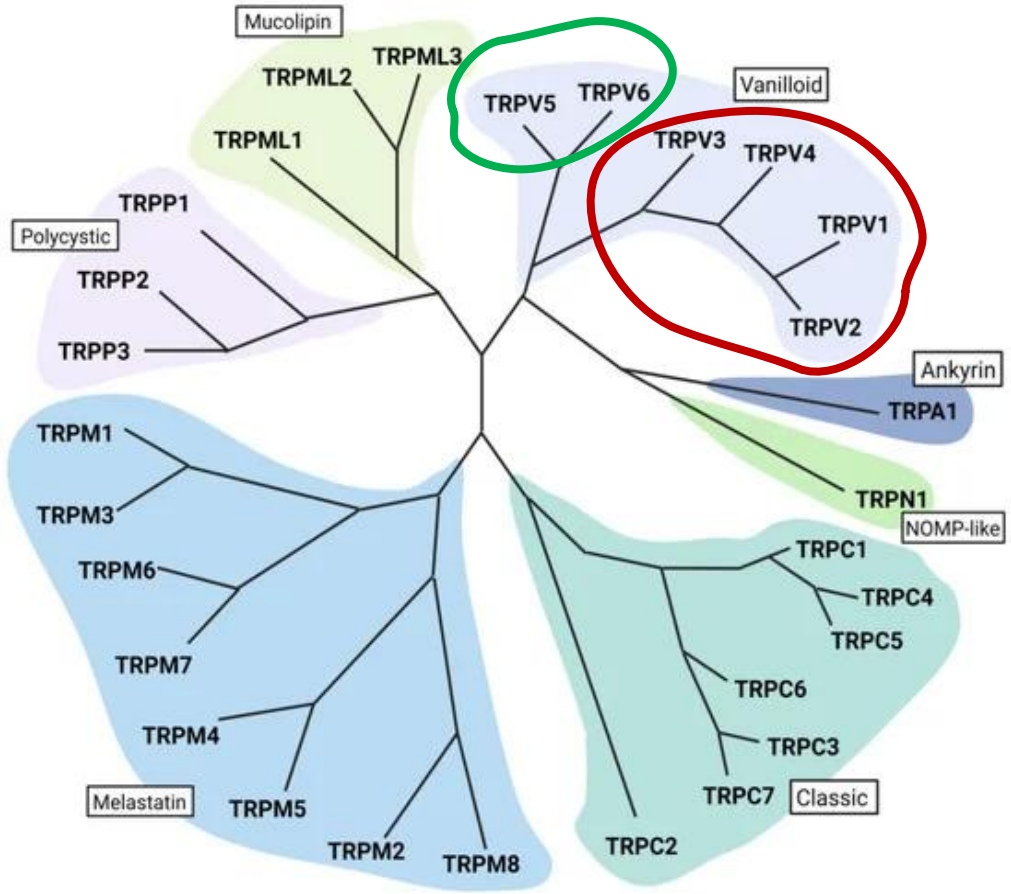
- Introduction – TRPV subfamily
- Structure and gating of conductive pore of TRPV
- Ligand regulation of TRPV functioning

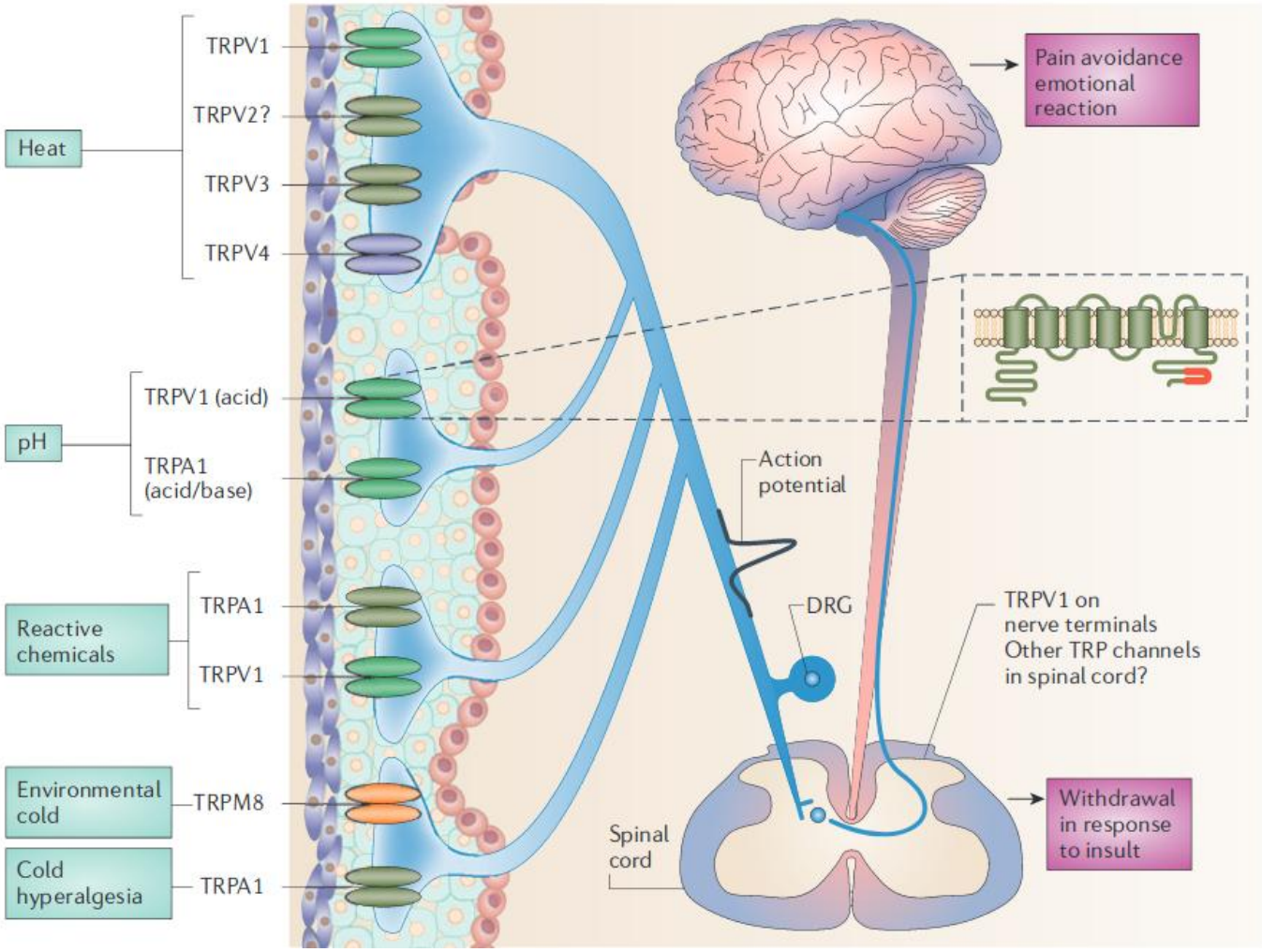


# TRPV ion channels

TRPV 1-4 – thermosensitive, nociception

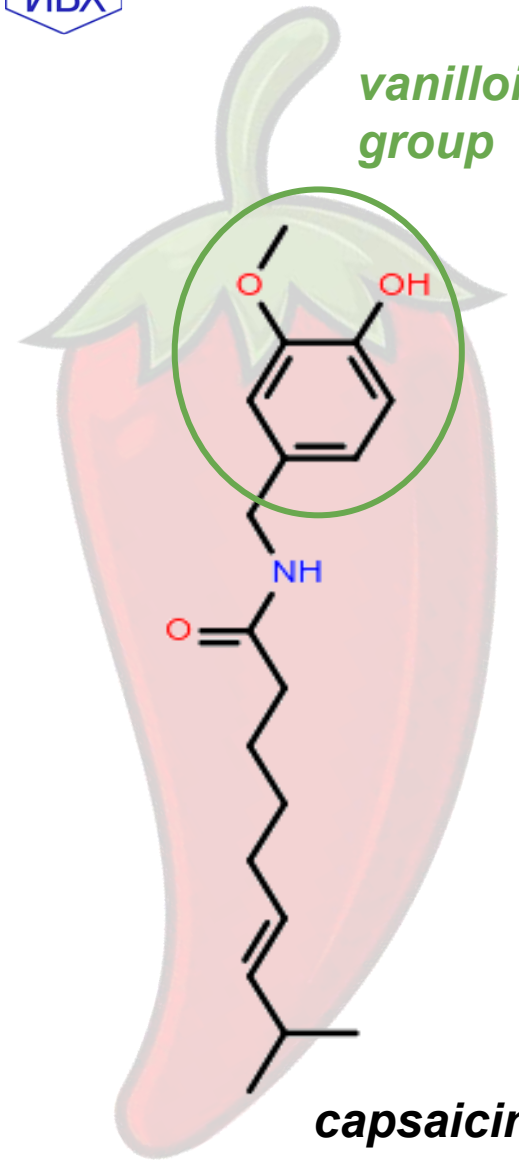
TRPV 5-6 – $Ca^{2+}$ uptake, oncochannels

