XXXII Symposium on Bioinformatics and Computer-Aided Drug Discovery

This work was supported by the MSHE Agreement № 075-15-2024-536

Ligand-mediated regulation of the oncochannel TRPV6 ion-conducting pore

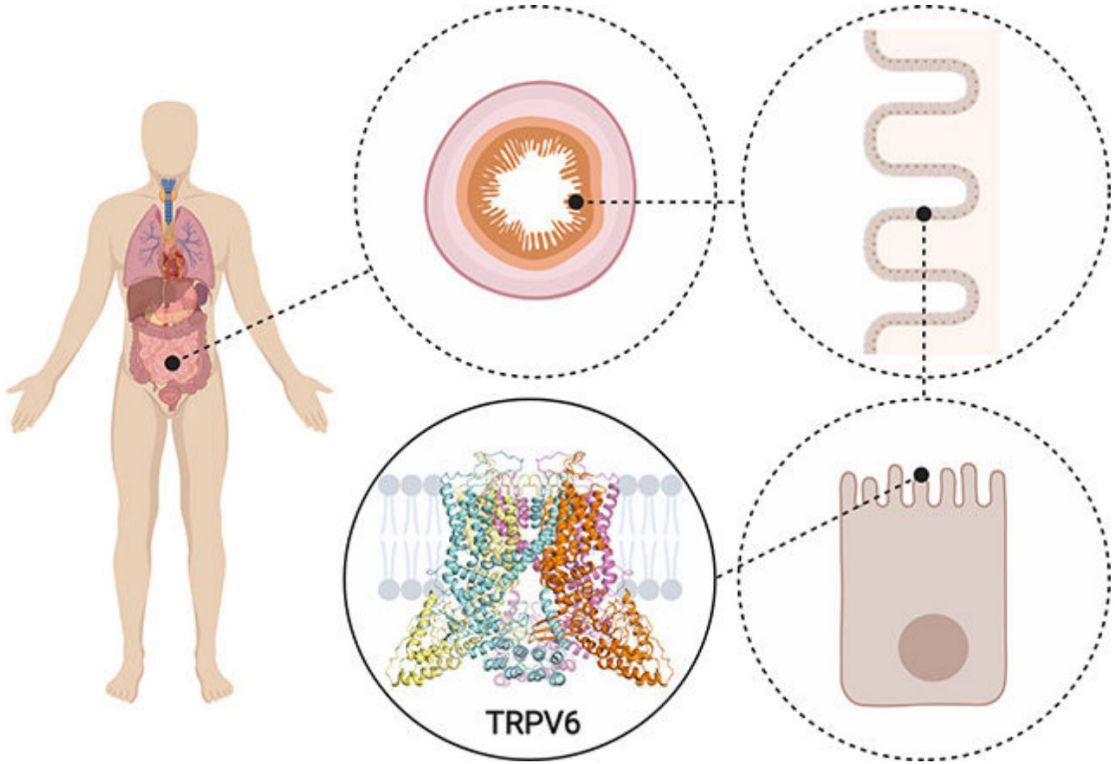
Veretenenko I.I.[1,2,3], Trofimov Y.A.[2], Efremov R.G.[1,2,4]

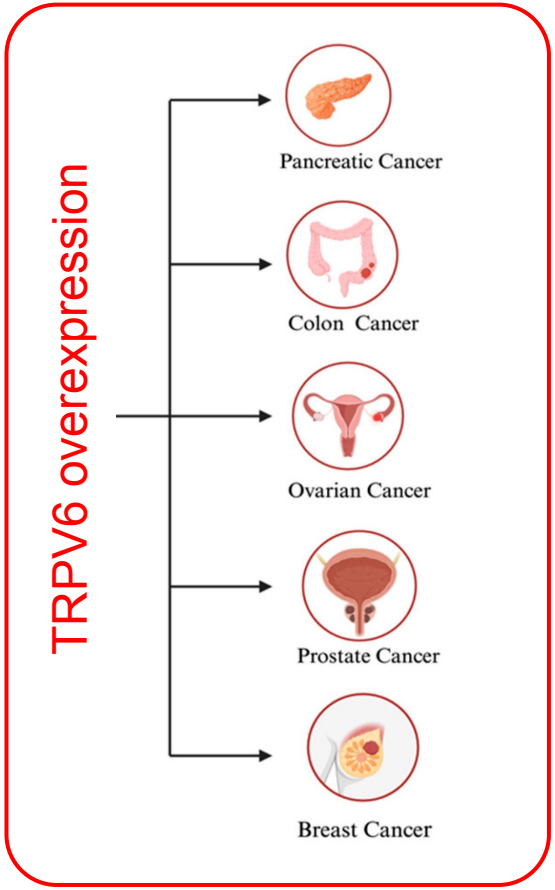
[1] Research Institute for Systems Biology and Medicine, Moscow, Russia
[2] Shemyakin–Ovchinnikov Institute of bioorganic chemistry RAS, Moscow, Russia
[3] Moscow Institute of Physics and Technology (National Research University), Dolgoprudny, Russia
[4] National Research University «Higher School of Economics», Moscow, Russia

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October 20, 2026

TRPV6 ion channel

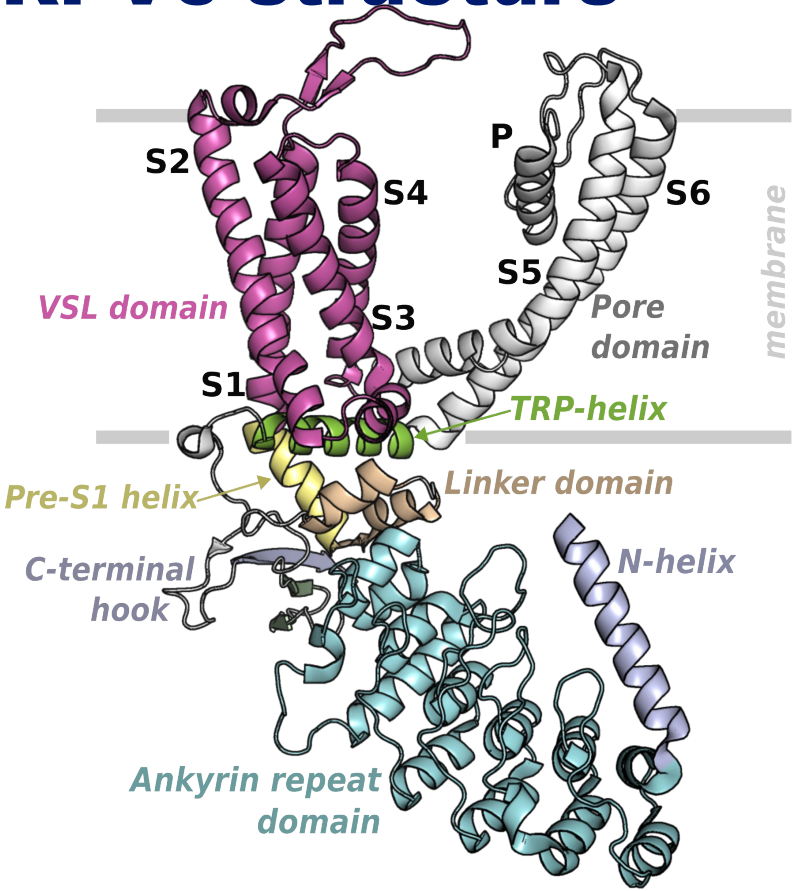


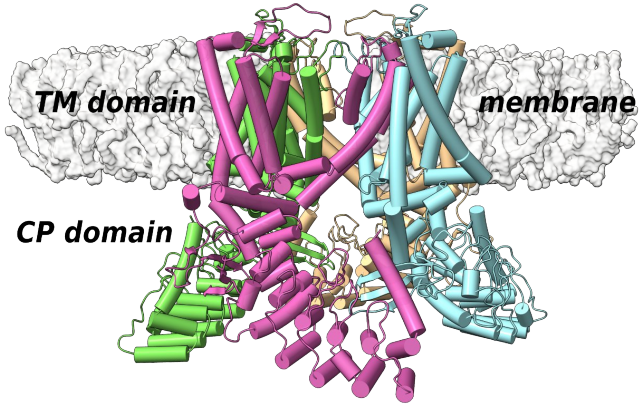


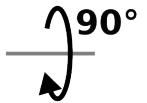
Yelshanskaya et al. (2021), doi: 10.1113/JP279024

