University of Debrecen
Medical and Health Science Center
Department of Biophysics and Cell Biology
Research Centre for Molecular Medicine

Regulation of Kv1.3 activity in human T lymphocytes: peptide blockers and molecular interactions

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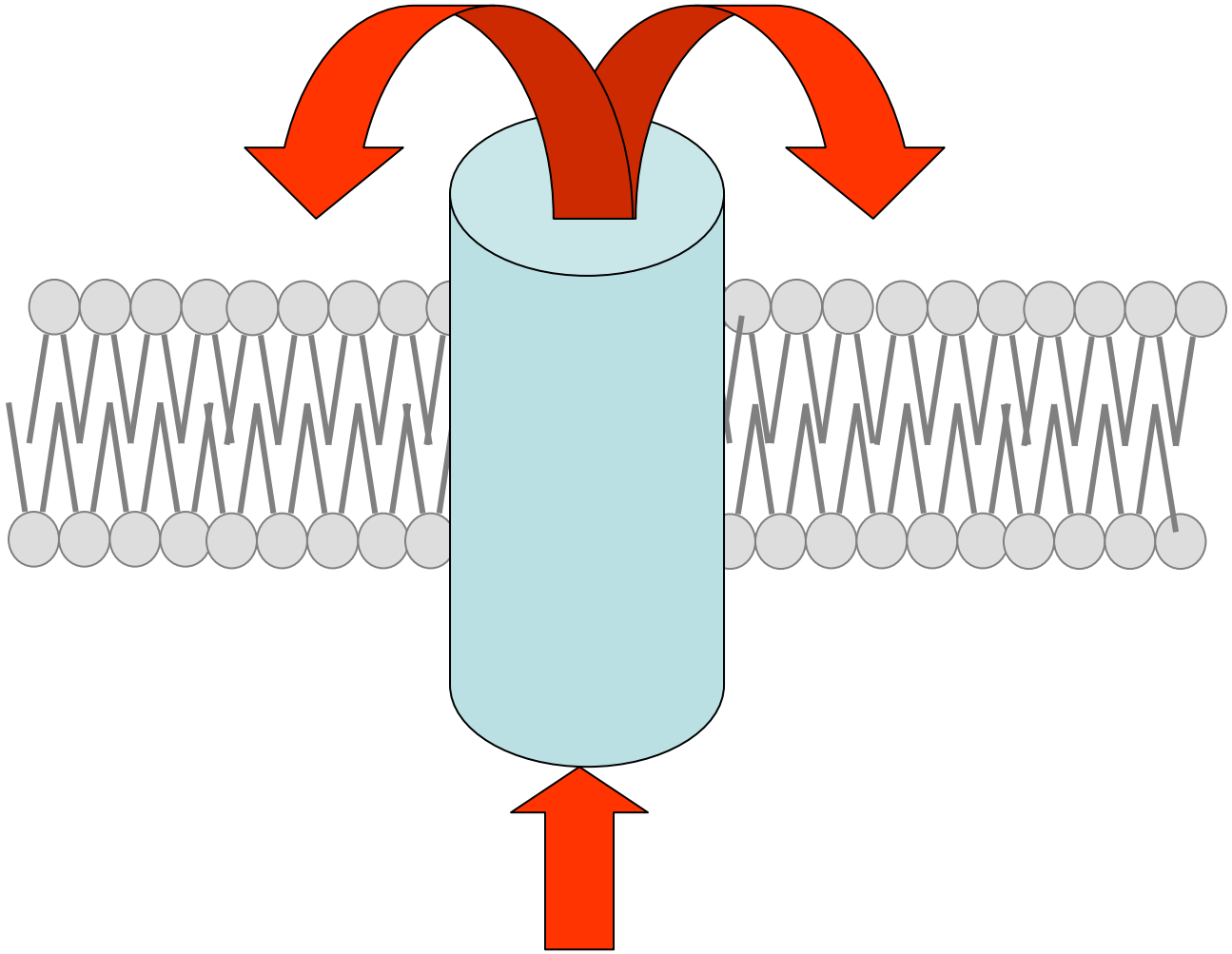
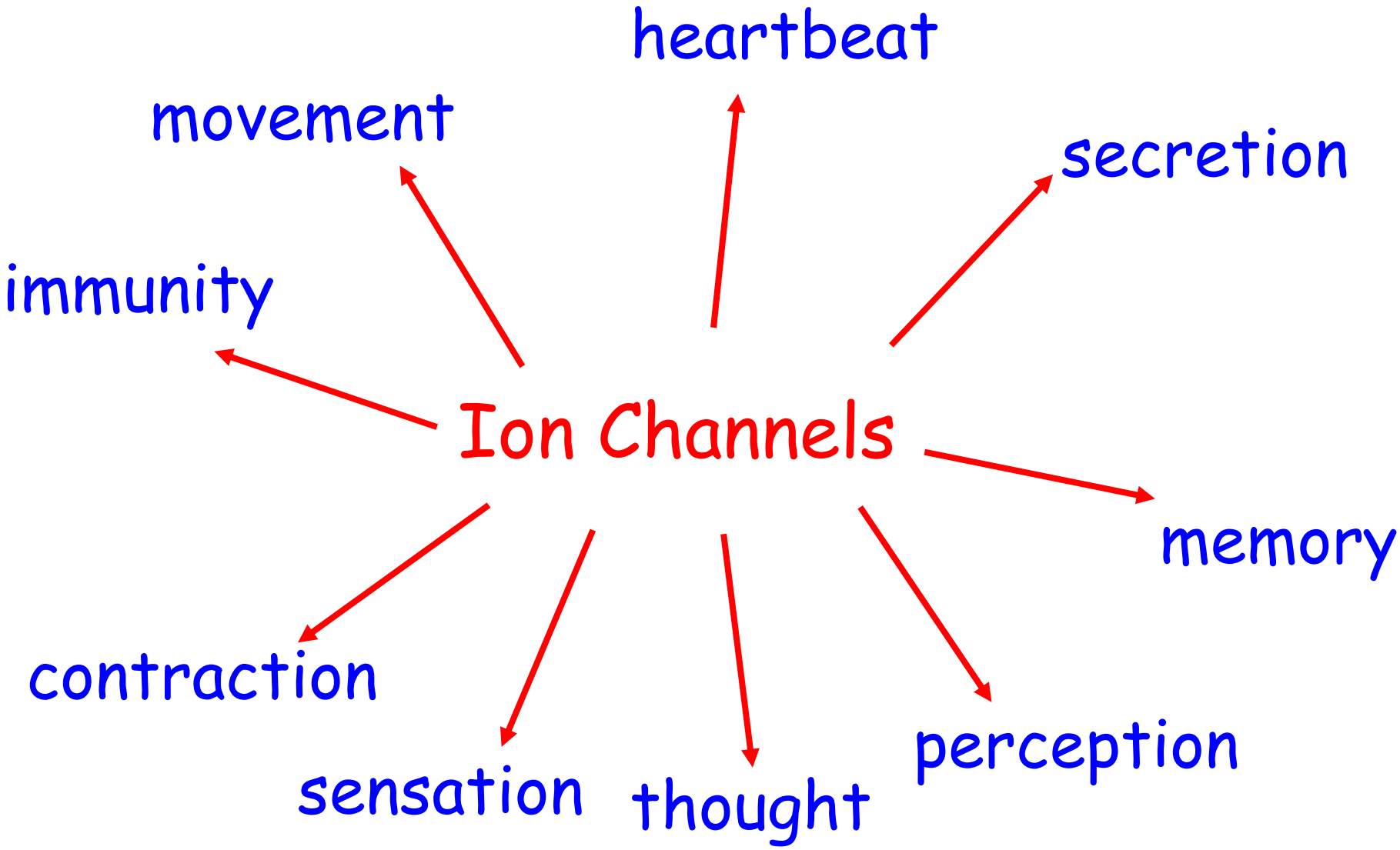
August 27, 2005, Montpellier