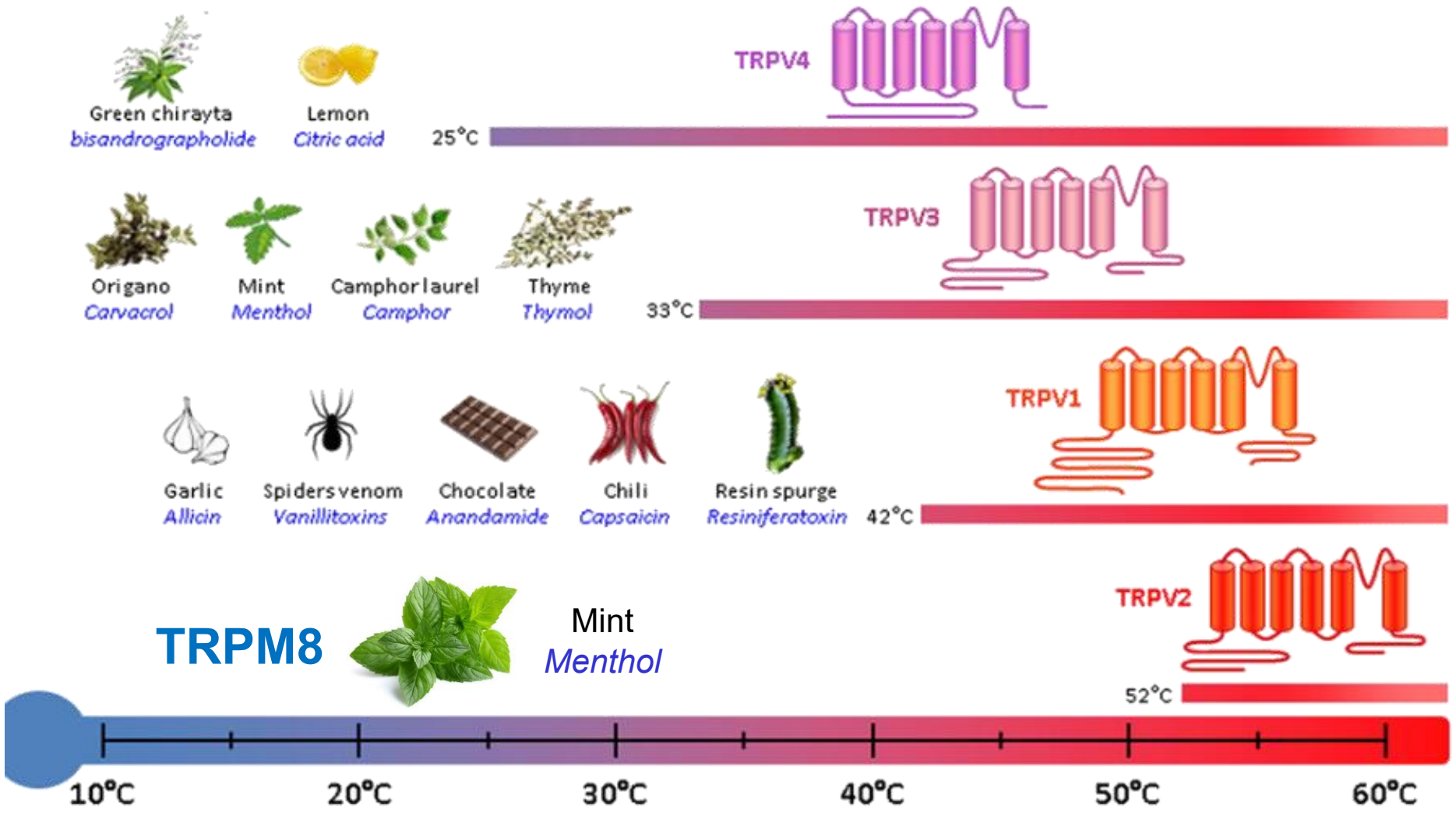



https://doi.org/10.3390/ijms24010700
https://doi.org/10.1038/nrd3456

# Thermo-TRPV activators

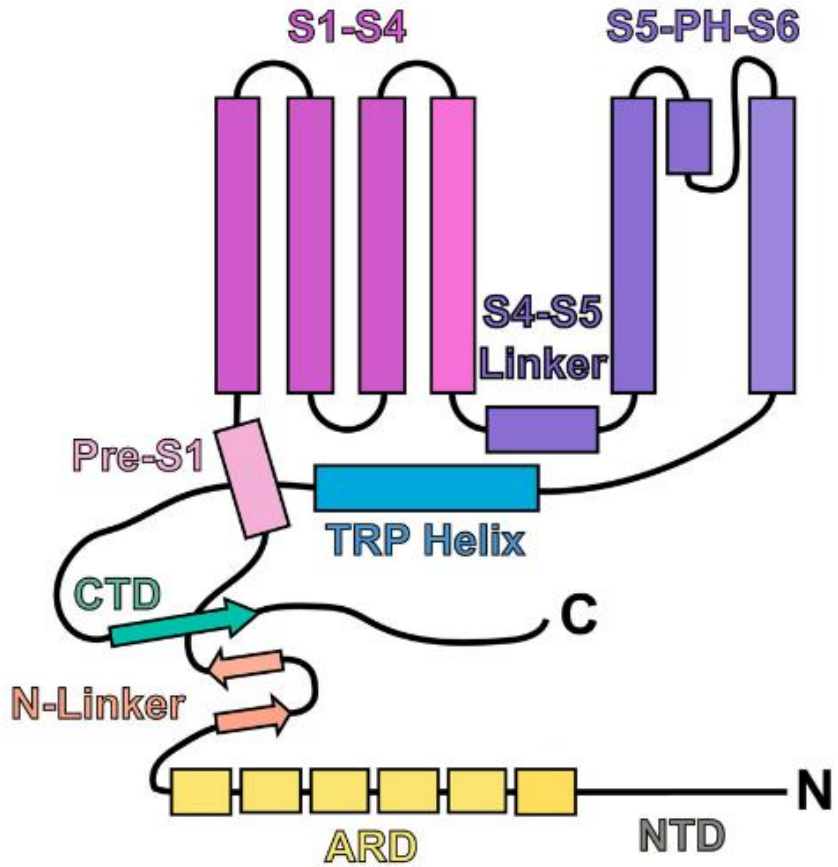


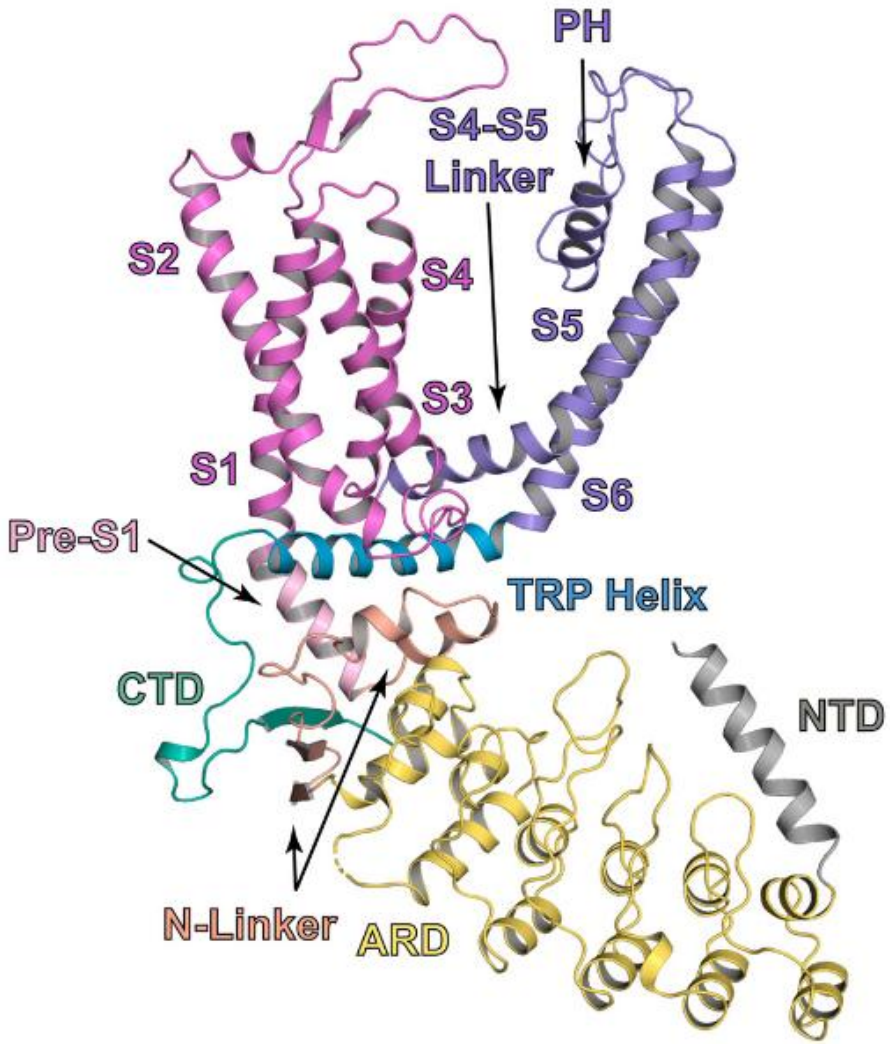




https://doi.org/10.1378/chest.10-3327

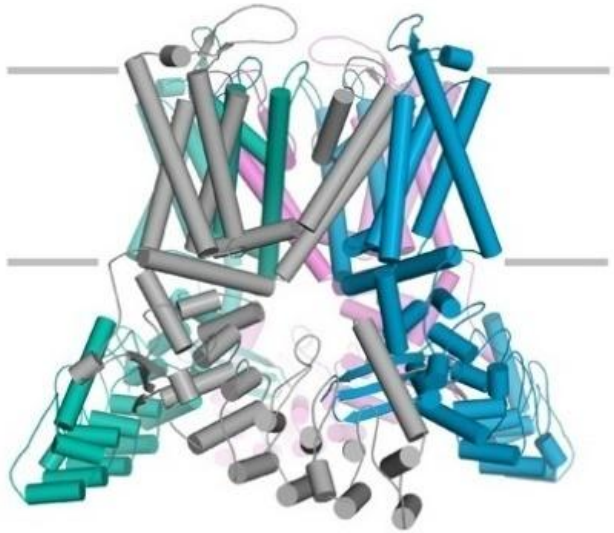
# TRPV molecular structure

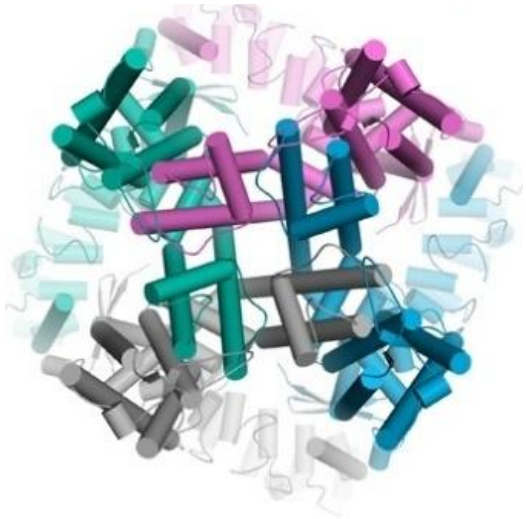
## Structure of one TRPV subunit



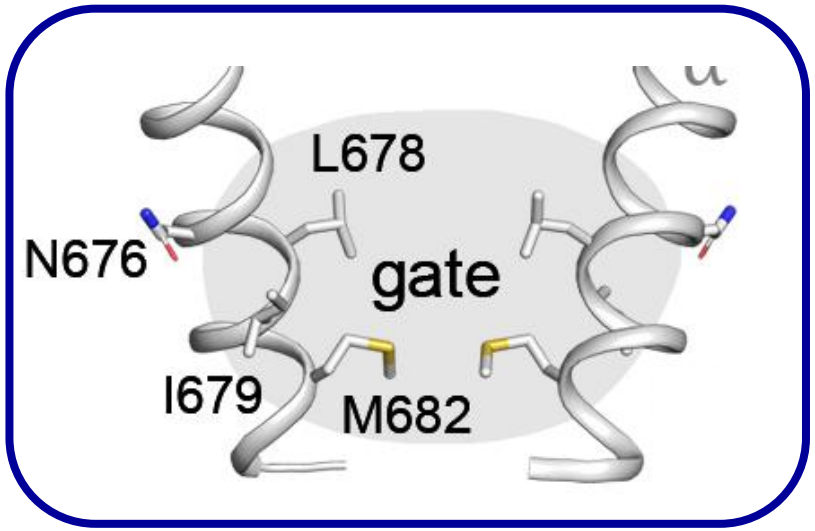