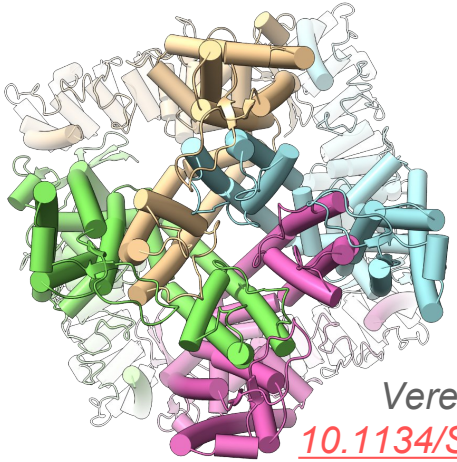
Wang et al. (2024), doi: 10.3390/biology13030168

TRPV6 structure



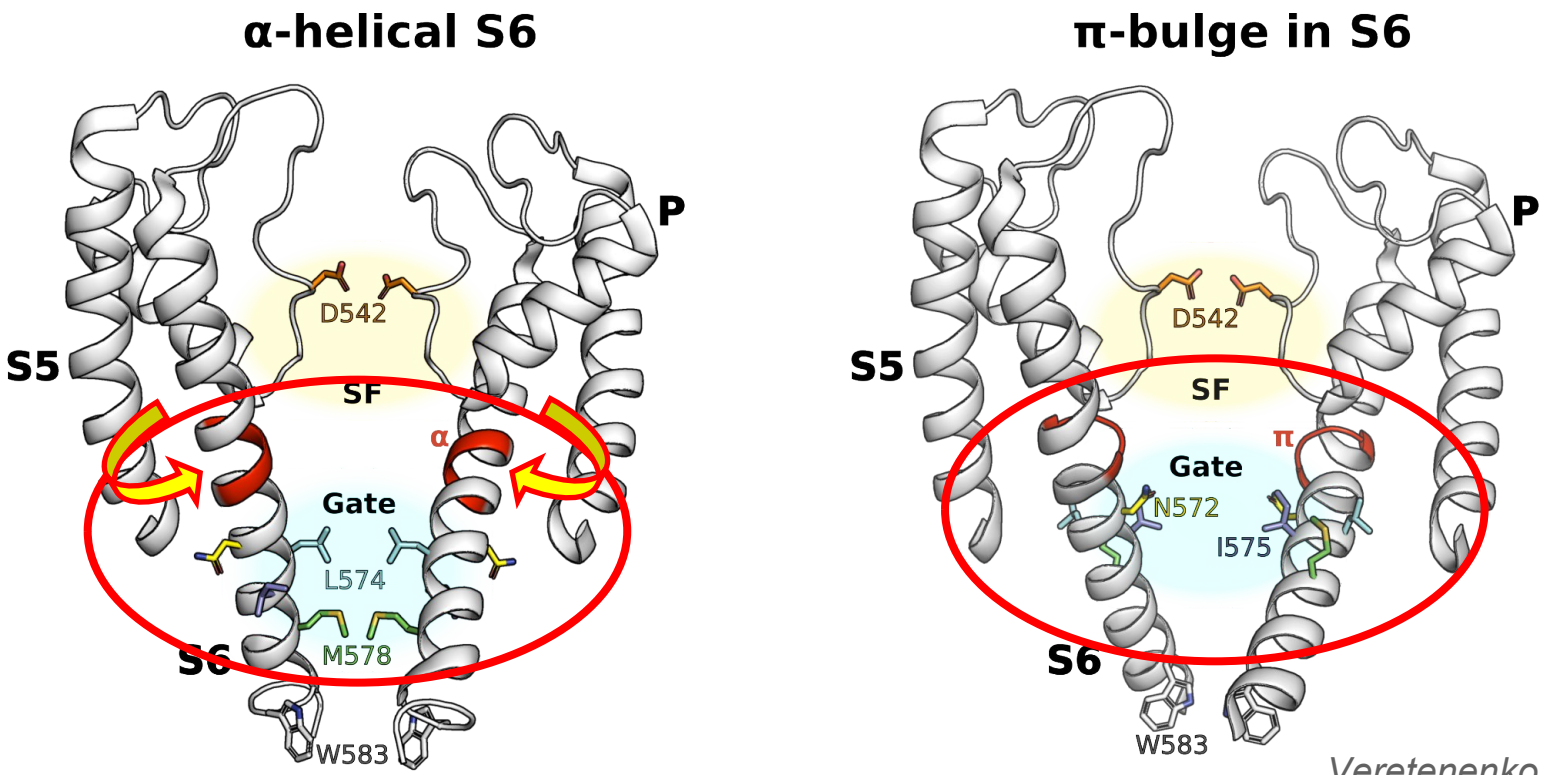






Veretenenko et al. (2026)
10.1134/S1068162026601643

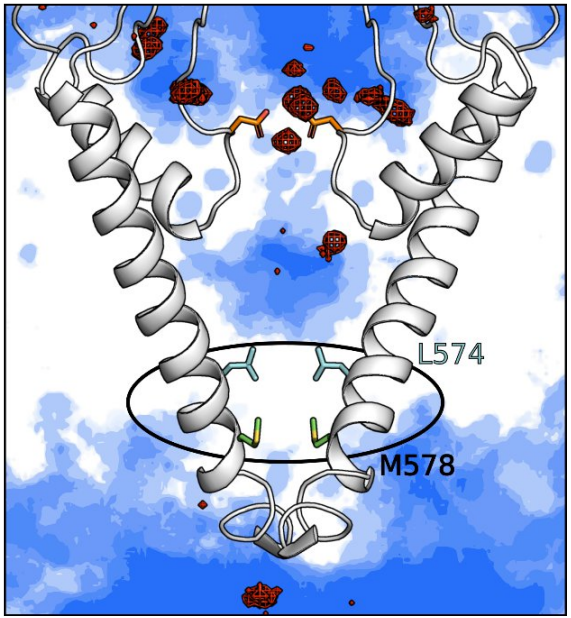
TRPV6 ion-conducting pore



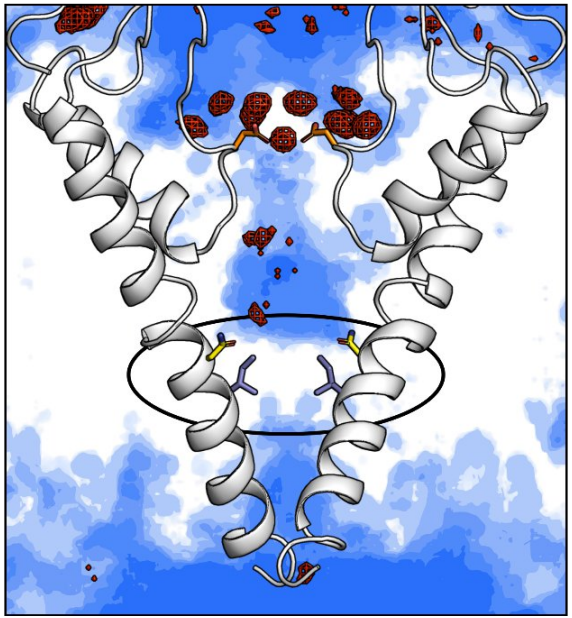
Veretenenko et al. (2026)
10.1134/S1068162026601643