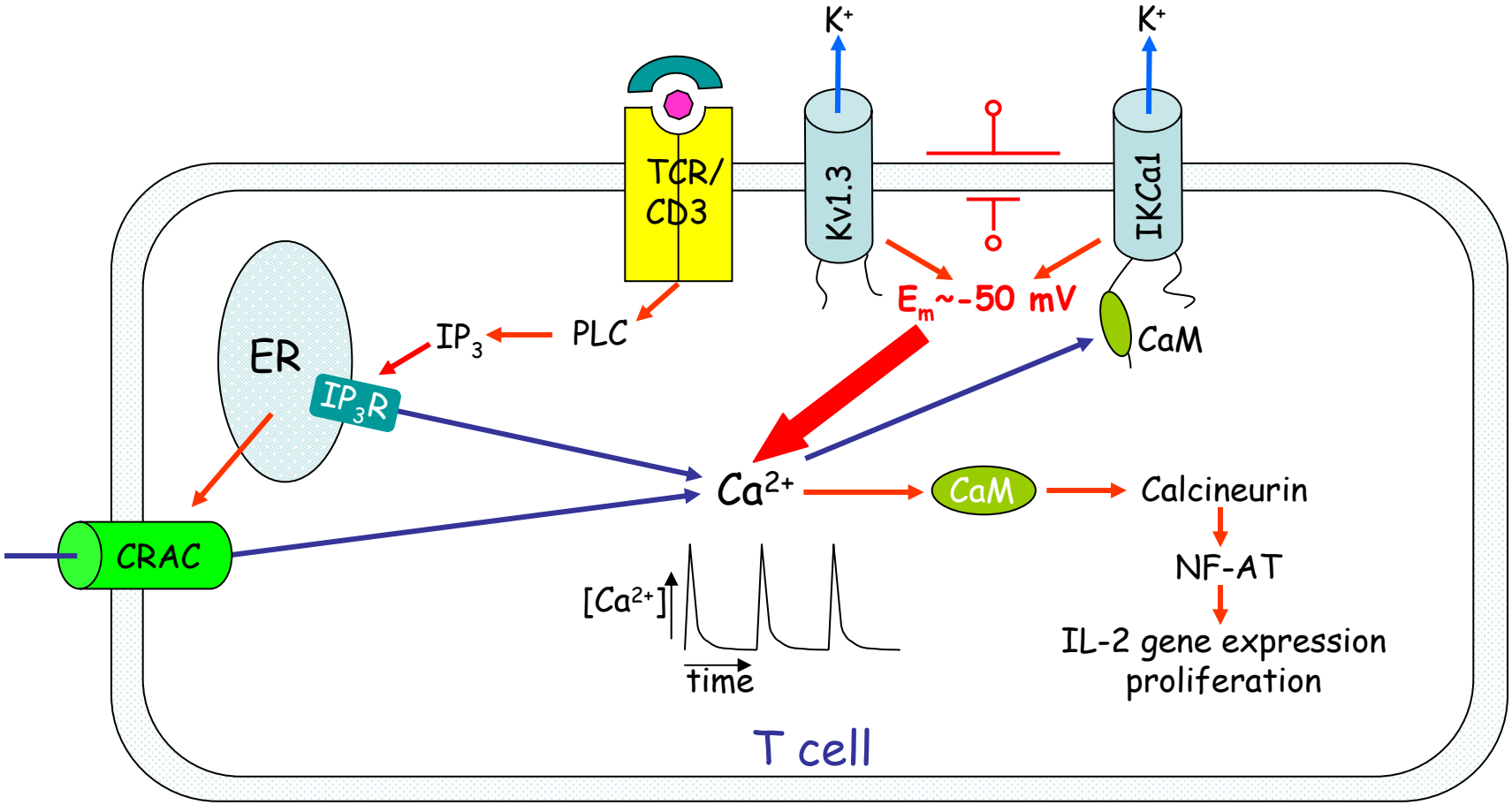
Simple view of an ion channel:

a hydrophilic pore allowing very rapid ion movement across the membrane (10^8 /s)



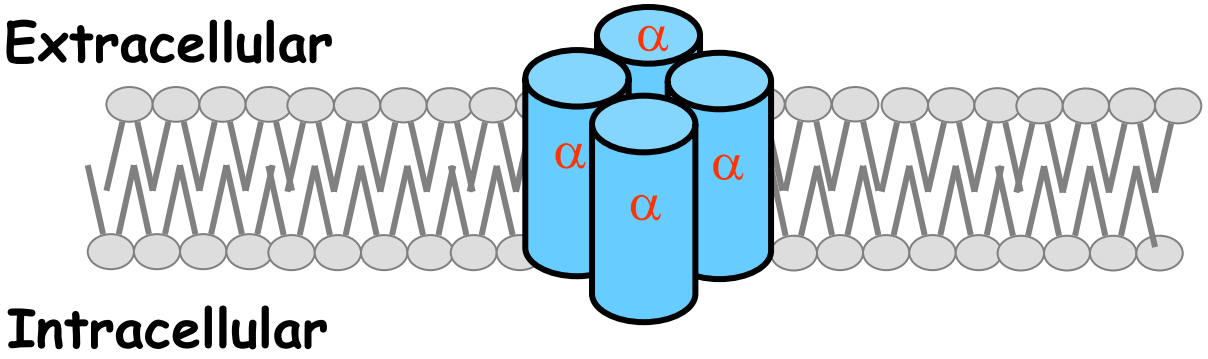

heartbeat
movement
secretion
immunity
Ion Channels
memory
contraction
sensation
thought
perception

