MAGNESIUM BINDING TO TRPV6 ION CHANNEL: INSIGHTS FROM MOLECULAR MODELING

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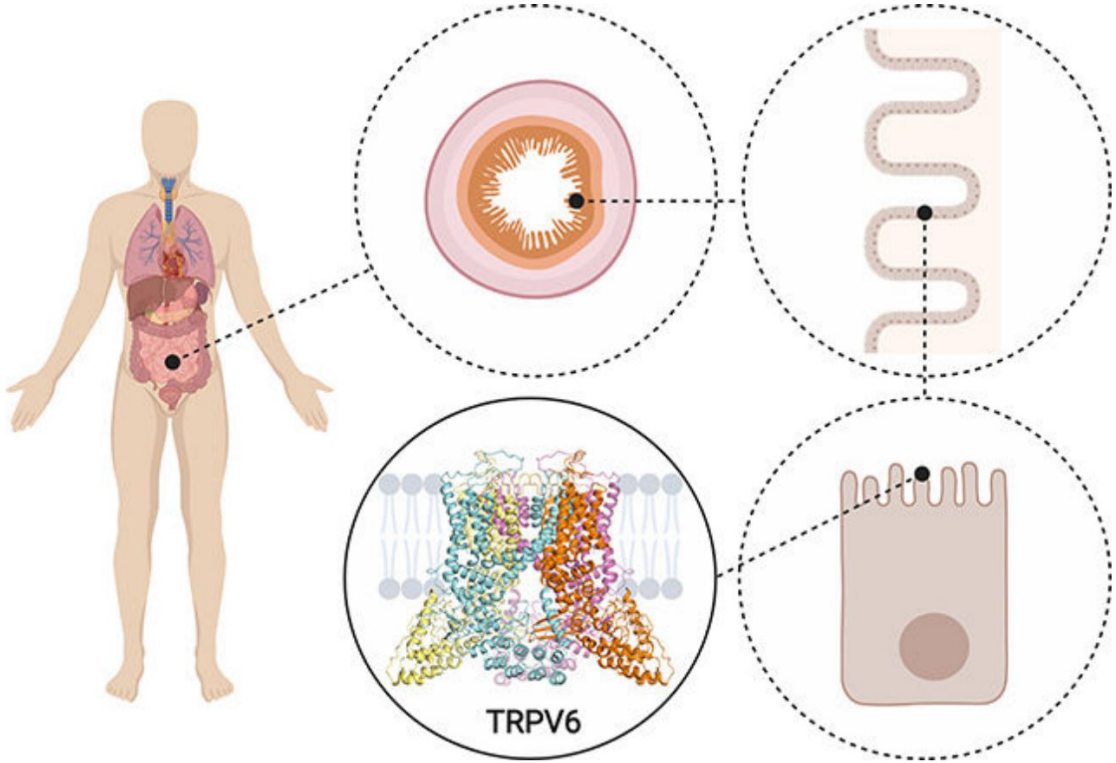
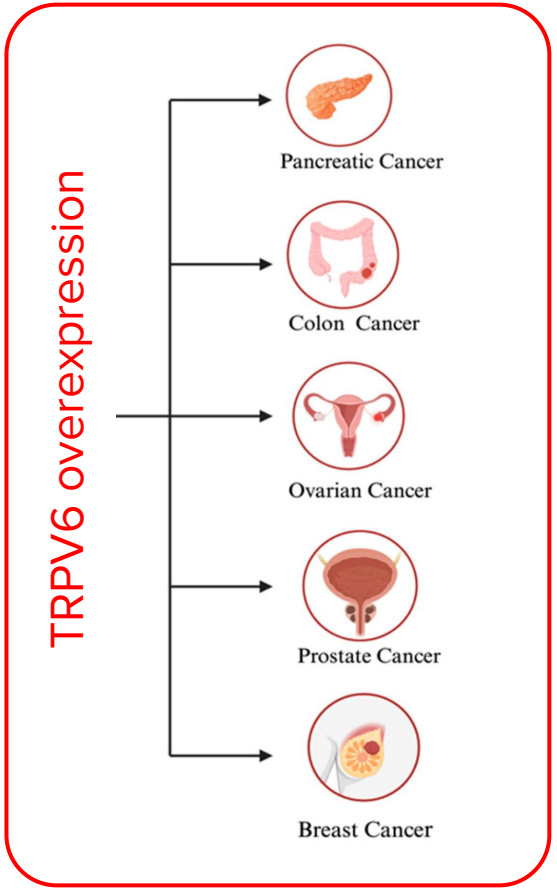
BCADD, 21st October 2025