TRPV ion-conducting pore states

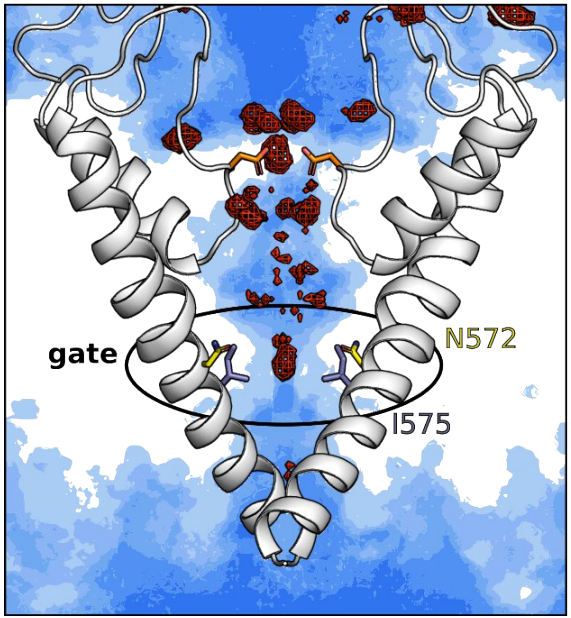
α-closed



π-closed



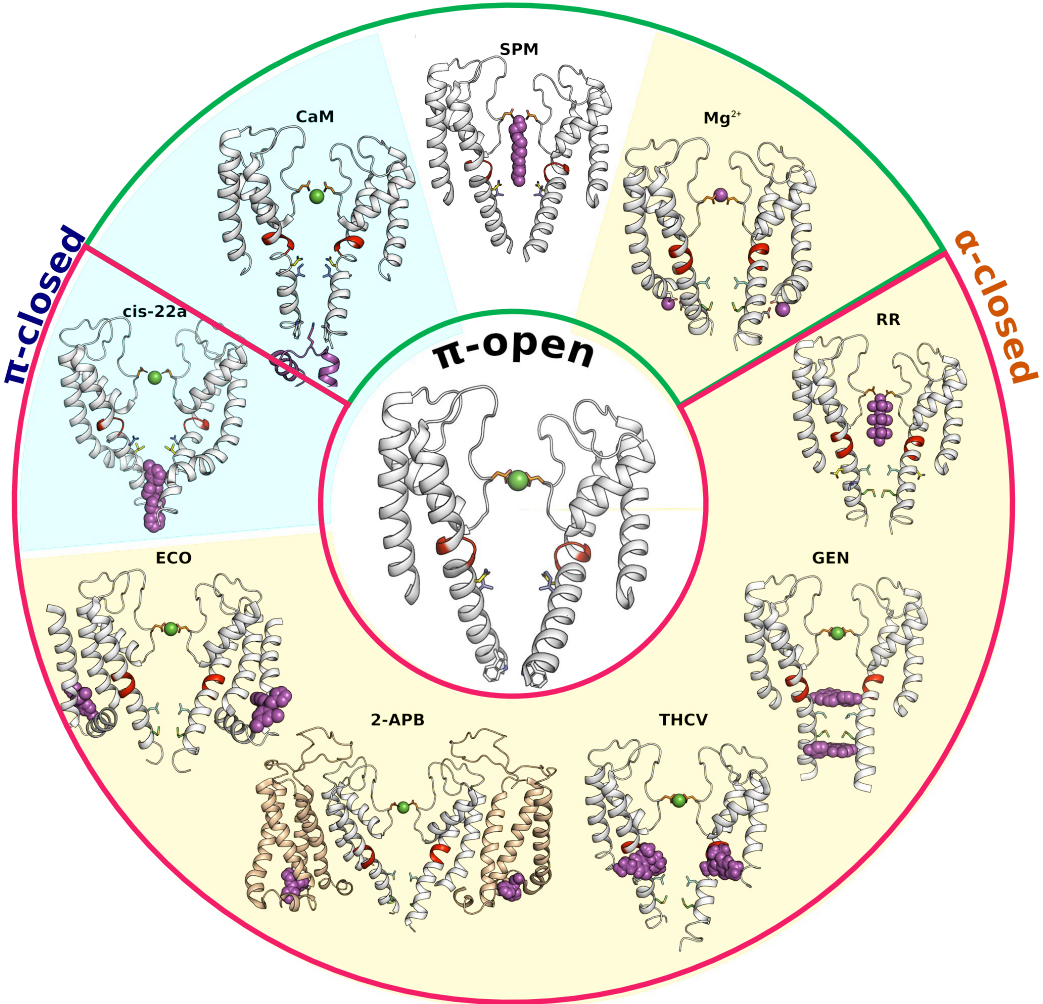
π-open



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

- Endogenous modulators
- Exogenous inhibitors

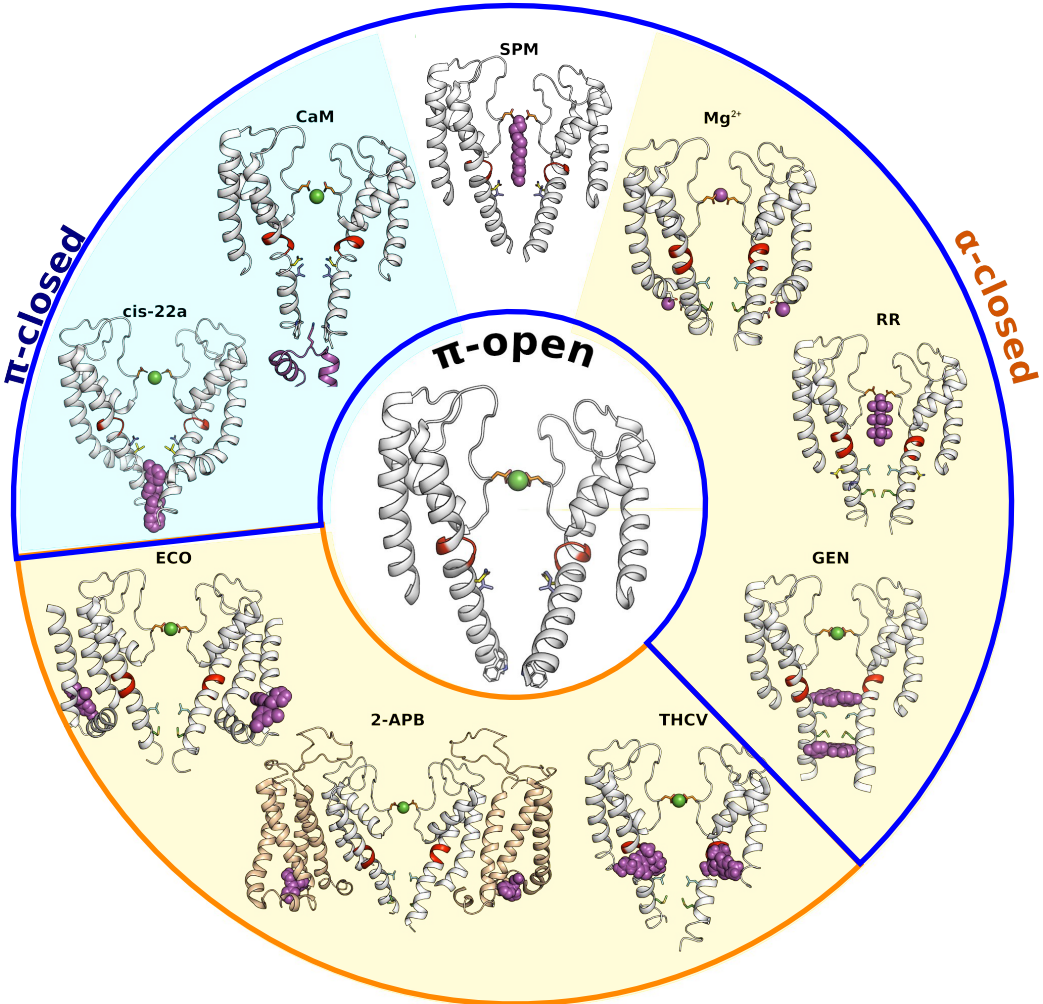
TRPV6 inhibitors



- Endogenous modulators
- Exogenous inhibitors

TRPV6 inhibitors

- Pore blockers
- Allosteric modulators

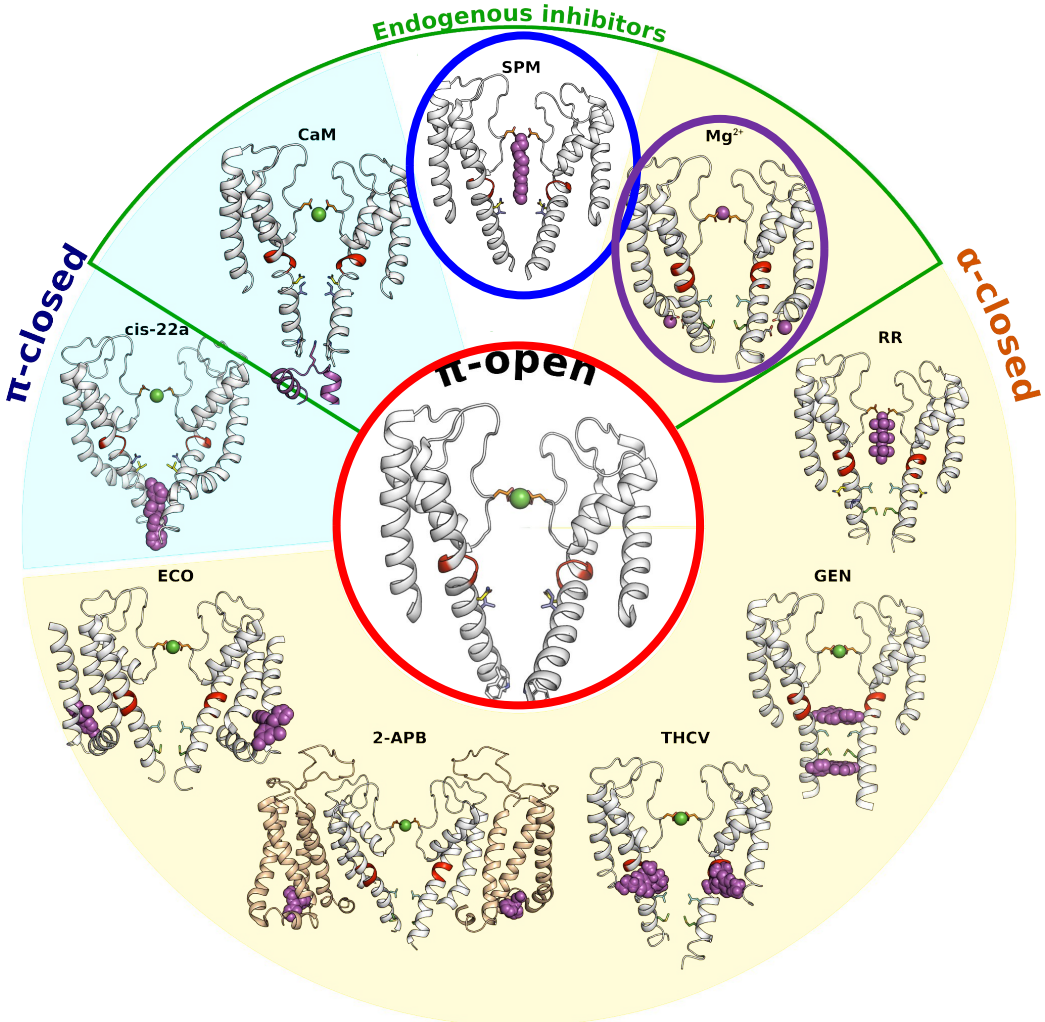


Aim of the work

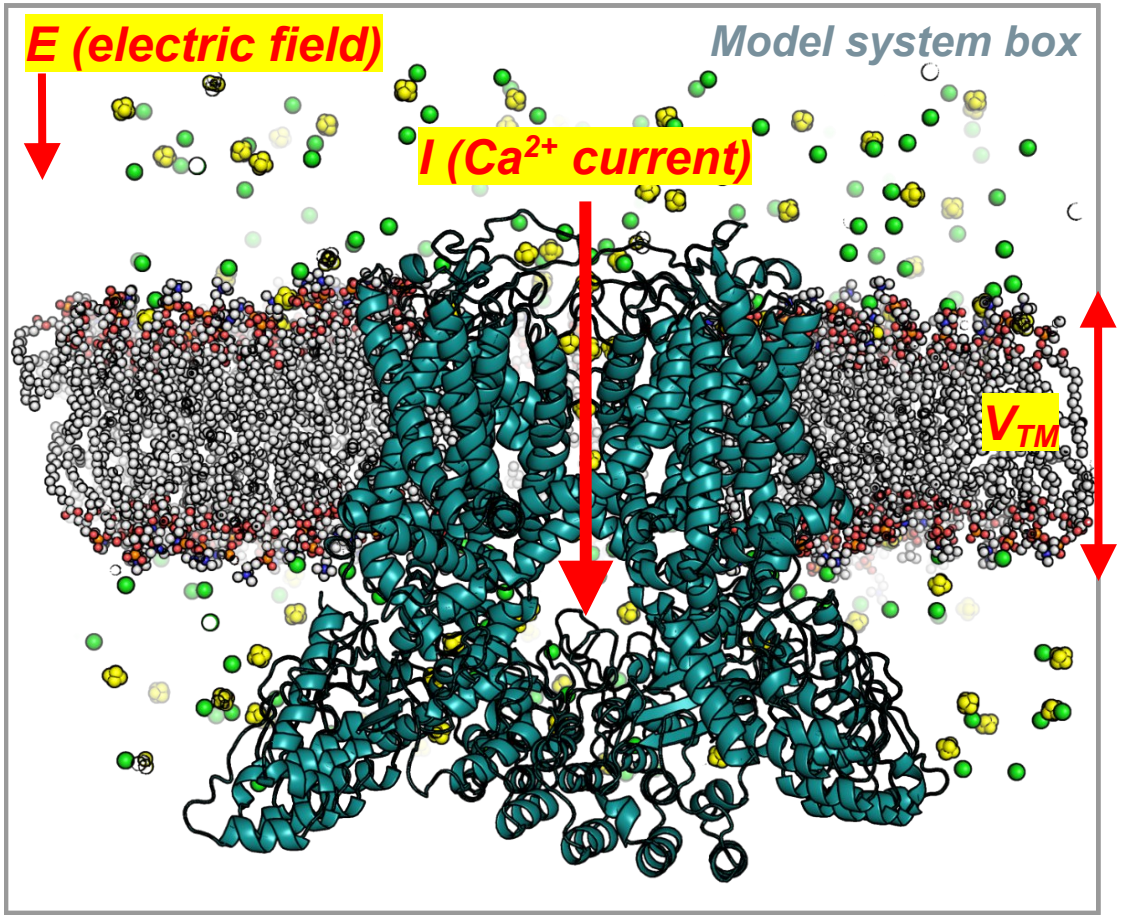
characterize *in silico* **conformational plasticity** of TRPV6 ion-conducting pore domain