## Homotetramer TRPV

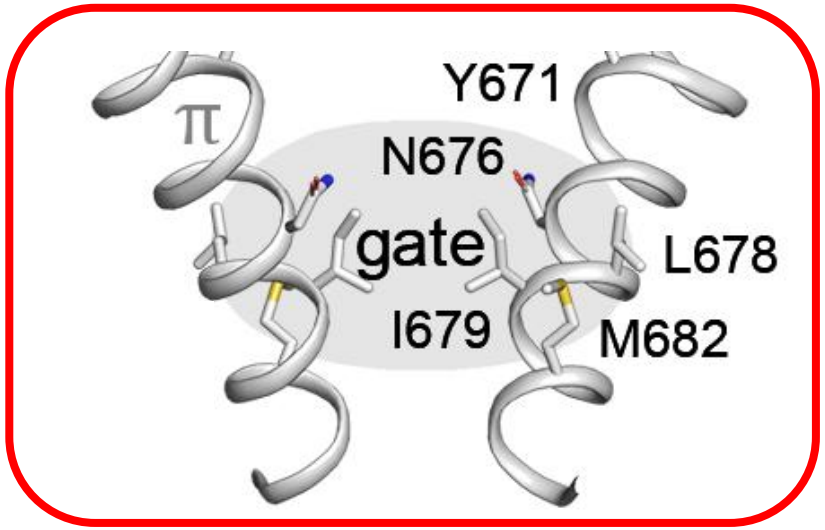


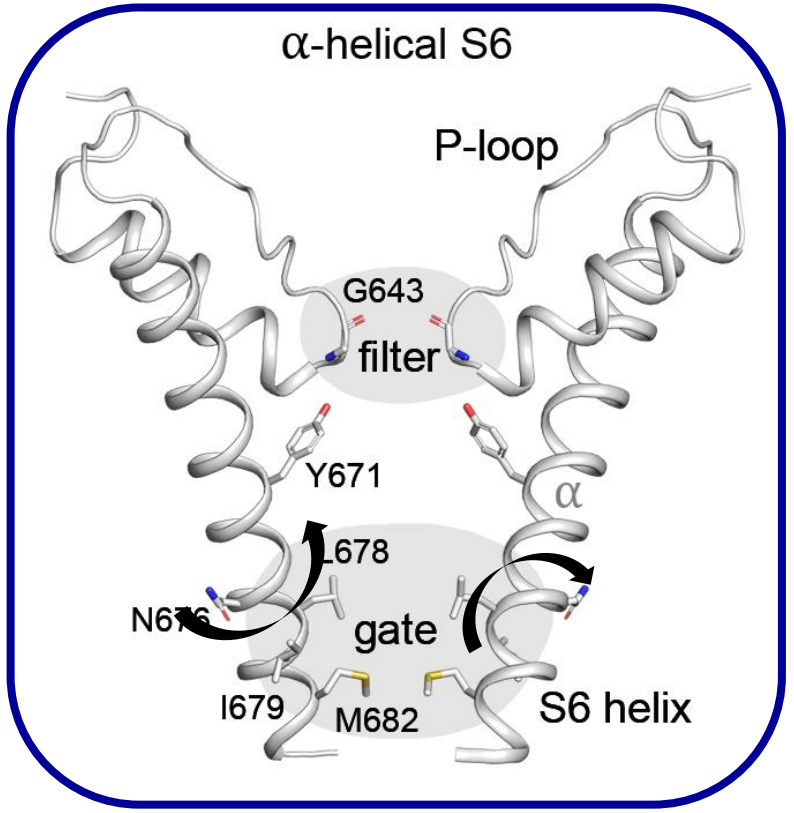


*Pumroy et al. (2020)*

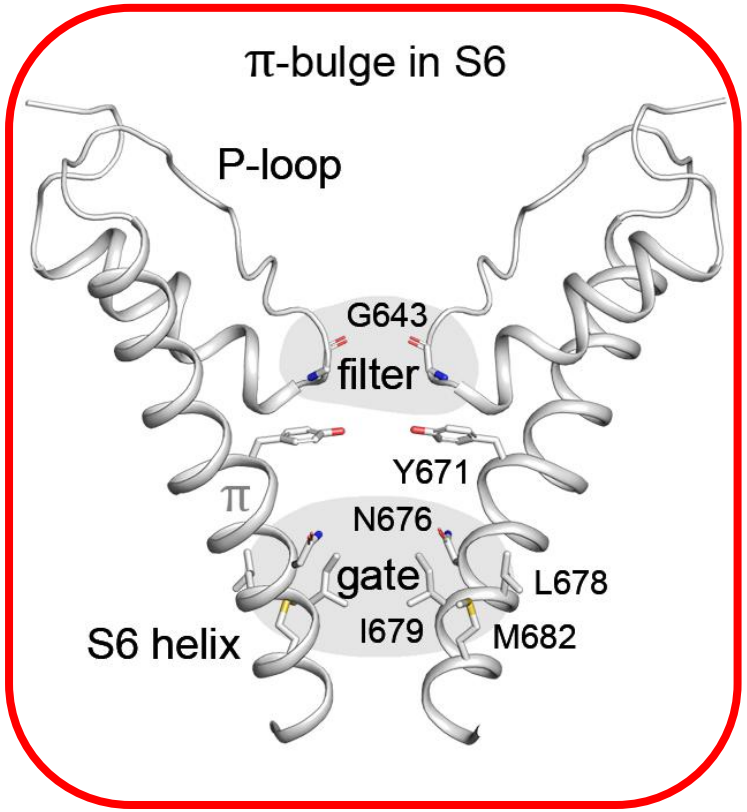
# Conductive pore of TRPV



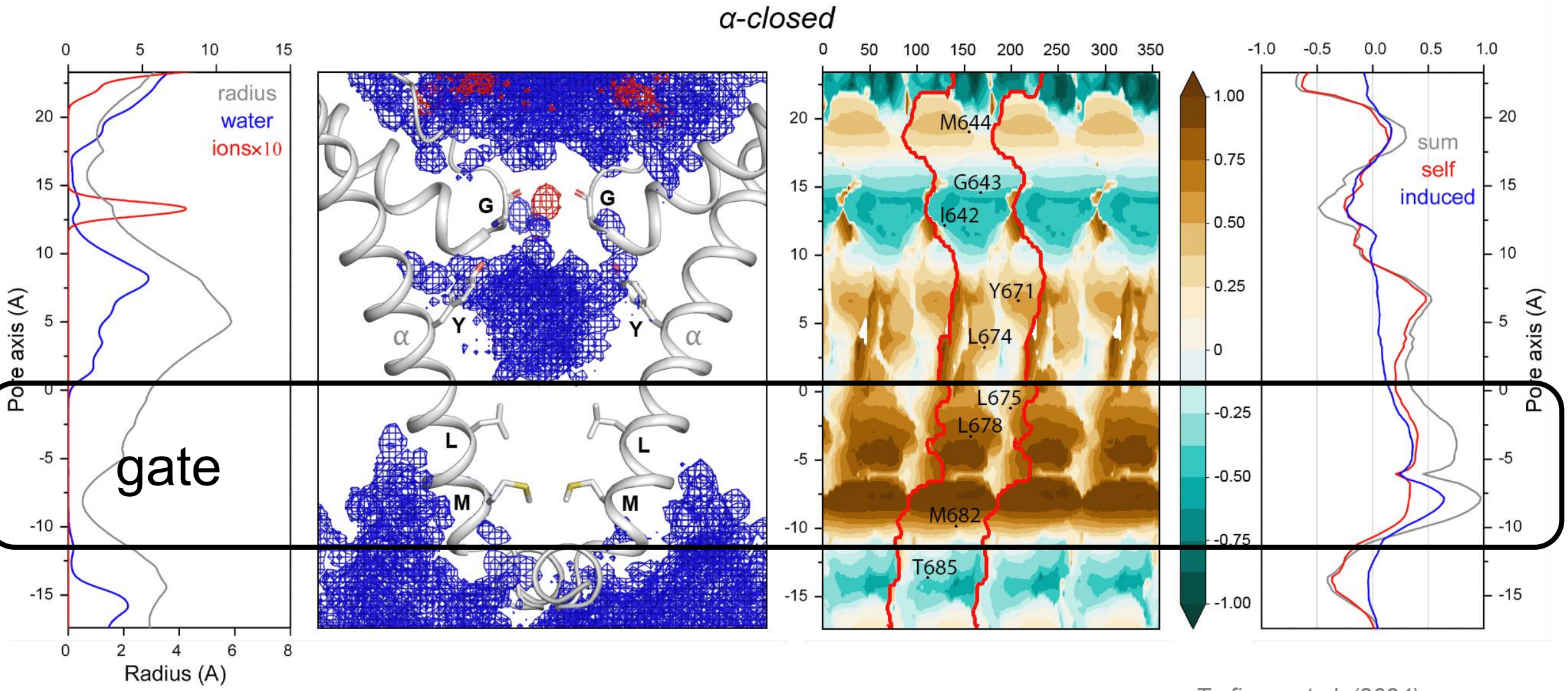

**α-helical state of S6-helix**




**π-bulge state of S6-helix**

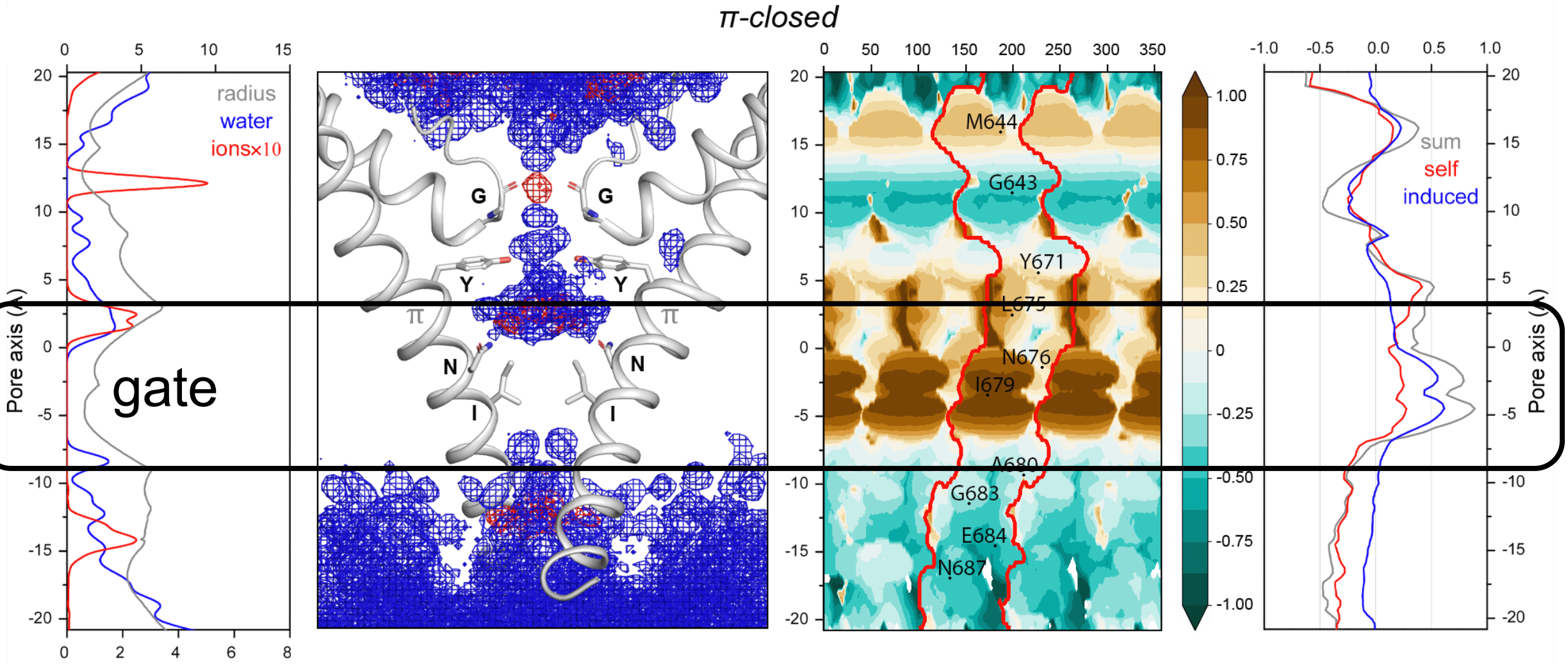
*Trofimov et al. (2024)*
*doi: 10.1038/s42004-024-01198-z*