TRPV6 ion channel

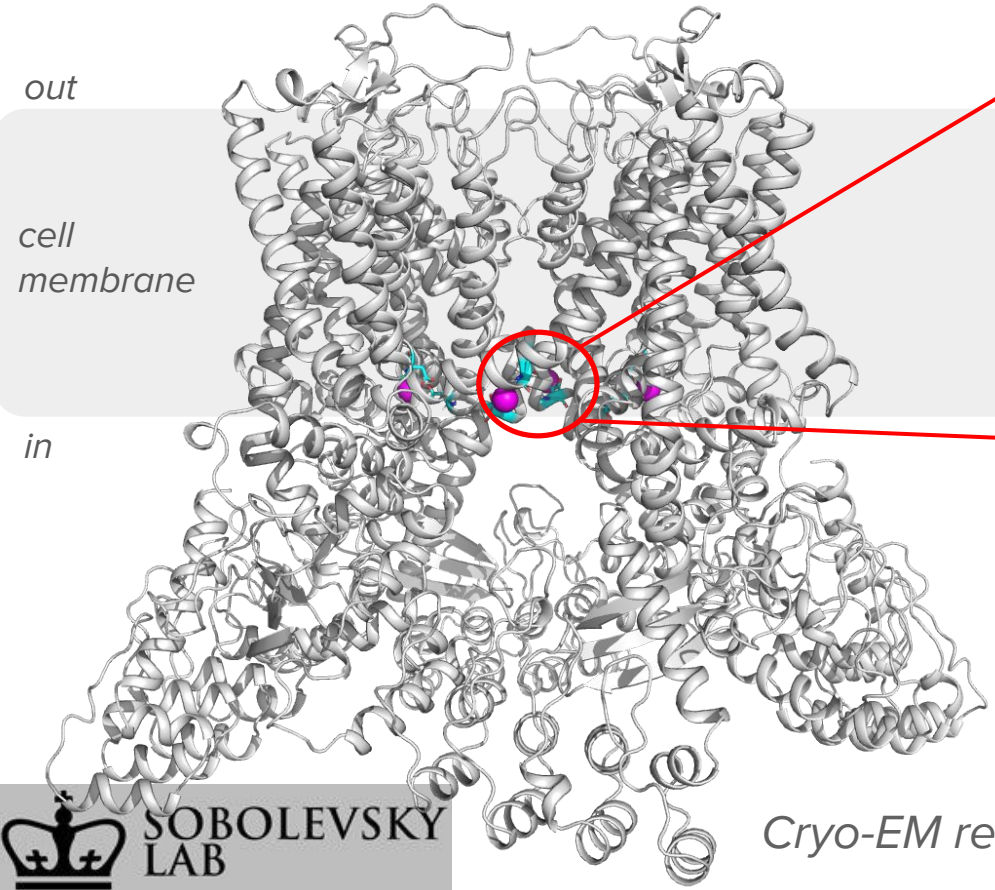




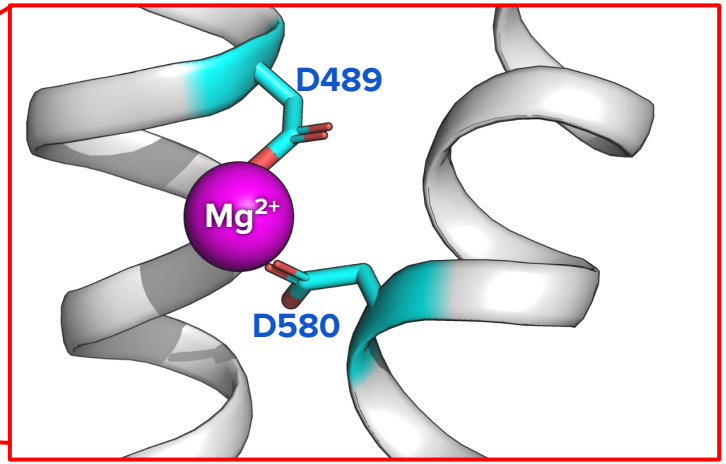
(Yelshanskaya et al, 2021)

(Wang et al, 2024)