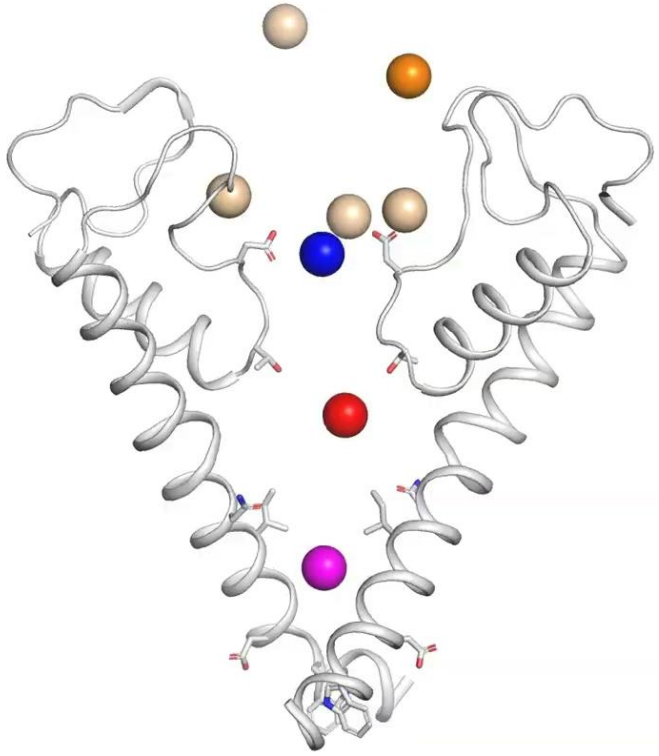
Plan

1. TRPV6 **Ca^{2+} conductivity** in π-open state
2. Endogenous modulators:
   - **Spermine** - π-open
   - **Mg^{2+}** - α-closed



MD modeling of Ca^{2+} current through TRPV6





Ca^{2+} current through hTRPV6 pore

Neuberger et al. (2025), doi: 10.1016/j.str.2024.10.018

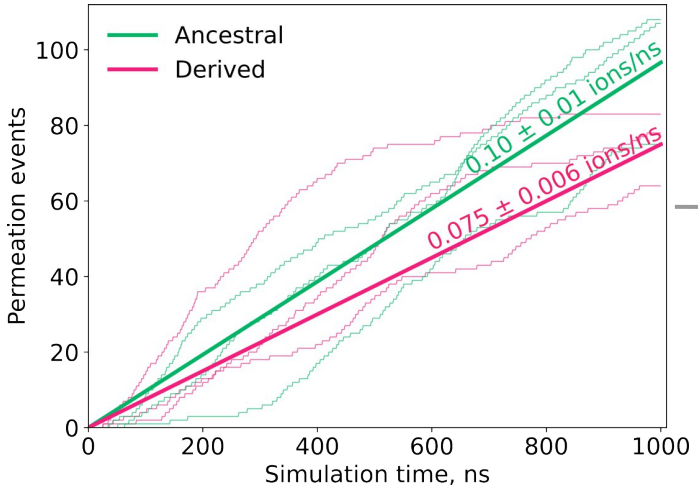
Ca^{2+} current TRPV6 of two haplotypes

Ancestral

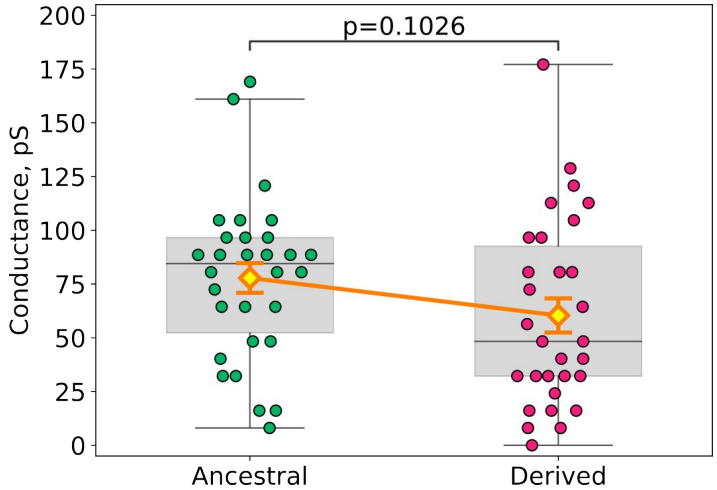
- more common in groups of African descent (50-60%)
- more frequent and aggressive form of cancers