# α-closed pore of TRPV1



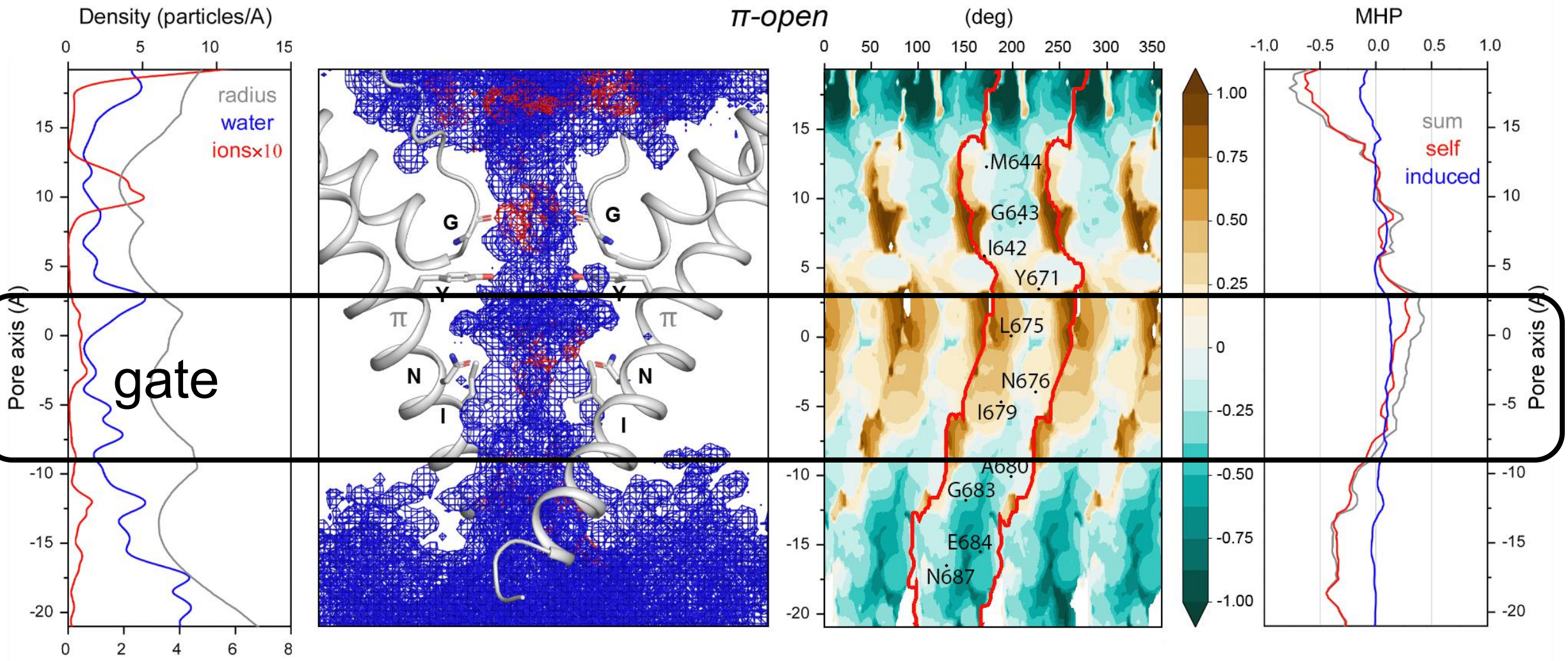

Trofimov et al. (2024)
doi: 10.1038/s42004-024-01198-z

# π-closed pore of TRPV1



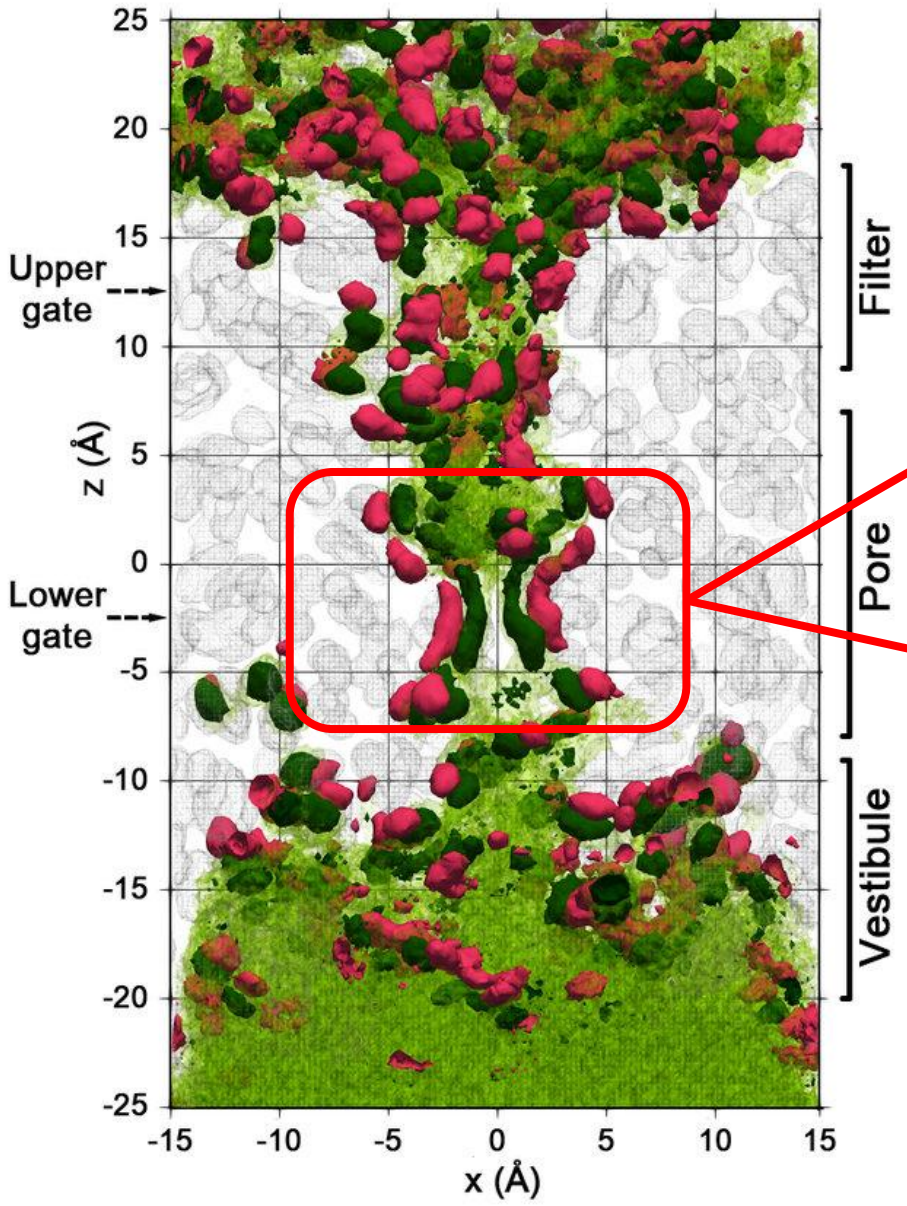

Trofimov et al. (2024)
doi: 10.1038/s42004-024-01198-z

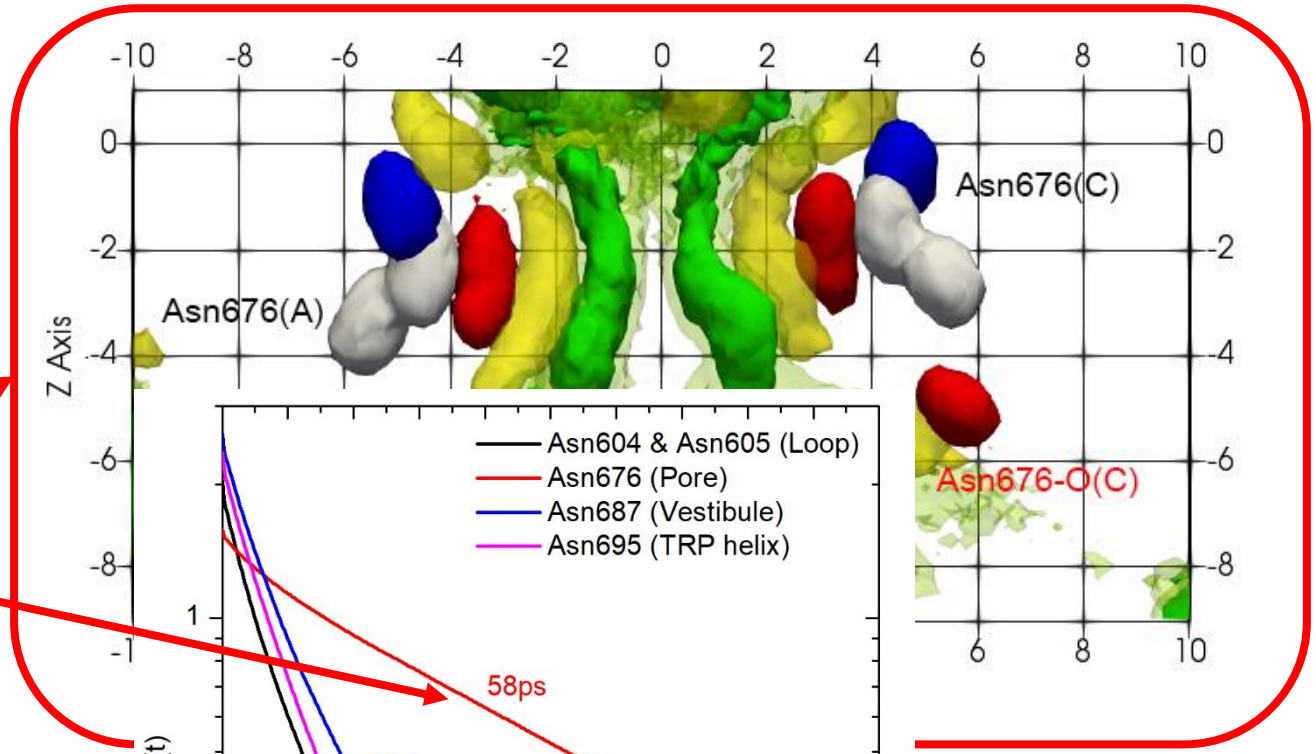
# π-open pore of TRPV1

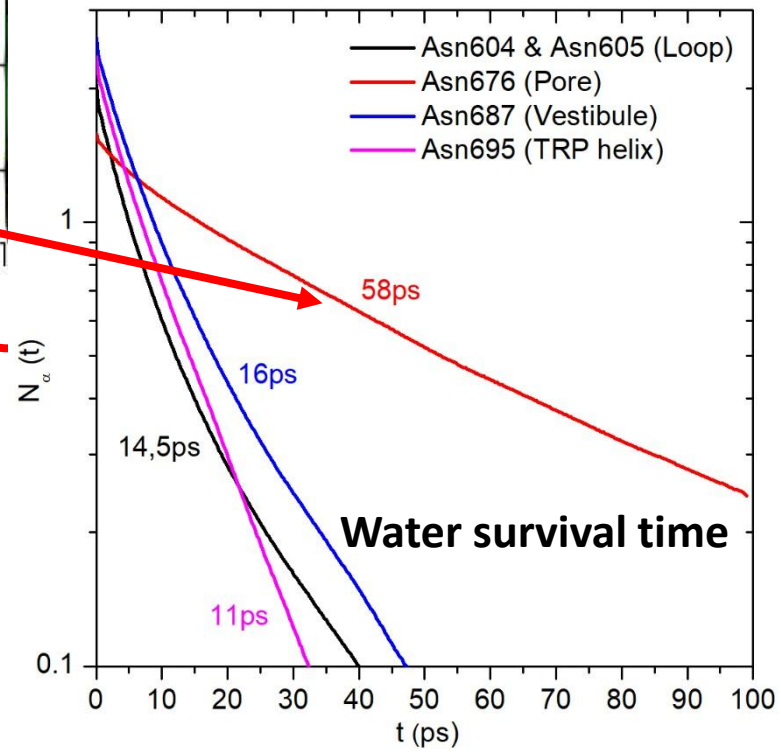



Trofimov et al. (2024)
doi: 10.1038/s42004-024-01198-z

# Confined dynamics of water in π-open pore

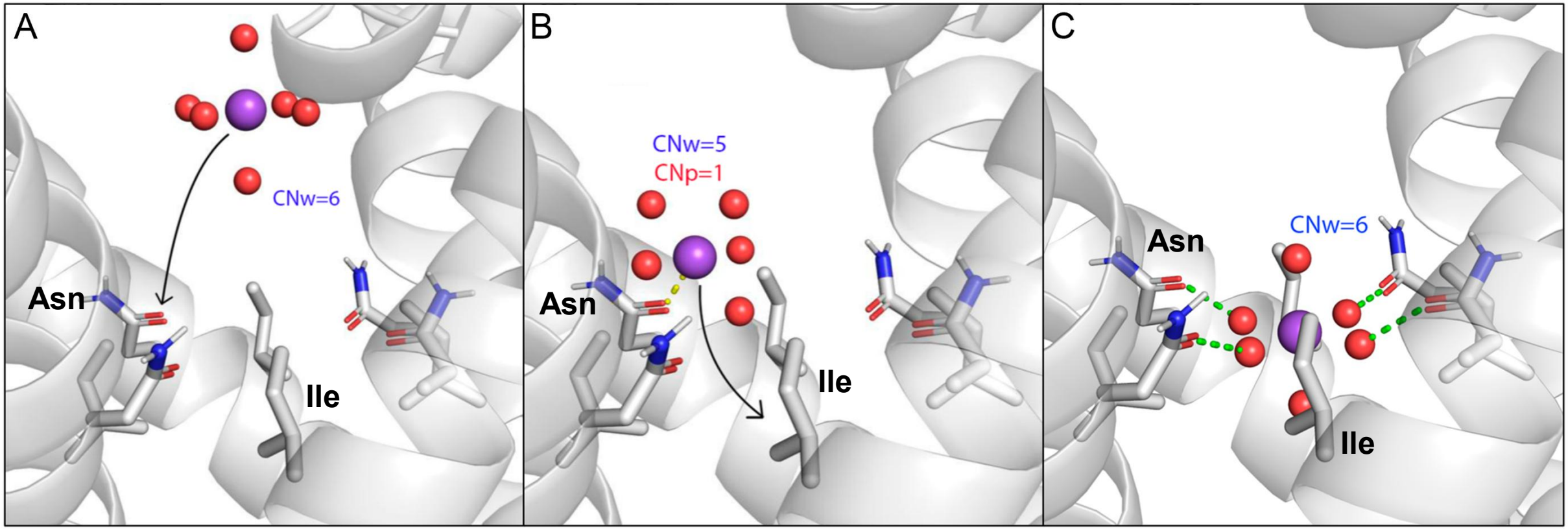



Trofimov et al. 2019

# “Shared” water conductance of cations though the TRPV gate




Fully hydrated cation approaches the gate

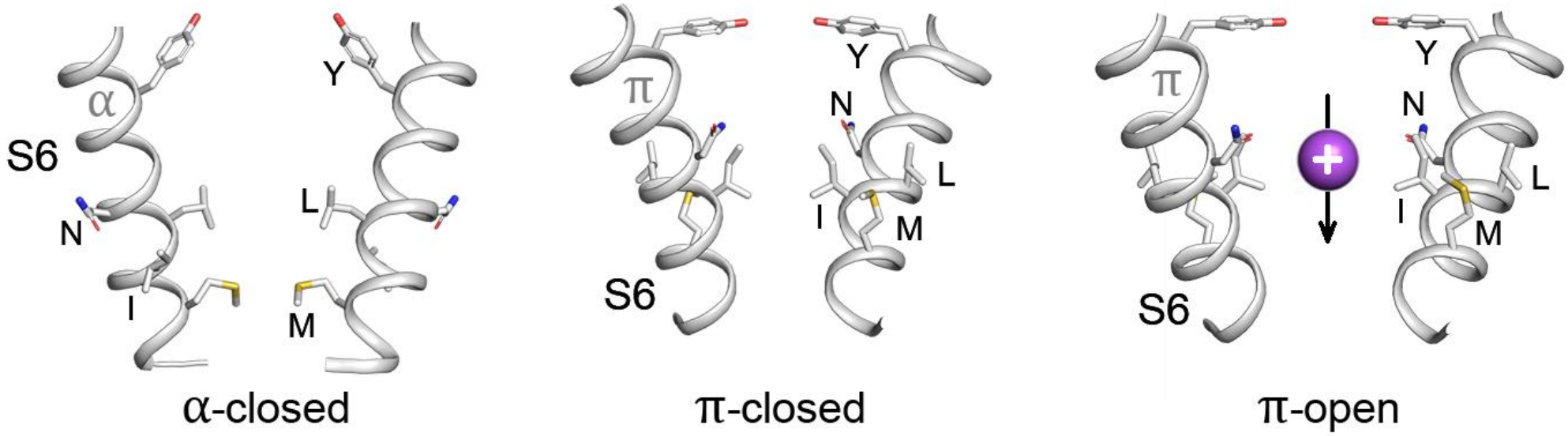
Cation binds to Asn and losing 1-2 waters