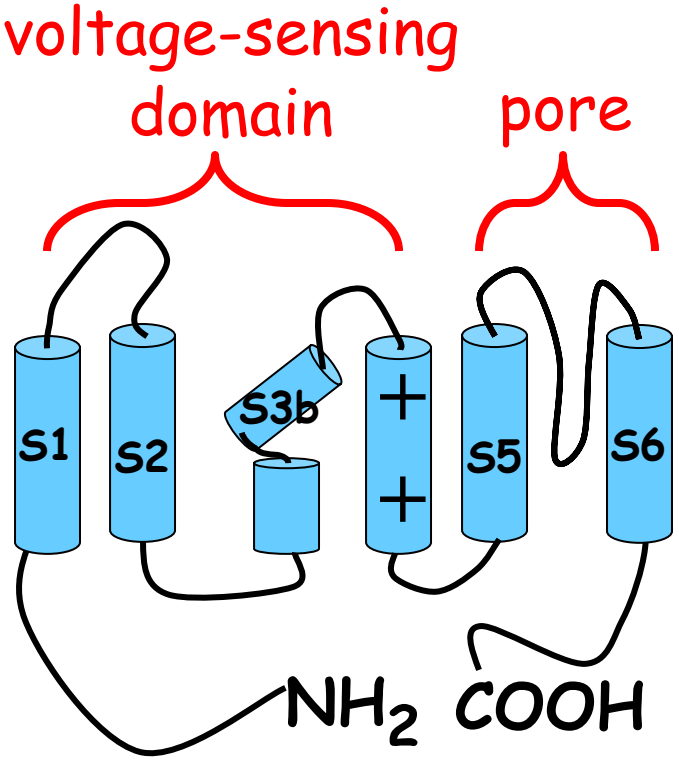
How do ion channels regulate the immune functions?



Panyi et al., Trends Immunol., 2004, 25: 565-569; Panyi et al., Imm. Lett., 2004, 92:55-66.

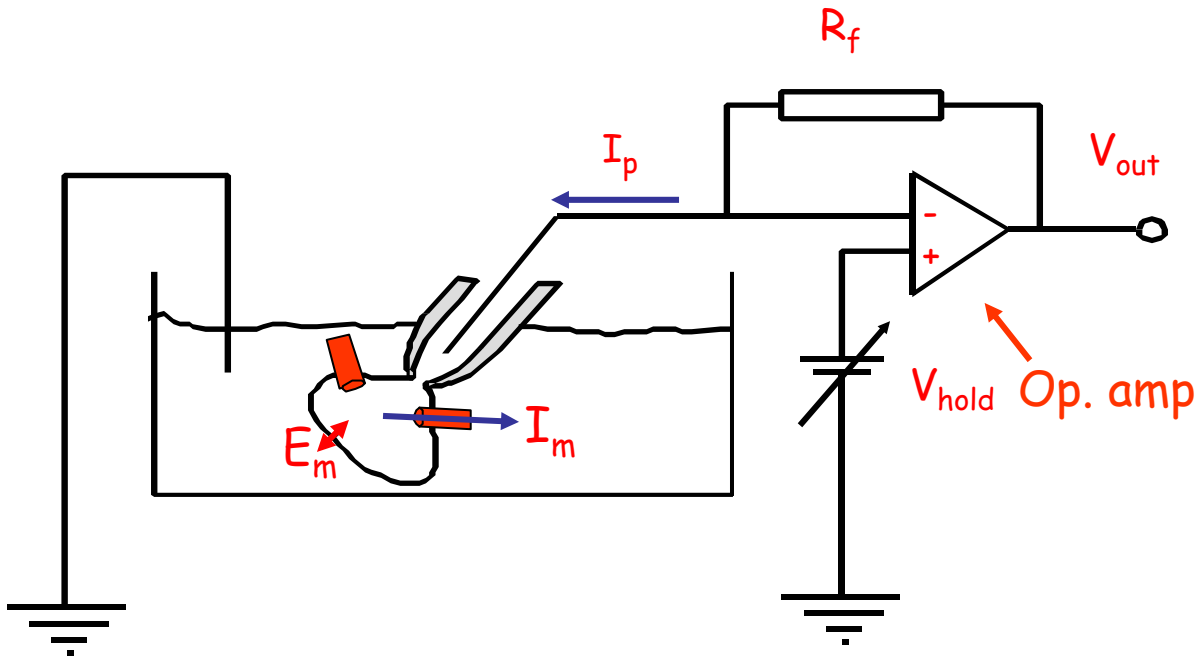
Ion channels are oligomeric transmembrane proteins