Derived

- Non-African groups (90-99%)
- 3 substitutions from Ancestral: C157R, M378V, M681T



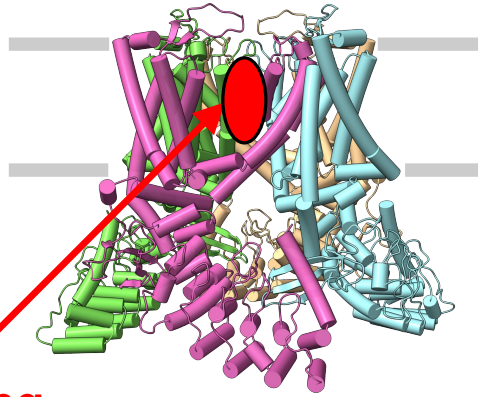
$$G = \frac{I}{V_{TM}} = \frac{Nq}{tEH_Z}$$



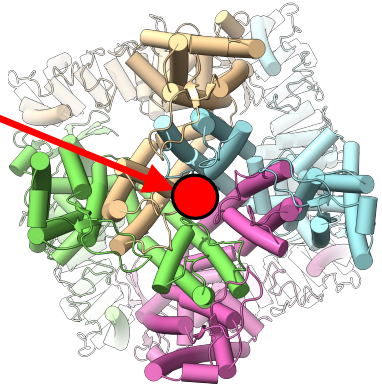
Number of Ca^{2+} permeation events, V_{TM} = -400 mV

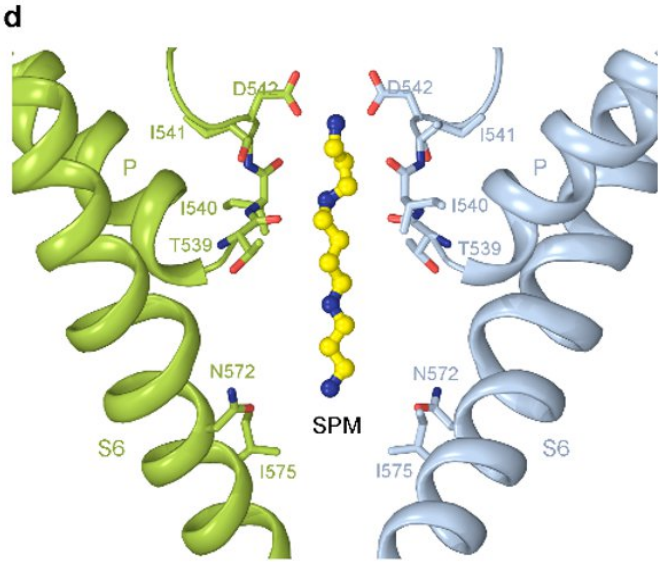
hTRPV6 conductance obtained from MD

Intracellular spermine (SPM_{in})