Cation recovers its hydration shell, and it is coordinated in the gate via water shared between cation and Asn.

*Trofimov et al. 2023*

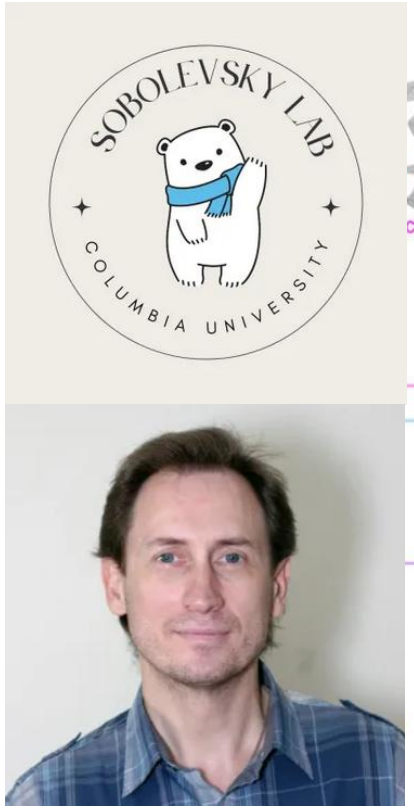
# Gating scheme of TRPV

- Only three major states of the ion-conducting pore exist that are common to the entire TRPV subfamily: α-closed, π-closed, and π-open.
- α-helical conformation of the pore-forming S6 helices provides highly hydrophobic narrow constriction at the gate, causing a non-conductive state of the pore only.
- π-bulge conformation of S6 leads to the more heterogeneous/amphiphilic structure the gate, which can be as conductive as non-conductive.
- Polar asparagine residues at the hydrophobic isoleucin environment provide the open gate hydration and cation coordination, which seems necessary for the pore conduction mechanism.