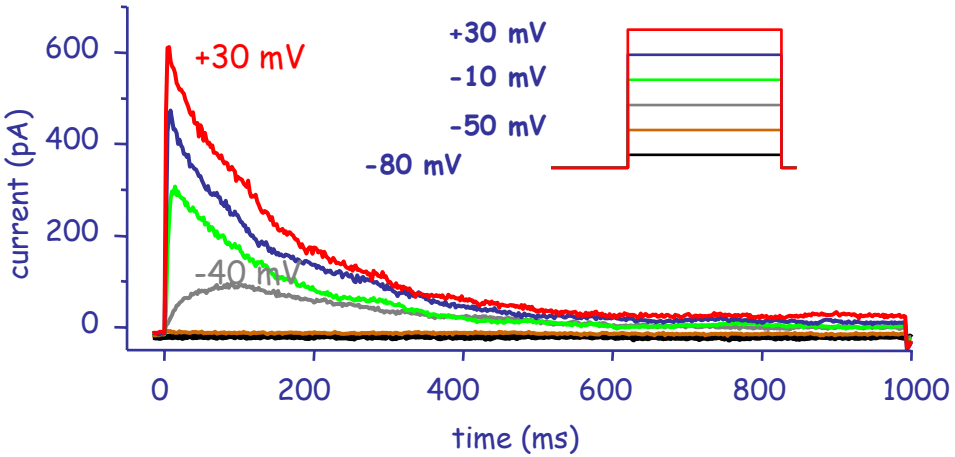




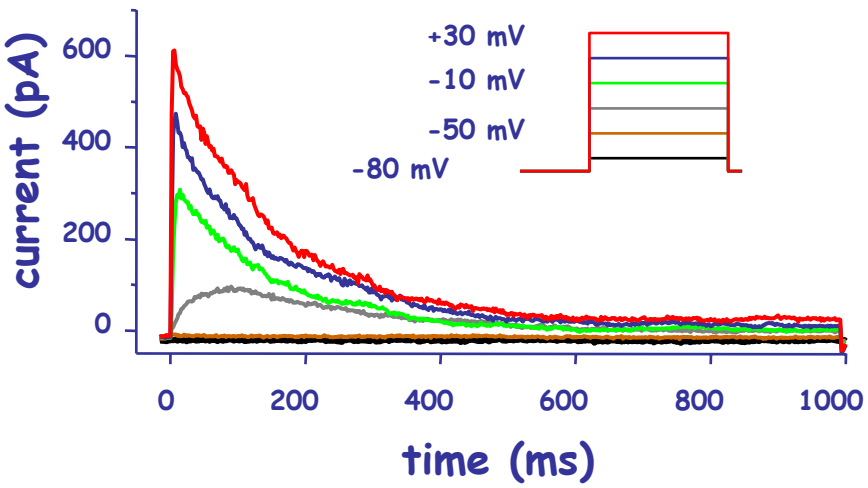
How do we study the channels?

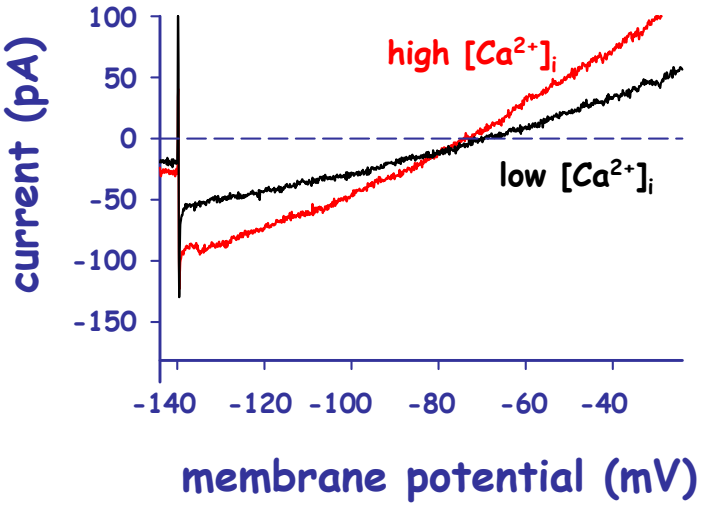
By measuring ionic currents using the patch-clamp technique





How do K^+ channels of T cells compare?





	Kv1.3	IKCa1
Gating:	voltage-gated	Ca^{2+}-activated
Single channel conductance	similar (~10 pS)	similar (~10 pS)
Selectivity	K^+ selective	K^+ selective
Block	different sensitivity to organic and inorganic compounds	