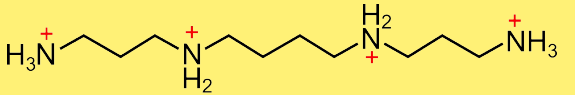


Binding site

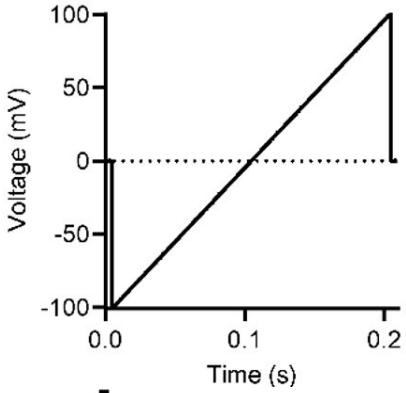


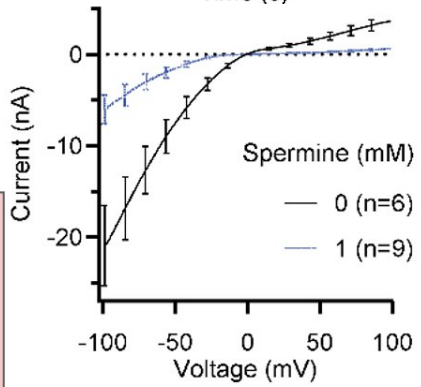


Open hTRPV6 pore blocked by SPM_{in} in the selectivity filter



$[SPM]_{in}$ = 10-100 µM

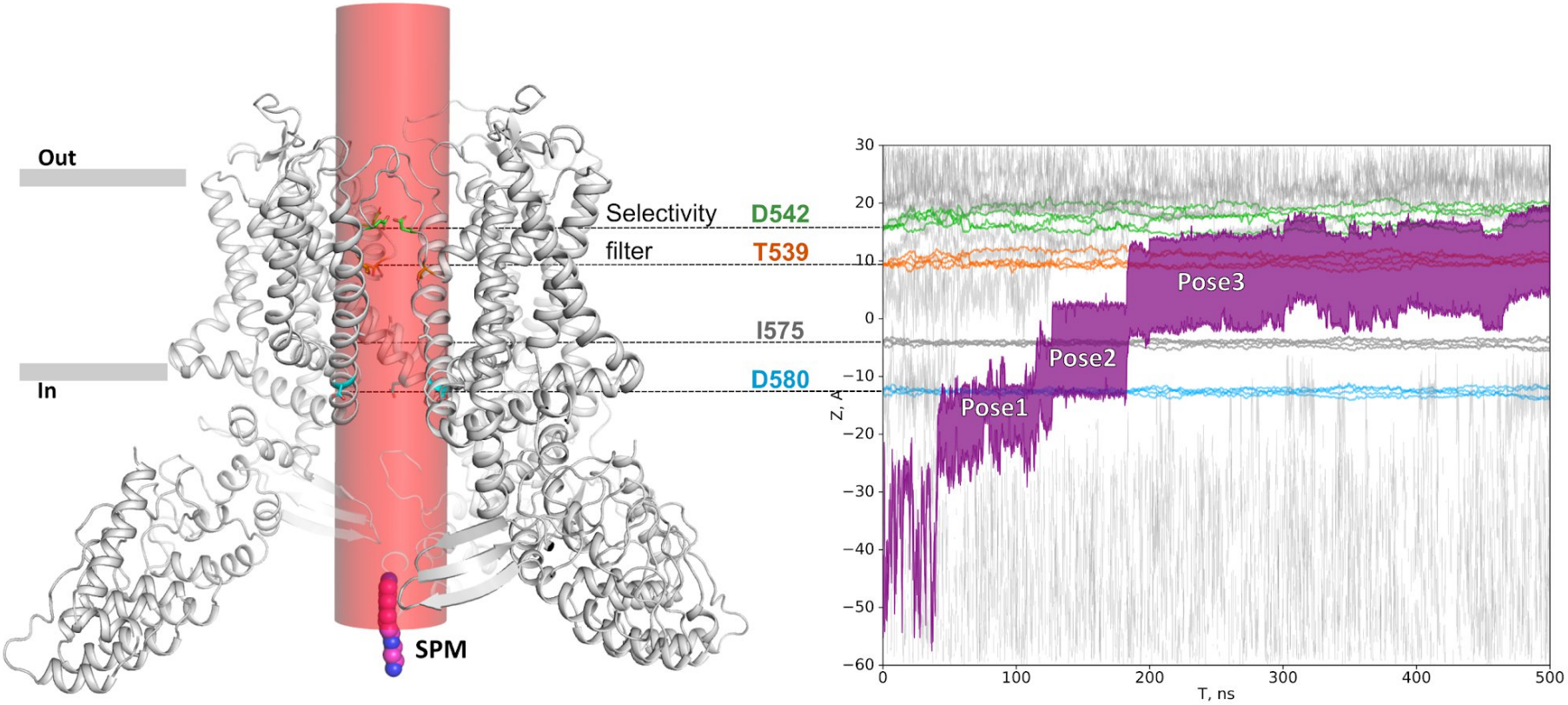




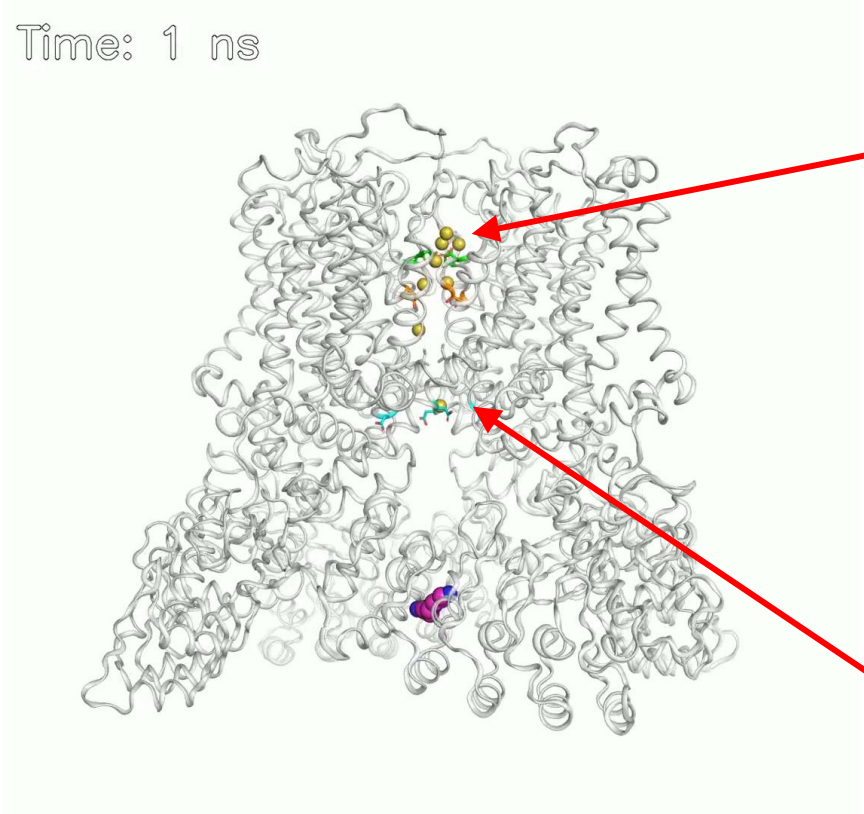
Elucidate the mechanism of hTRPV6 blockade by SPM_{in}

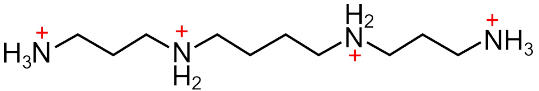
Neuberger et al. (2026), doi: 10.1038/s41467-026-73653-5

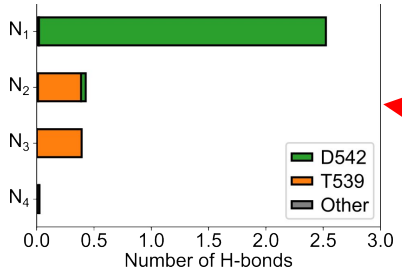
MD-simulation of SPM_{in} pore blockade



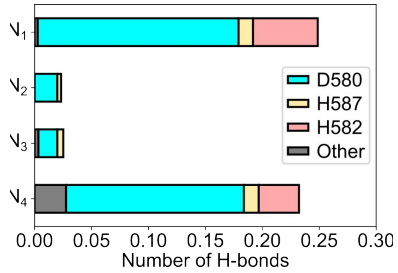
MD-simulation of SPM_{in} pore blockade

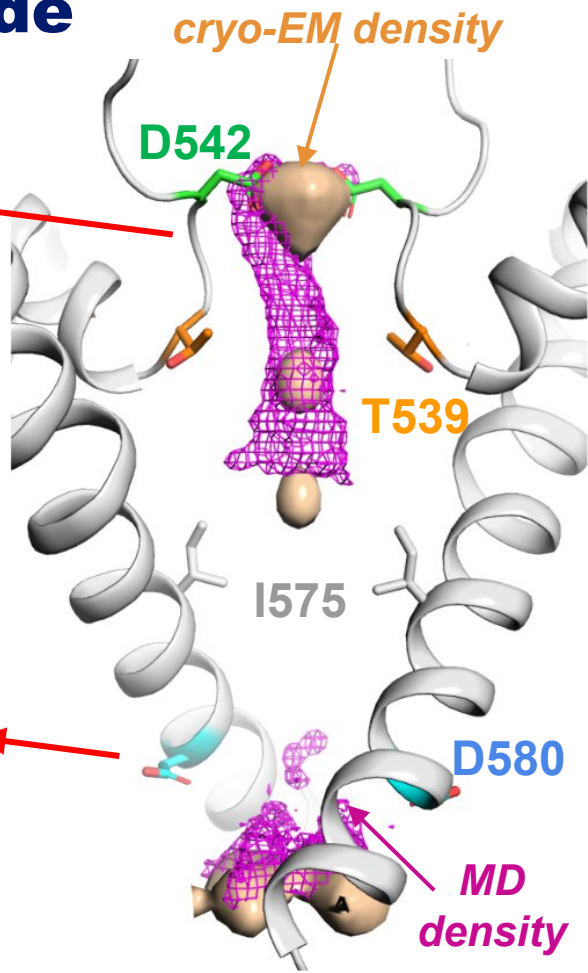




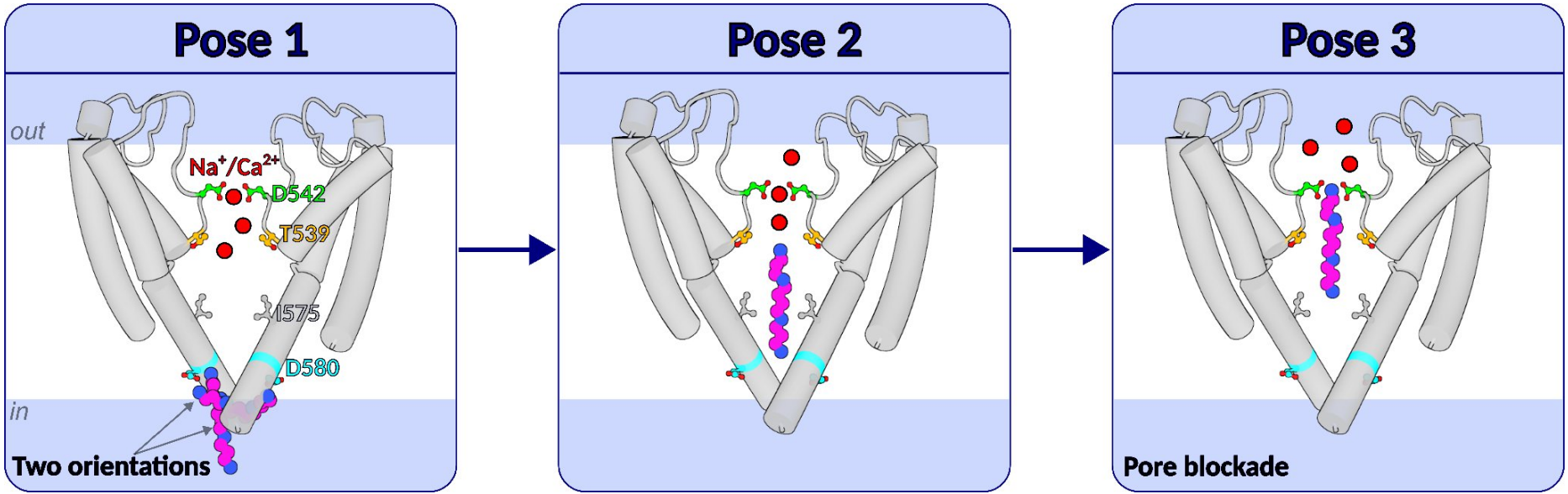


H-bonds between SPM nitrogens and TRPV6





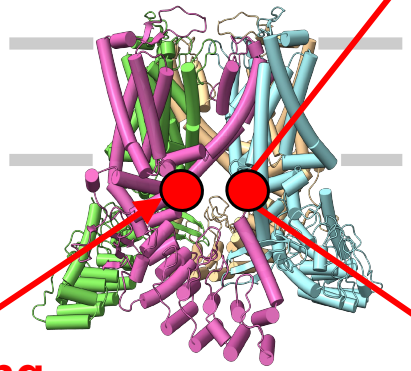
Mechanism of TRPV6 inhibition by SPM_{in}