Problem statement



potential Mg^{2+} ion binding site



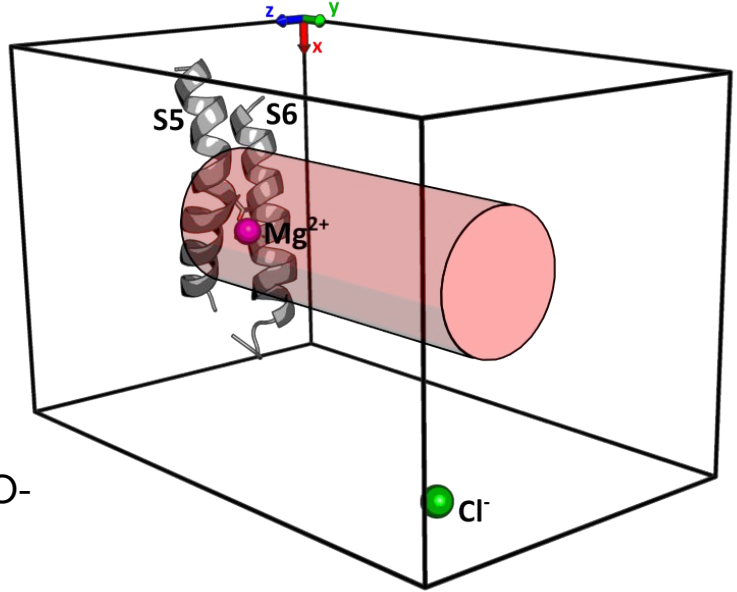
prove Mg^{2+} selectivity of D489-D580 site