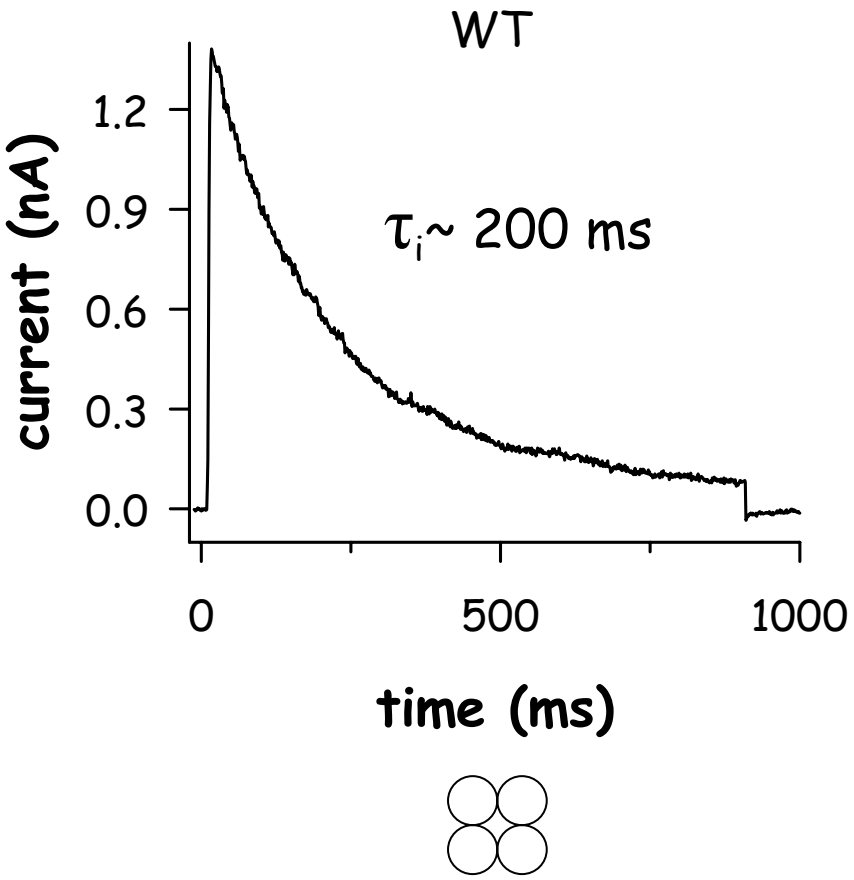
three important problems

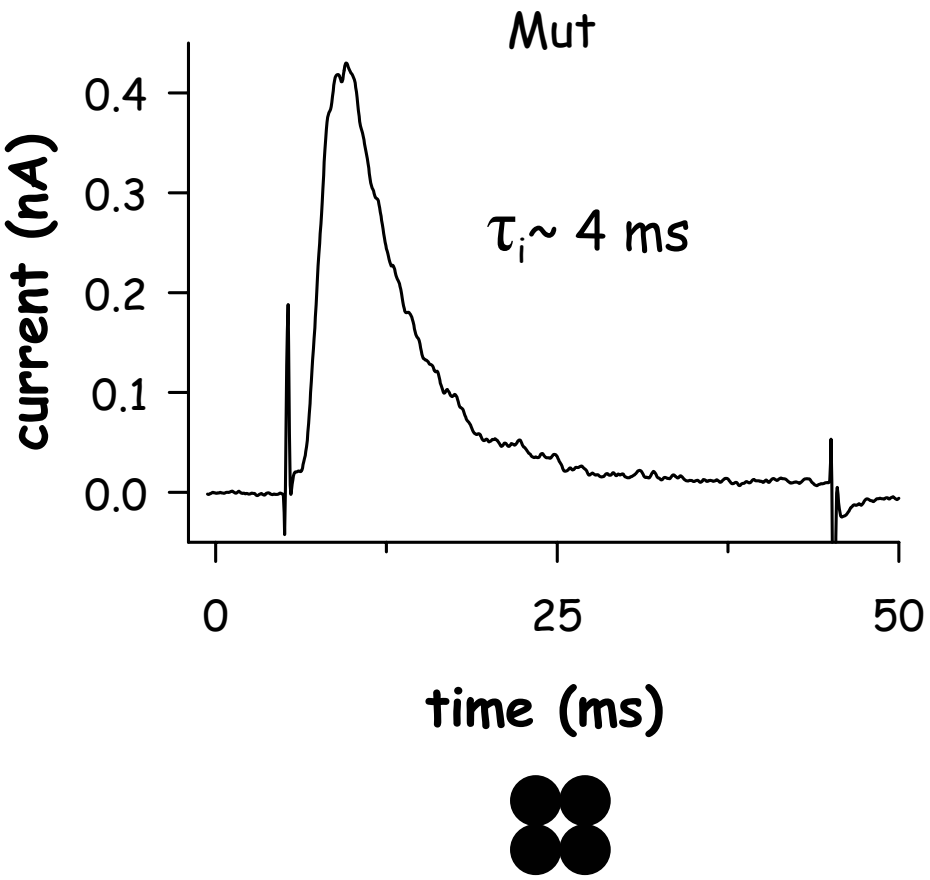
How does each subunit contribute to gating, specifically slow inactivation?

What kind of molecules inhibit Kv1.3 and IKCa1 channels?