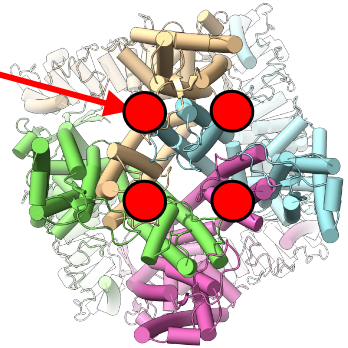
Neuberger et al. (2026), doi: 10.1038/s41467-026-73653-5

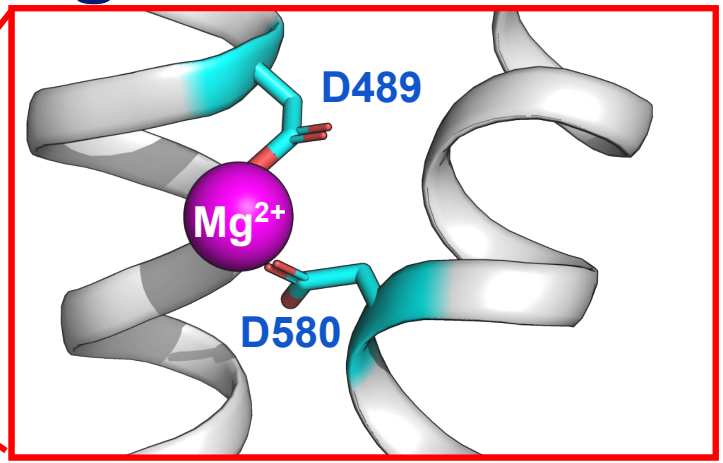
Intracellular Mg^{2+}

$[Mg^{2+}]_{in}$ ~ 1mM

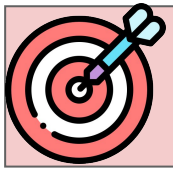


Binding sites

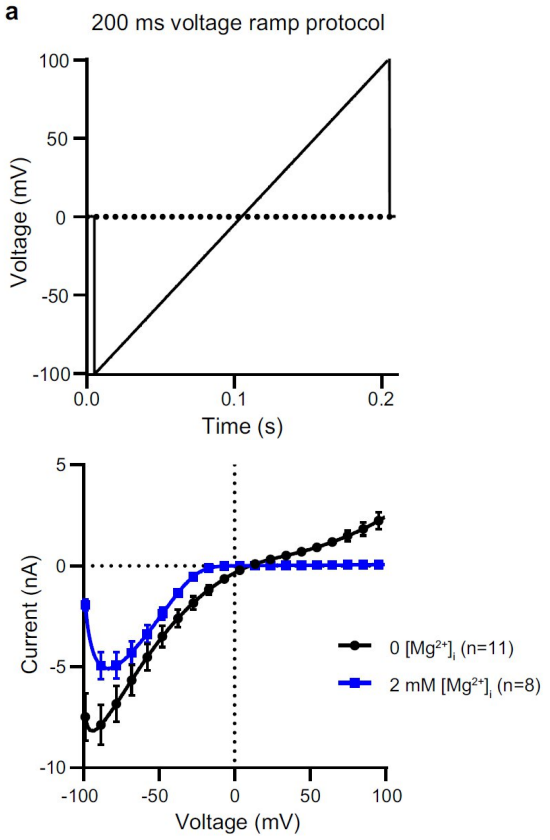




Potential Mg^{2+} binding site D489-D580



prove Mg^{2+} selectivity of D489-D580 site

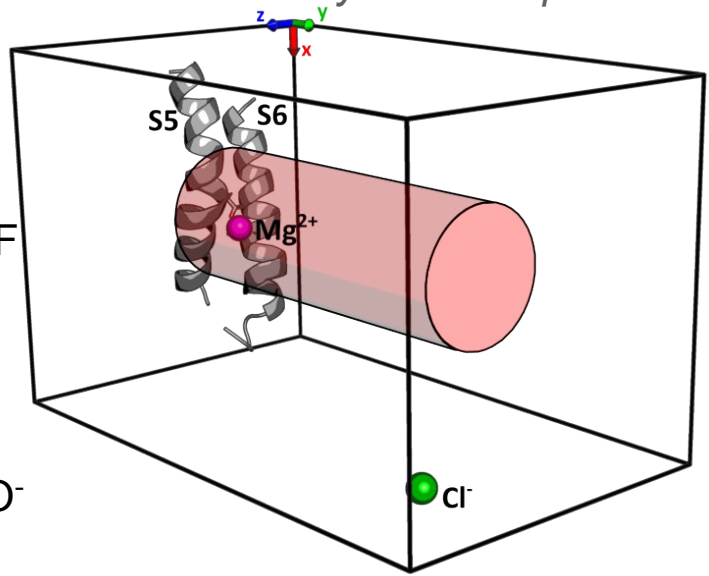


Neuberger et al. (2025), doi: 10.1038/s41467-025-65919-1

Methodology

- Model system: **D489-D580 site** with **Mg^{2+} or Ca^{2+}**
- **Electronic Continuum Correction** + Amber-99sd-ildn FF
- **Well-Tempered Metadynamics** with CVs:
  - **CN_w** - number of H_2O oxygen atoms in the 1st coordination shell of the cation;
  - **L_1, L_2** - distances between the carbon atoms of COO^- groups and the cation.

Model system composition



Verification



Acetate ion

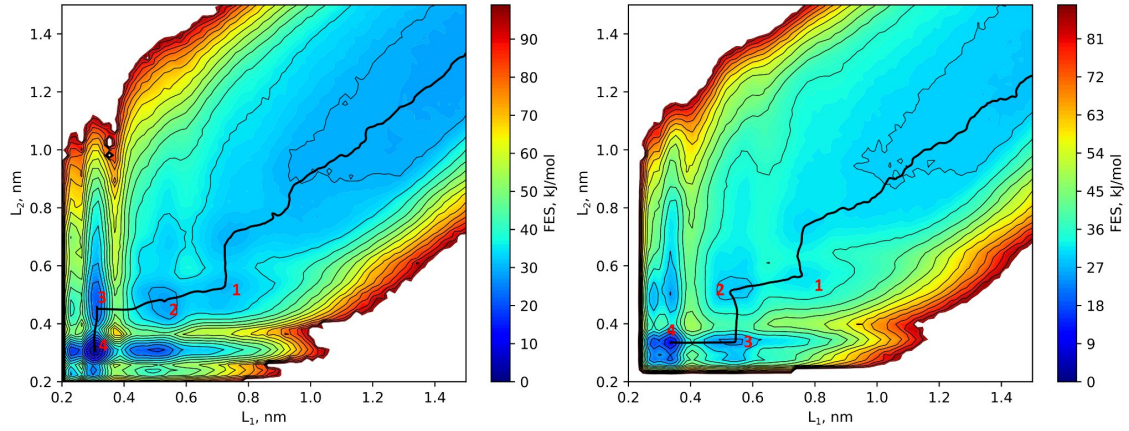
ΔG^0 (kJ/mol) CH_3COO^--cation system with different ECC scaling factors (SF)

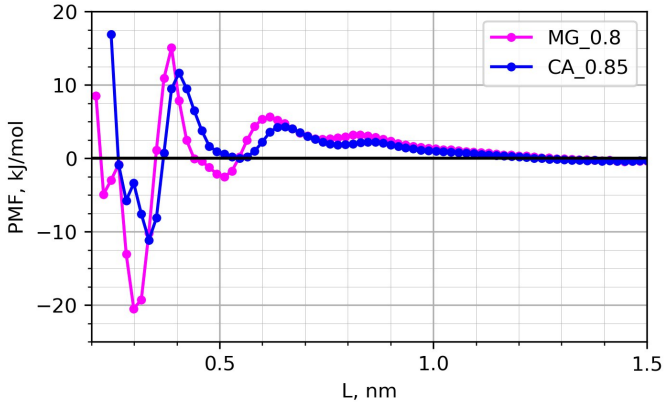
	Experiment	*SF=0.8*	*SF=0.85*	*SF=1*
Mg^{2+}	(-7.3) - (−3.4)	-3.7 ± 0.1	-	6 ± 13
Ca^{2+}	(-6.8) - (-2.5)	0.0 ± 0.4	-3.0 ± 0.2	-11.7 ± 0.1