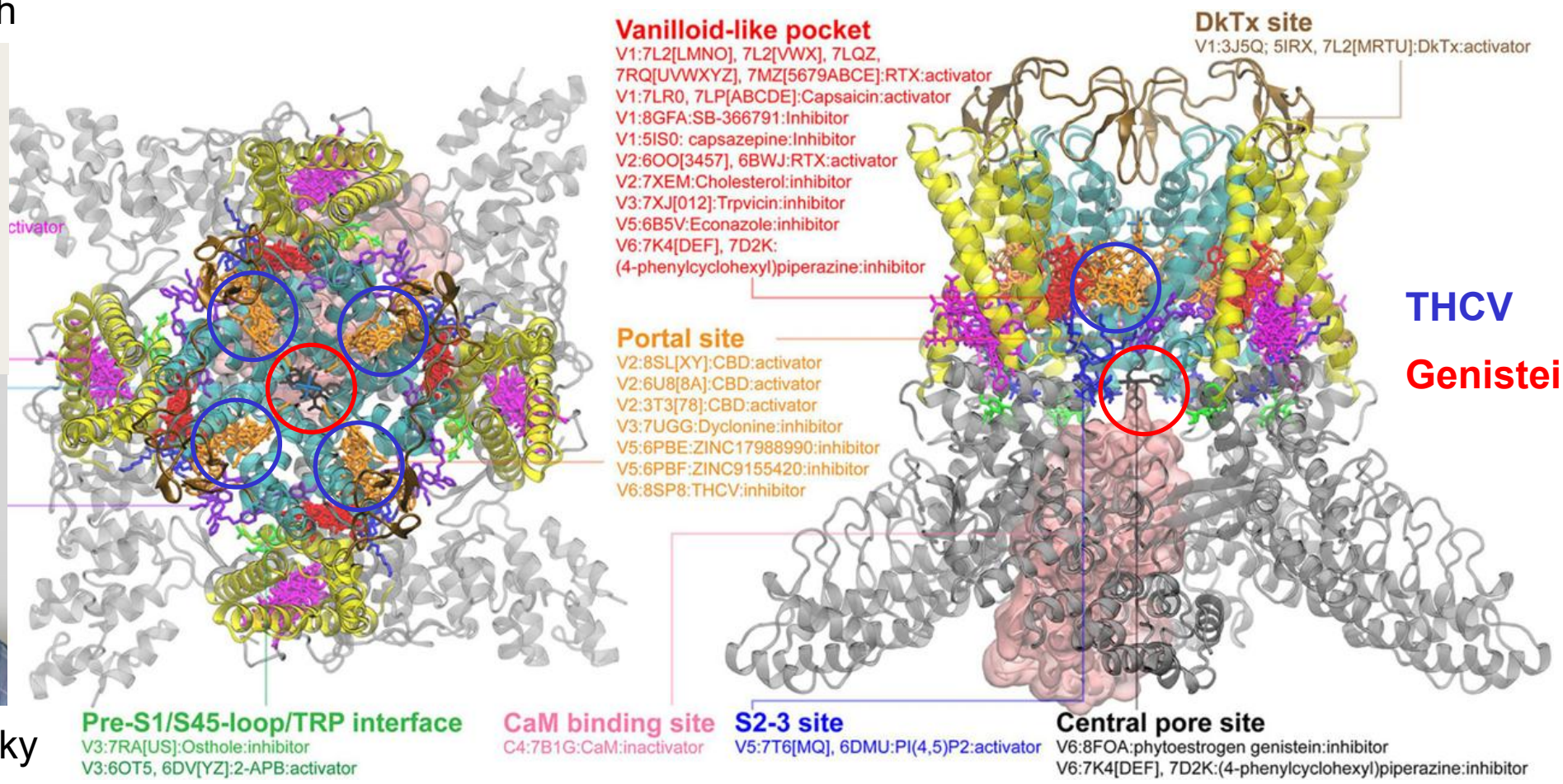
# TRPV regulation by ligands

In collaboration with





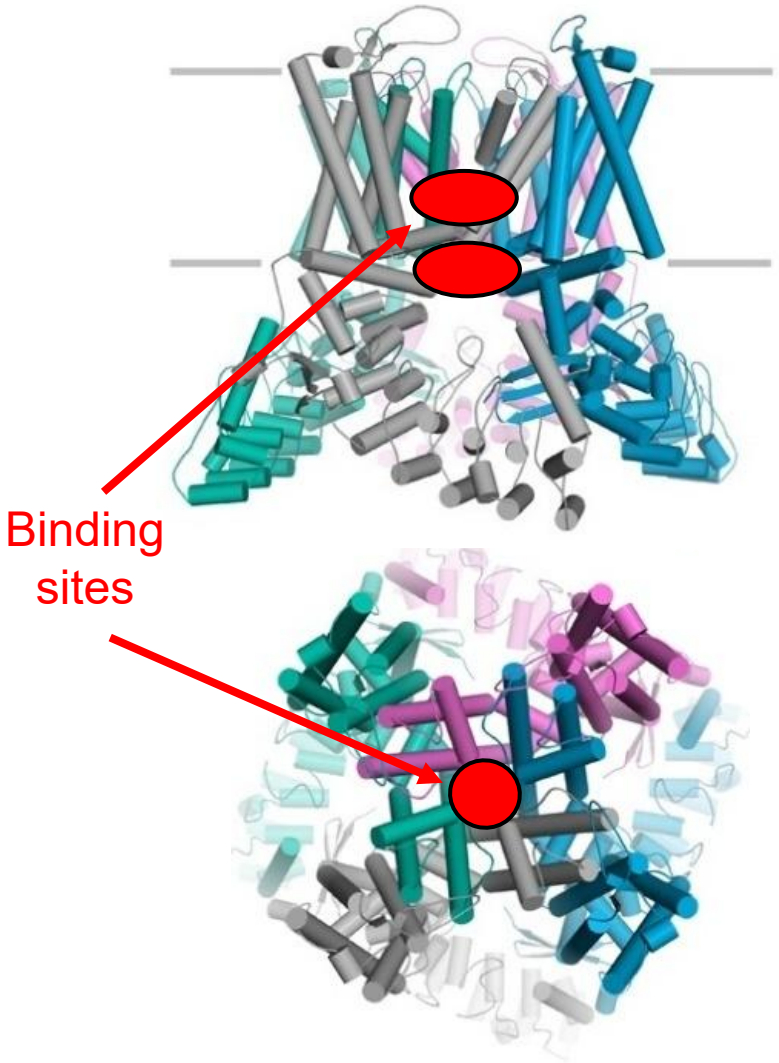

Alexander Sobolevsky

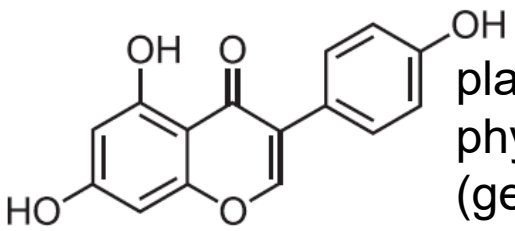



**Ligand binding sites in TRPV channels**

DOI: 10.3389/fnmol.2023.1334370

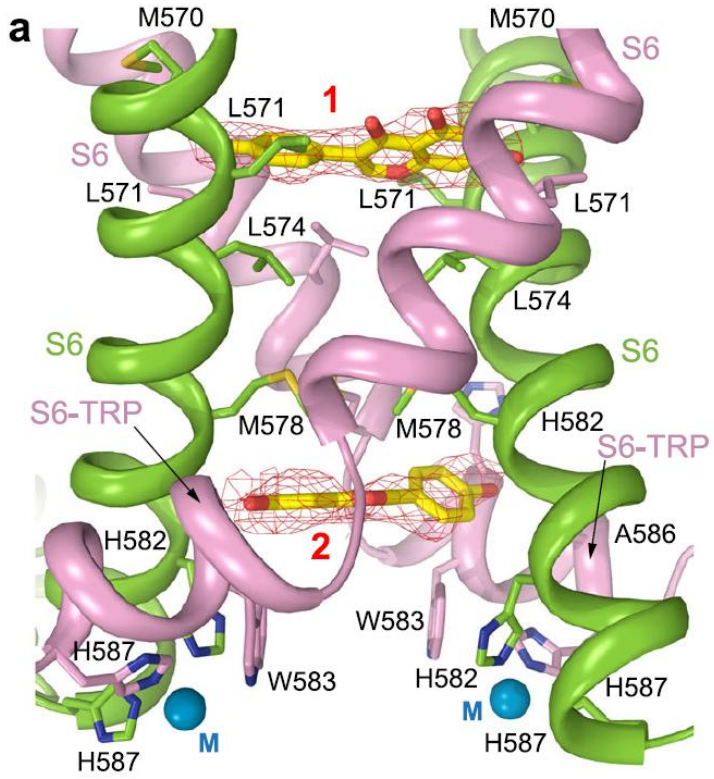
# TRPV6 inhibition by natural phytoestrogen genistein



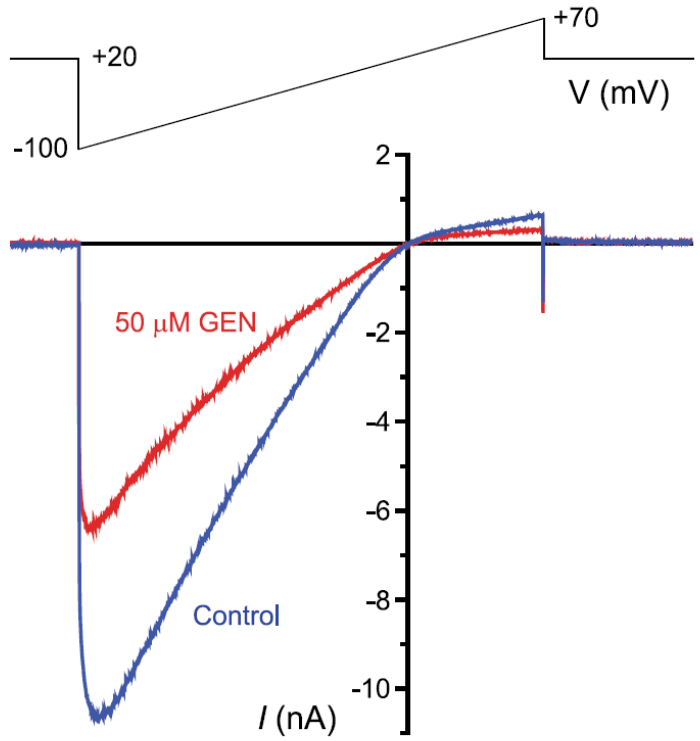




plant-derived phytoestrogen genistein (gen)