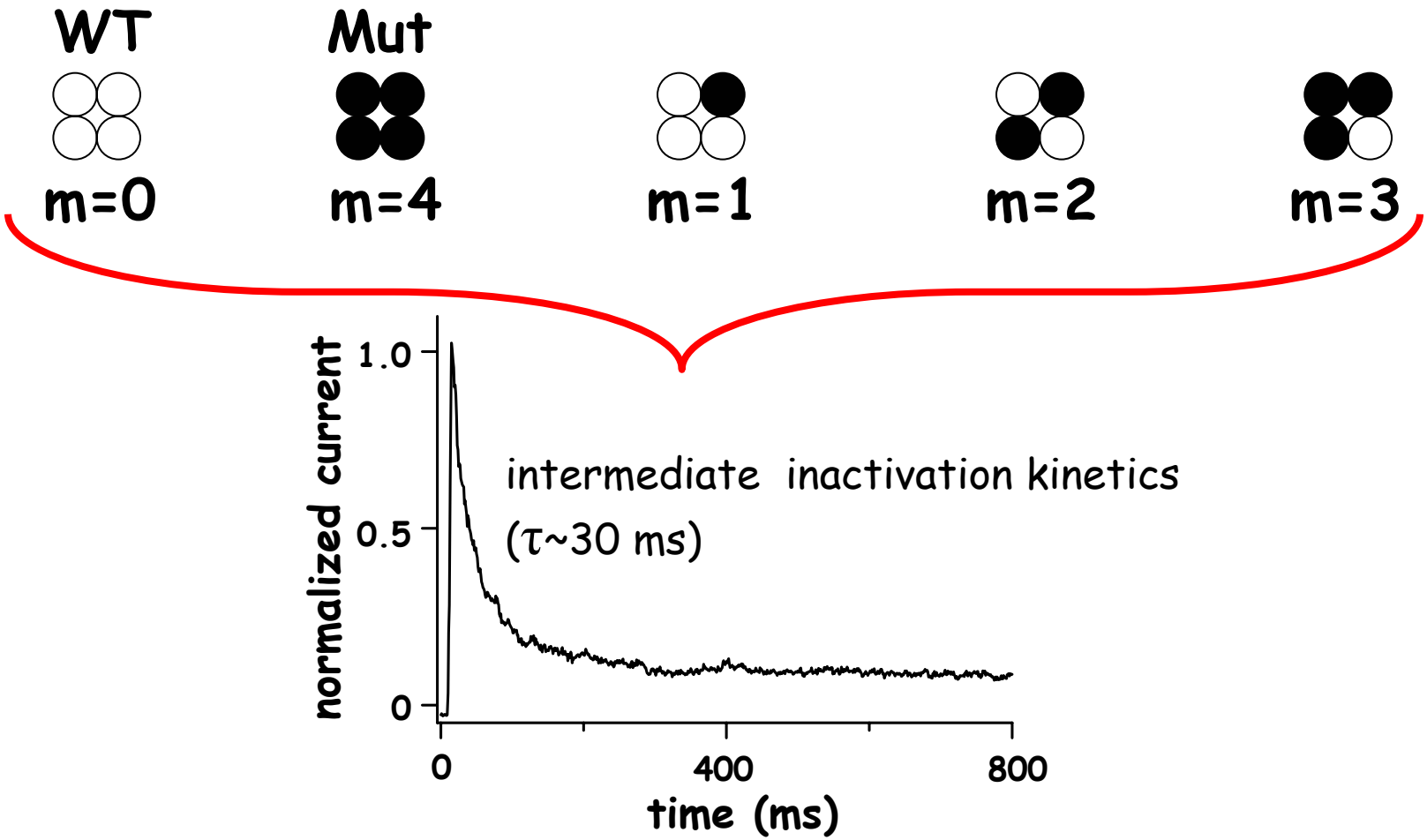
Can the microenvironment of the membrane alter the channels' behavior?

How does each subunit contribute to gating, specifically slow inactivation?





Panyi et al., Biophys. J., 1995, 69: 896-903; Panyi and Deutsch, J.Gen.Physiol., 1996, 107:409-420.