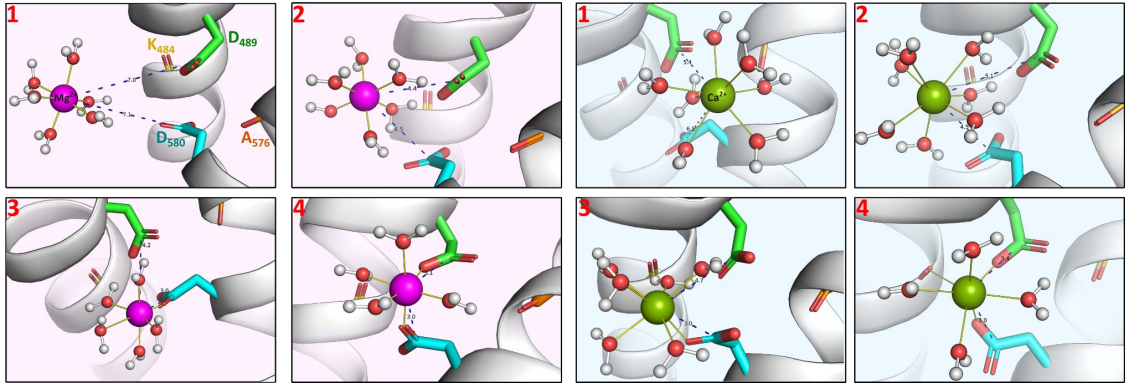
de Oliveira et al. (2020), doi: 10.1039/d0cp02987d

Modeling of Mg^{2+}/ Ca^{2+} binding to D489-D580

Mg^{2+} Ca^{2+}





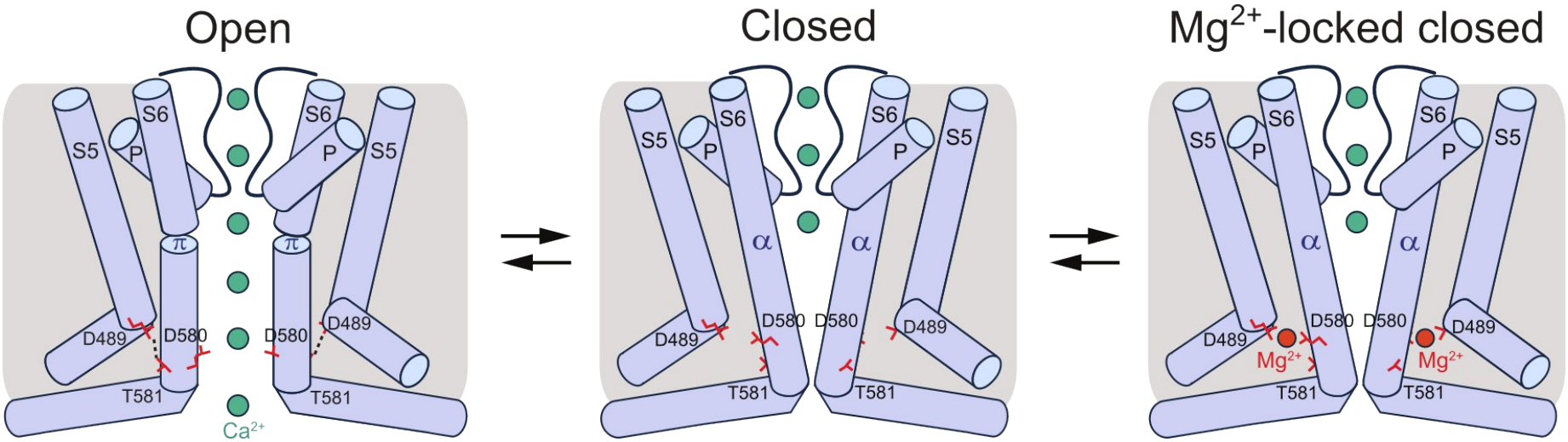


$\Delta G^0(Mg^{2+})$ = **–12.9 ± 0.4** kJ/mol

$\Delta G^0(Ca^{2+})$ = **–3.7 ± 0.6** kJ/mol

~35-fold preference for Mg^{2+}

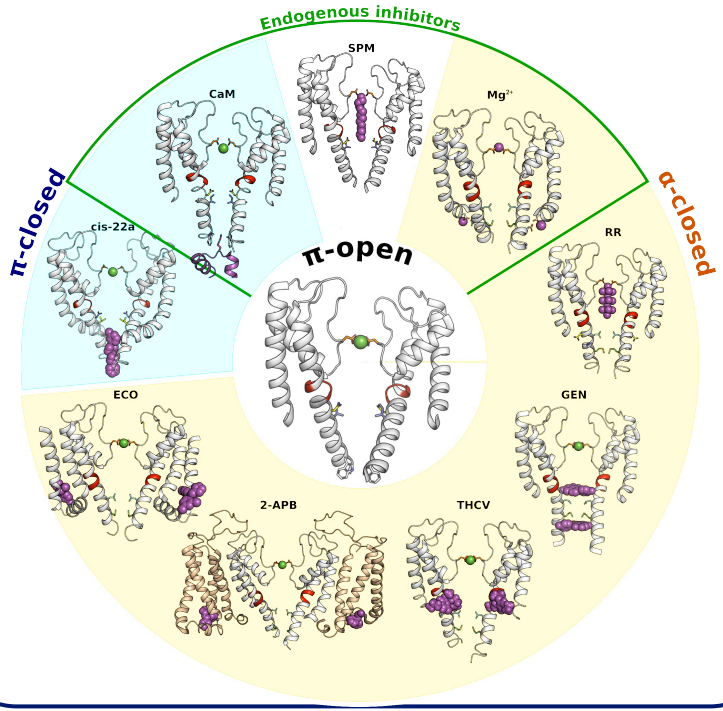
Mechanism of TRPV6 inhibition by Mg^{2+}_{in}



Neuberger et al. (2025),
doi: 10.1038/s41467-025-65919-1

Conclusion

1. Ion-conducting **pore** of **hTRPV6** reveals high **conformational plasticity**



2. MD – a **powerful tool** for studying **ligand-protein interactions**

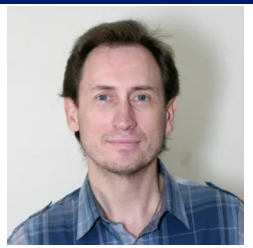
- **Classical MD-trajectories**: atomic-level binding dynamics
- **Enhanced sampling techniques**: ↑ statistics, ΔG calculations

Combining MD with **cryo-EM** and **electrophysiology** opens new possibilities for the **rational design** of **selective TRPV6 inhibitors**

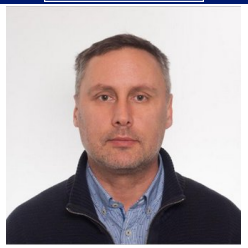
Thank you for your attention!



Roman Efremov



Alexander Sobolevsky



Vladimir Chubanov

Structure

CellPress

Article

Structure-function analyses of human TRPV6 ancestral and derived haplotypes

Arthur Neuberger,[1] Alexey Shalygin,[2] Yury A. Trofimov,[3] Irina I. Veretenenko,[3] Kirill D. Nadezhdin,[1] Nikolay A. Krylov,[3] Thomas Gudermann,[2,4] Roman G. Efremov,[3,5] Vladimir Chubanov,[2] and Alexander I. Sobolevsky[1,6,*]

nature communications

Article

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The locking mechanism of human TRPV6 inhibition by intracellular magnesium

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Arthur Neuberger[1,7], Alexey Shalygin[2,7], Irina I. Veretenenko[3,7], Yury A. Trofimov[3,4], Thomas Gudermann[2,5], Vladimir Chubanov[2] ✉, Roman G. Efremov[3,4,6] ✉ & Alexander I. Sobolevsky[1] ✉

nature communications

Article

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Open-channel block of human TRPV6 by polyamine spermine

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Arthur Neuberger[1,7], Irina I. Veretenenko[2,3,7], Alexey Shalygin[4,7], Yury A. Trofimov[2,5], Thomas Gudermann[4,5], Vladimir Chubanov[4], Roman G. Efremov[2,3,6] ✉ & Alexander I. Sobolevsky[1] ✉

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A REVIEW

Ligand-Mediated Conformational Plasticity of the Pore Domain of TRPV6 Ion Channel

I. I. Veretenenko[a,b,c], V. V. Vantsev[a,b], Y. A. Trofimov[a,c], and R. G. Efremov[a,b,c,d,*]