Japanese pagoda tree

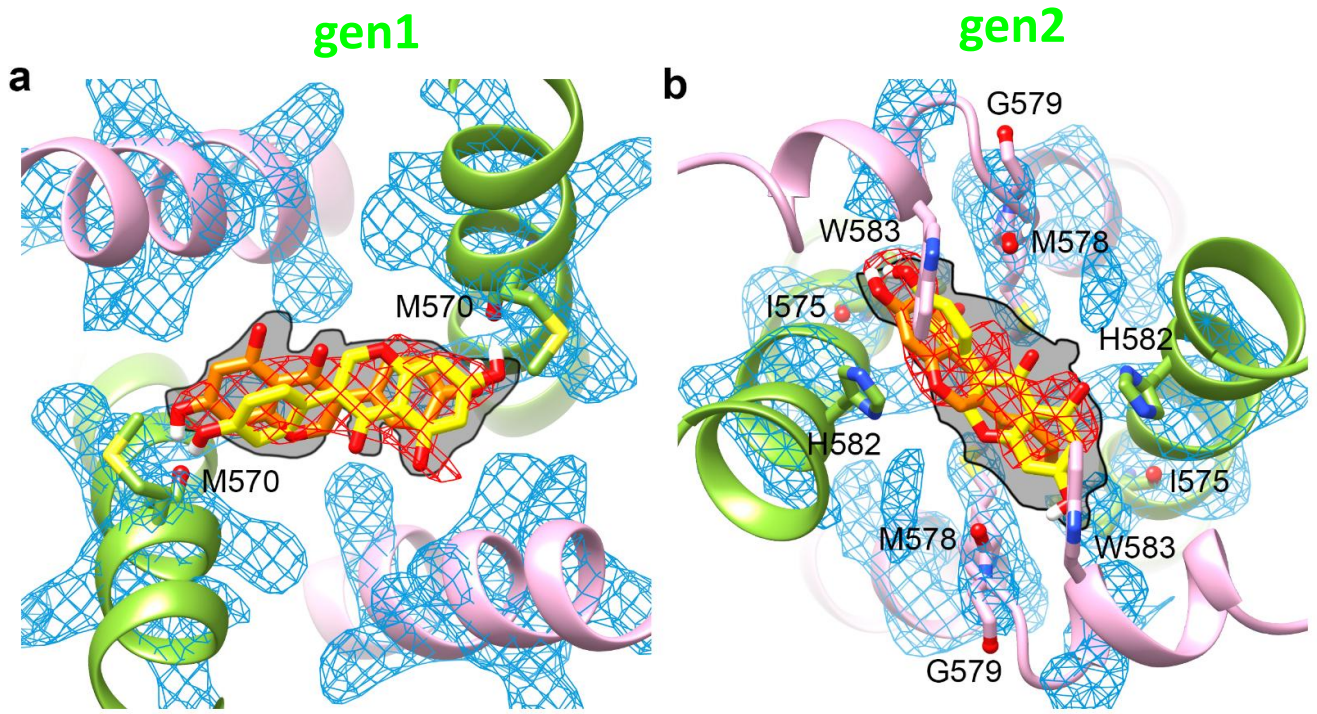



Cryo-EM structure of TRPV6 pore with two gen molecules

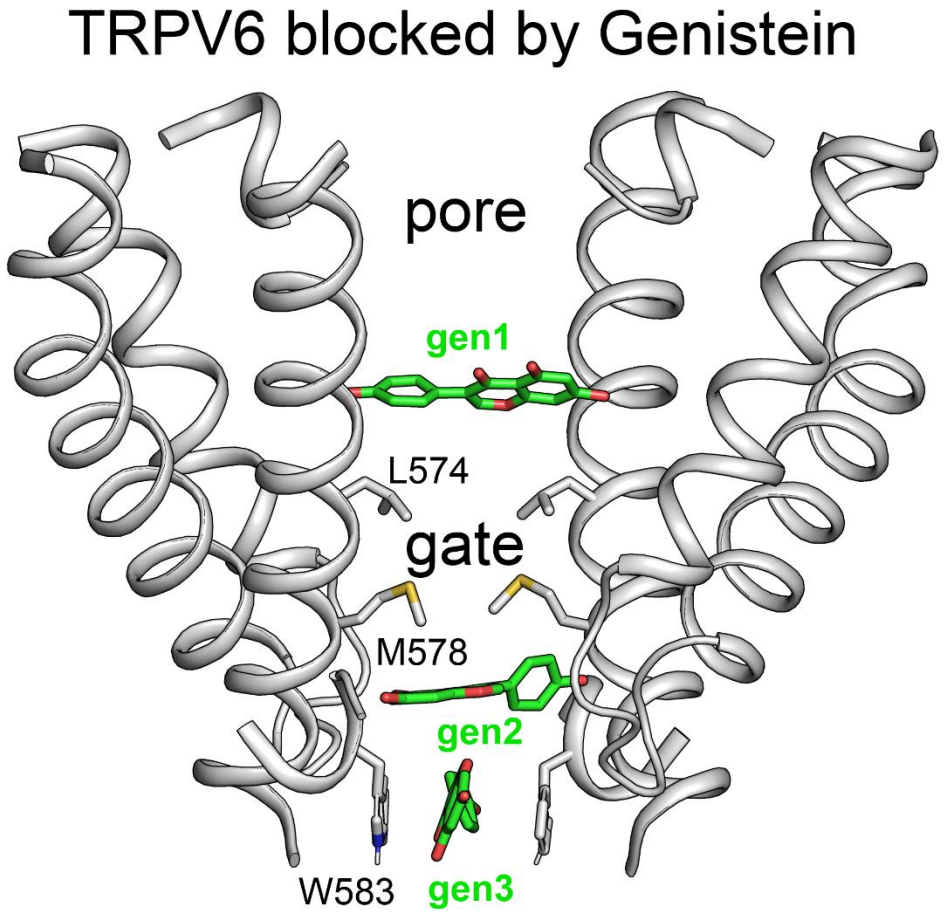



*Neuberger et al. (2023)*
*doi: 10.1038/s41467-023-38352-5*

# TRPV6 inhibition by natural phytoestrogen genistein

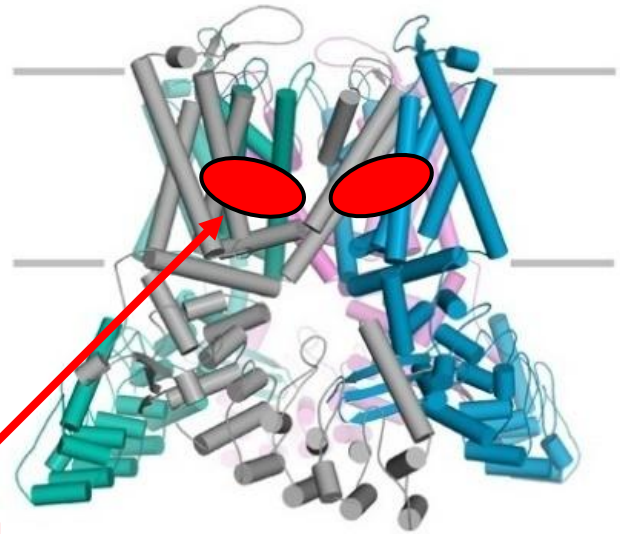



Gray shadows – MD averaged densities imposed on cryo-EM densities (mesh)

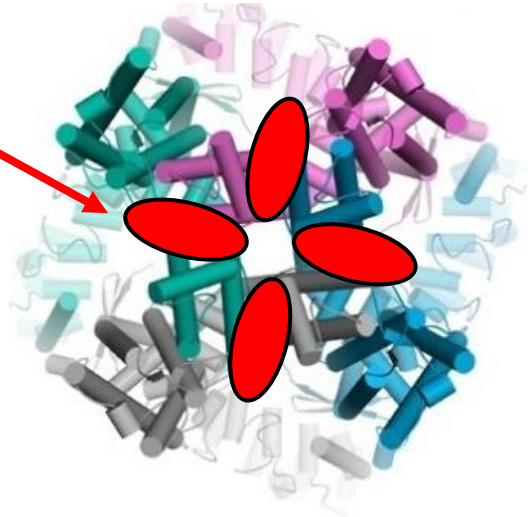


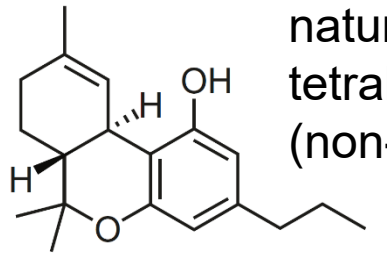

*Neuberger et al. (2023)*
*doi: 10.1038/s41467-023-38352-5*

# TRPV6 inhibition by phytocannabinoid tetrahydrocannabivarin



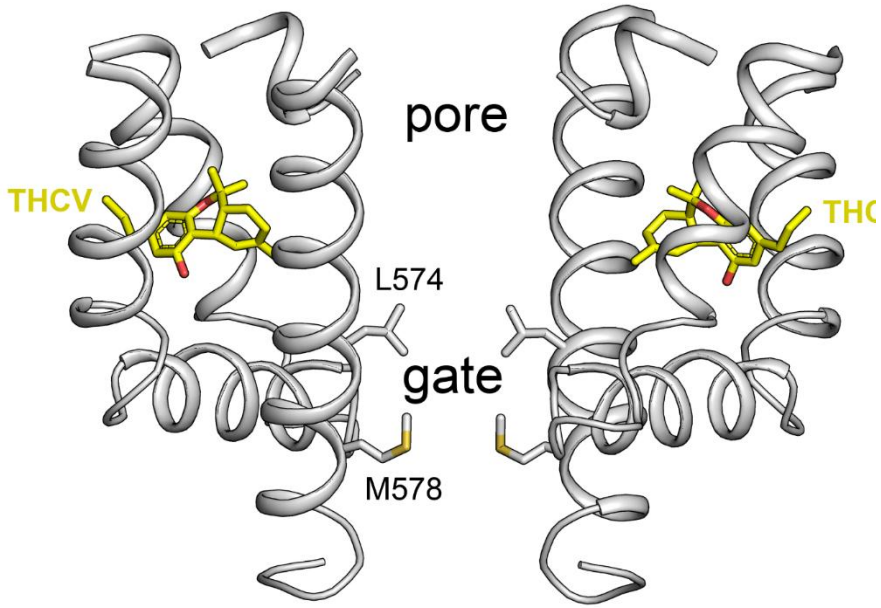
Binding sites



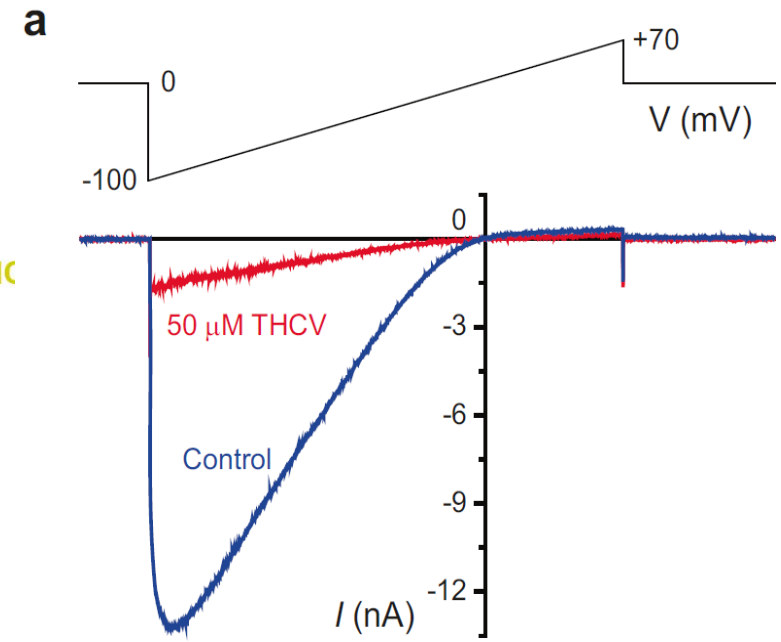



natural cannabinoid
tetrahydrocannabivarin (THCV)
(non-psychoactive)