Cryo-EM reconstruction of closed TRPV6

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

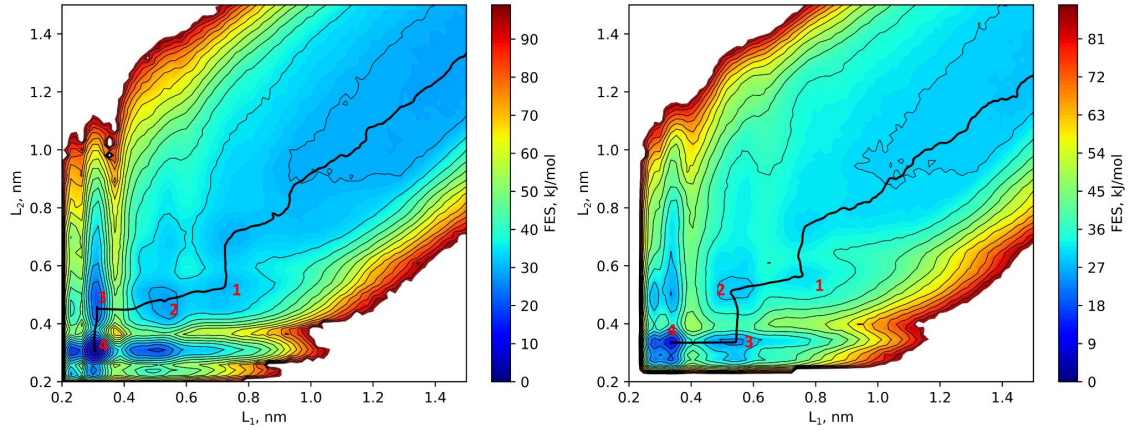
Acetate ion

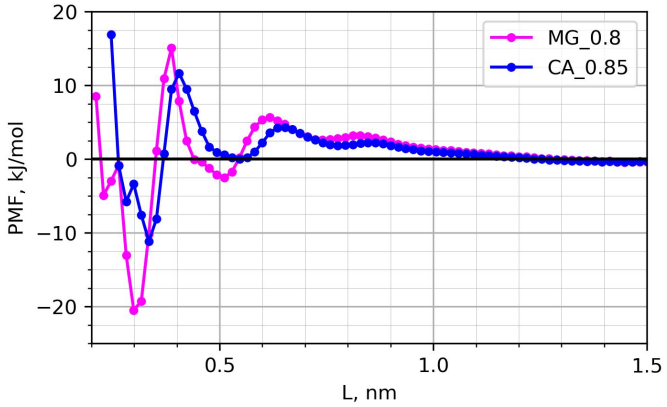
ΔG^0 (kJ/mol) CH_3COO^--cation system with different ECC scaling factors (SF)

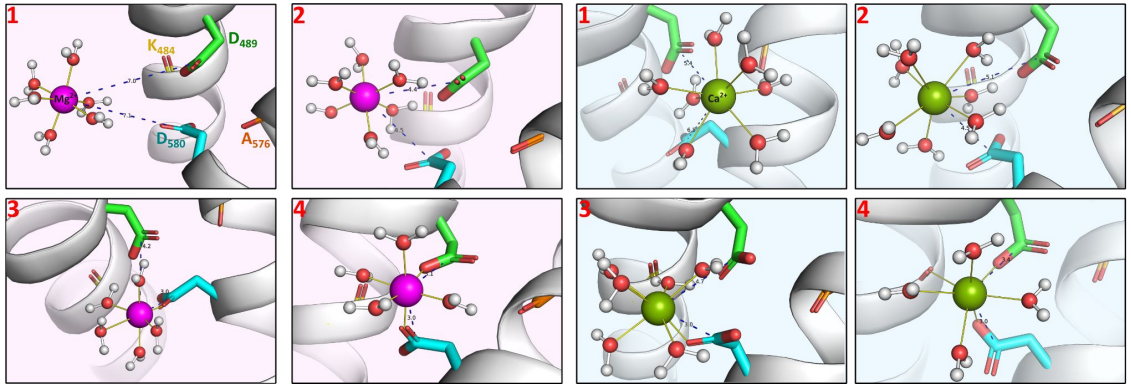
	Experiment	*SF=0.8*	*SF=0.85*	*SF=1*
Mg^{2+}	(-7.3) - (−3.4)	-3.7 ± 0.1	-	6 ± 13
Ca^{2+}	(-6.8) - (-2.5)	0.0 ± 0.4	-3.0 ± 0.2	-11.7 ± 0.1

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

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







$\Delta G^0(Mg^{2+}) = -\mathbf{12.9 \pm 0.4}$ kJ/mol

$\Delta G^0(Ca^{2+}) = -\mathbf{3.7 \pm 0.6}$ kJ/mol

~35 times preferability of Mg^{2+}

Conclusion

The **developed protocol** for calculating binding free energy (ΔG^0) at ion-binding sites was **validated using experimental** CH_3COO^- data.

A **novel** intracellular site **(D489-D580)** in TRPV6 shows **high selectivity for Mg^{2+}**

These results **aligns** with the findings from **cryo-electron microscopy** and **electrophysiology** studies

Proposed mechanism:
intracellular Mg^{2+} binding to D489-D580 site stabilizes TRPV6 in a closed state

Significance:
The obtained results open new avenues for developing therapies targeting TRPV6-associated diseases, including cancers.

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This study was supported by RSF grant N°23-14-00313

Thank you for attention!

Neuberger, A., Shalygin, A., Veretenenko, I. et al.
The locking mechanism of human TRPV6 inhibition by intracellular magnesium.
Nat Commun (in press)