Cannabis sativa

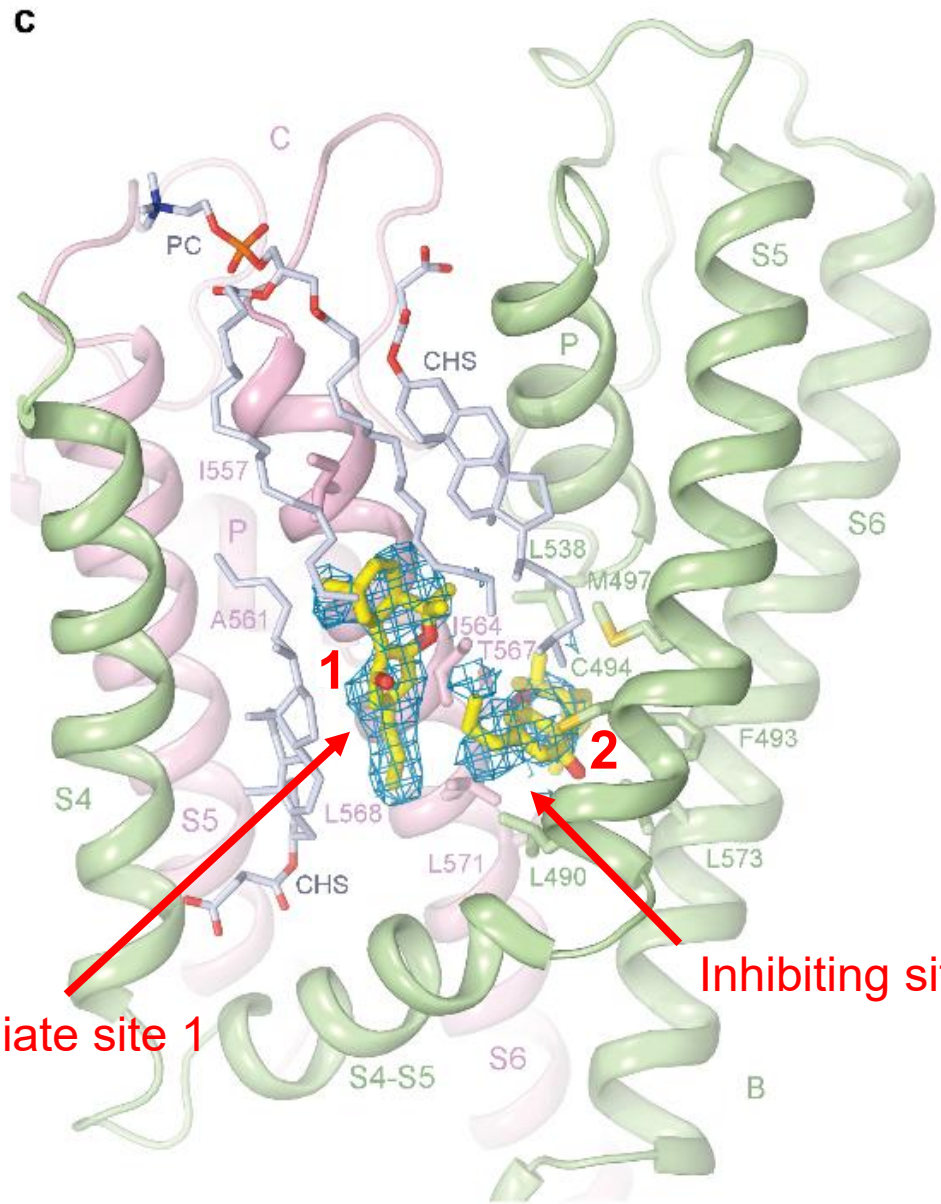



TRPV6 pore with two THCV molecules in portal sites



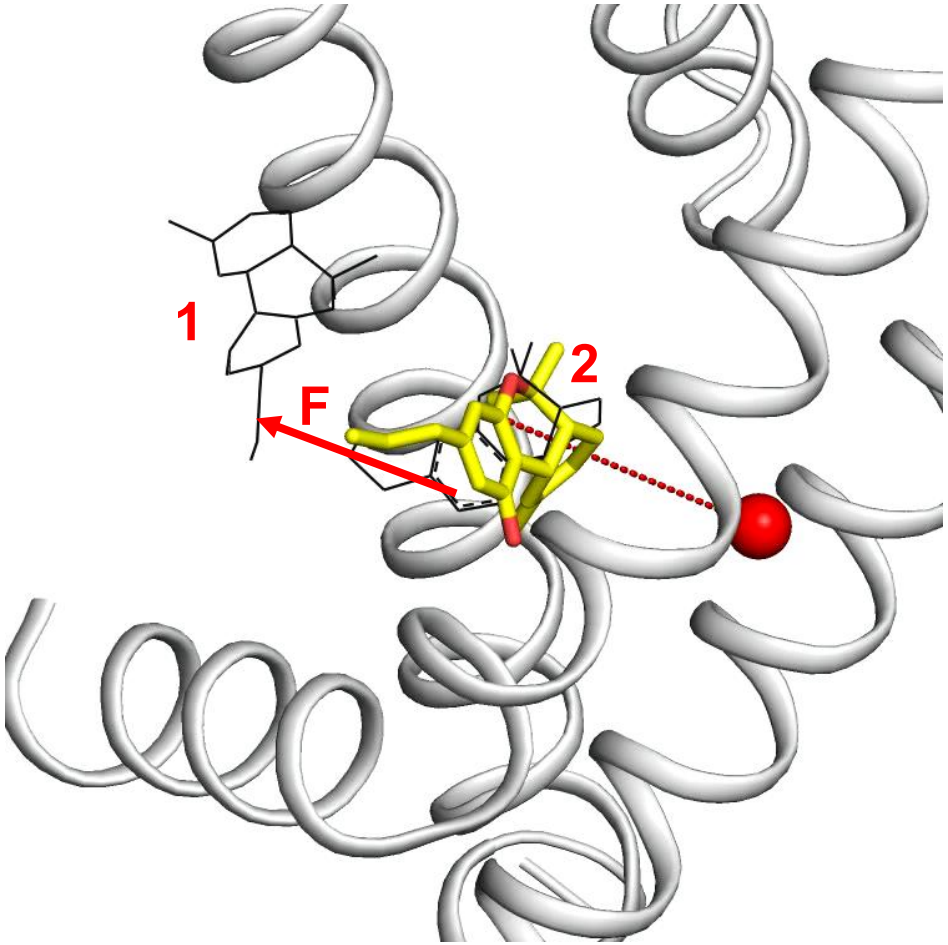

*Neuberger et al. 2023*
*doi: 10.1038/s41467-023-40362-2*

# Molecular pathway of THCV binding




Intermediate site 1

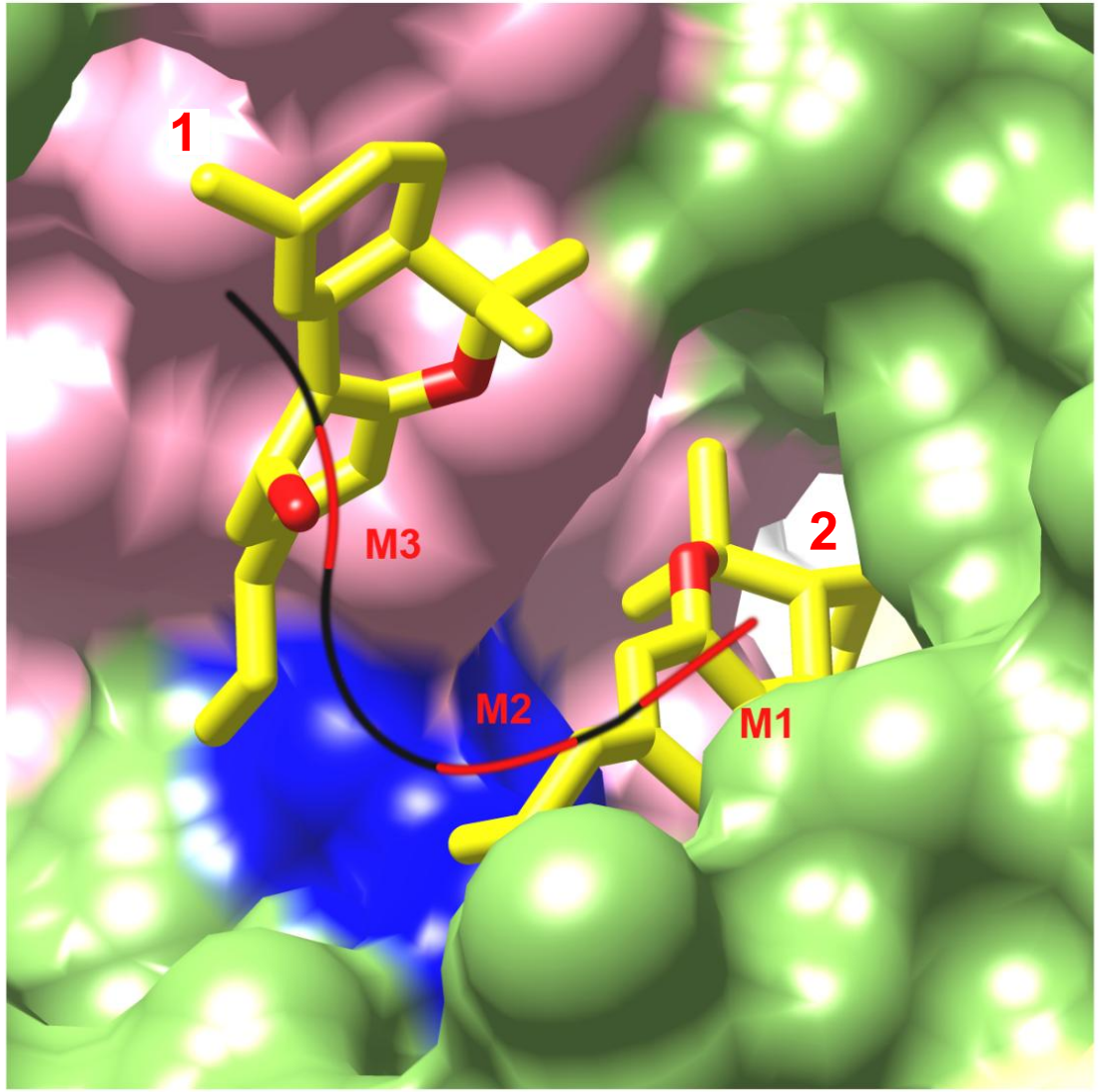
Inhibiting site 2

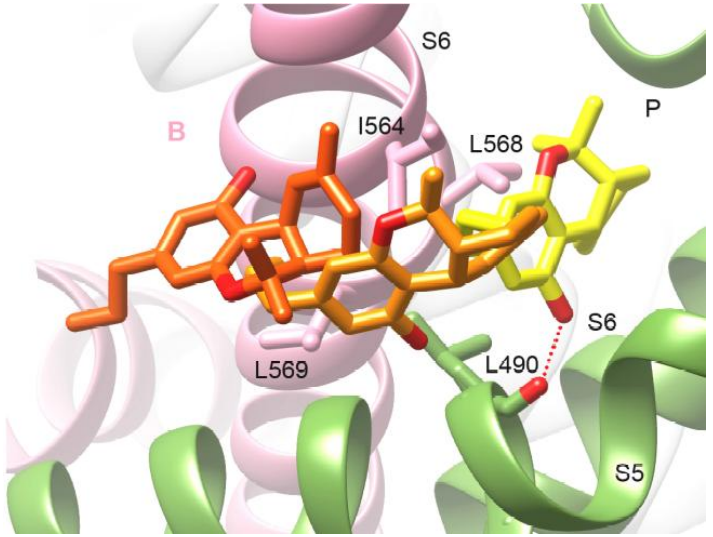


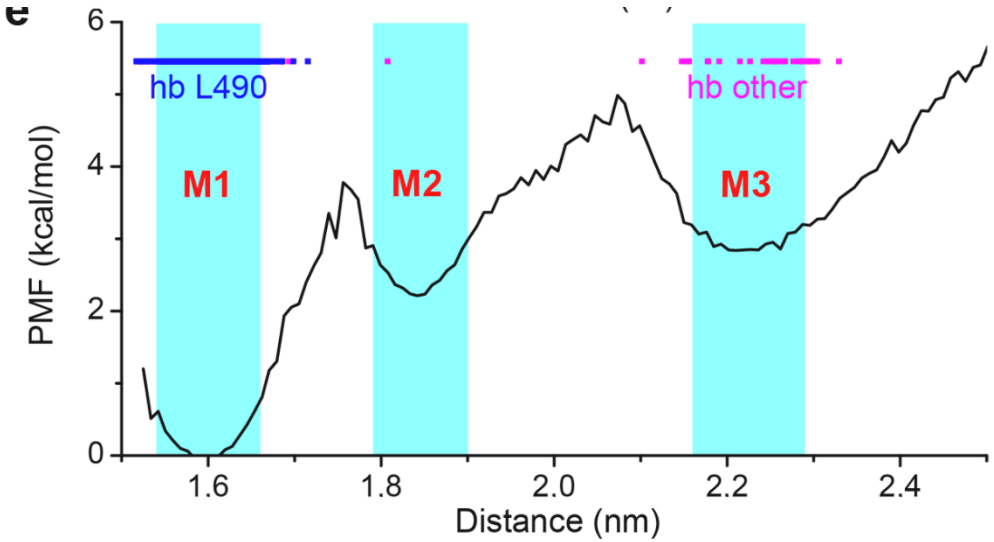

Pulling MD simulation

*Neuberger et al. 2023*
*doi: 10.1038/s41467-023-40362-2*

# Molecular pathway of THCV binding




*Neuberger et al. 2023*
*doi: 10.1038/s41467-023-40362-2*

# Announcement

***Ivan Lazarev***
*THE POLAR PATCH IN THE HYDROPHOBIC GATE OF THE TRPV1 CHANNEL AND ITS FUNCTIONAL ROLE*
*Tuesday 17:20*

***Irina Veretenenko***
*MAGNESIUM BINDING TO TRPV6 ION CHANNEL: INSIGHTS FROM MOLECULAR MODELING*
*Tuesday 15:30*

***Anton Chugunov***
*A LONG, HARD ROAD TO PHYSICALLY CORRECT CALCULATION OF PROTEIN–PROTEIN BINDING FREE ENERGIES*
*Wednesday 11:00*

# Thank you for your attention!