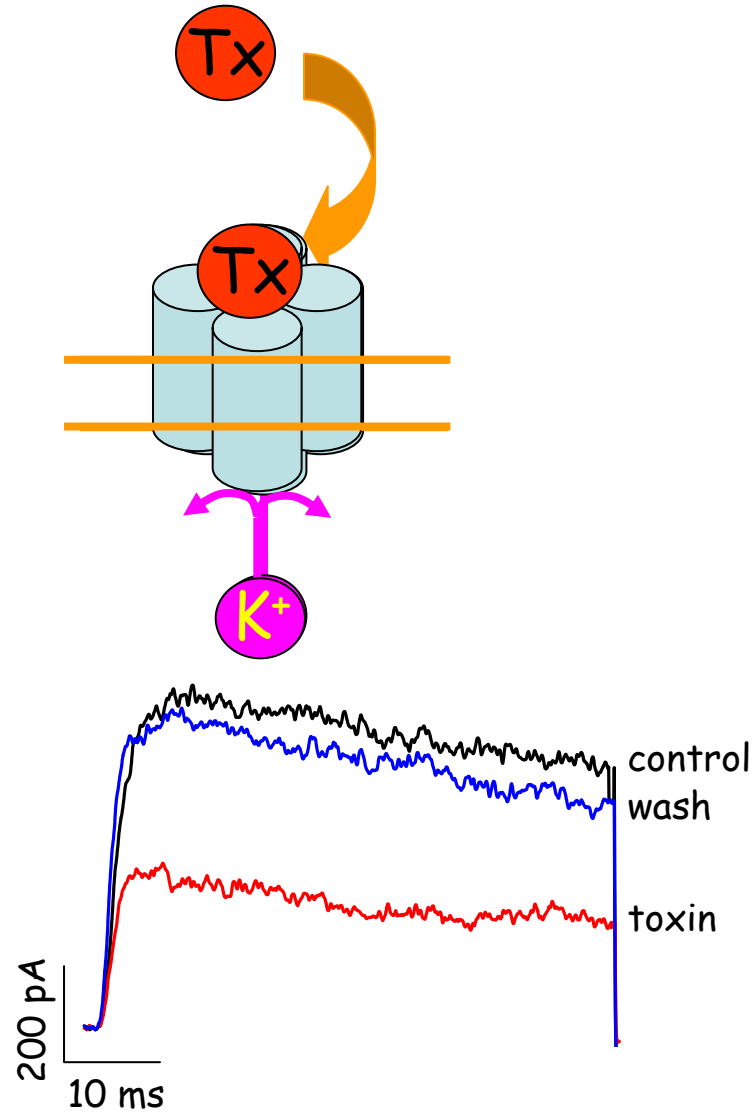


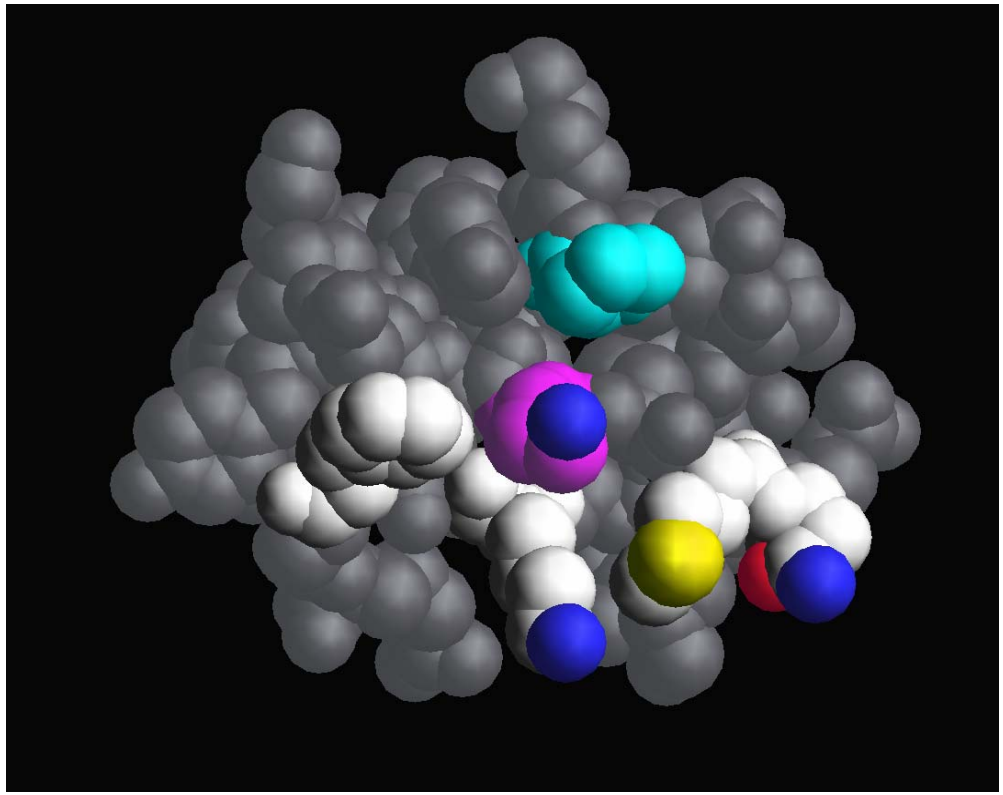
- cooperative interaction between subunits
- each subunit contributes equal free energy to inactivation
- constraints the possible physical models of inactivation

Panyi et al., Biophys. J., 1995, 69: 896-903; Panyi and Deutsch, J.Gen.Physiol., 1996, 107:409-420.

What kind of molecules inhibit Kv1.3 and IKCa1 channels differentially?

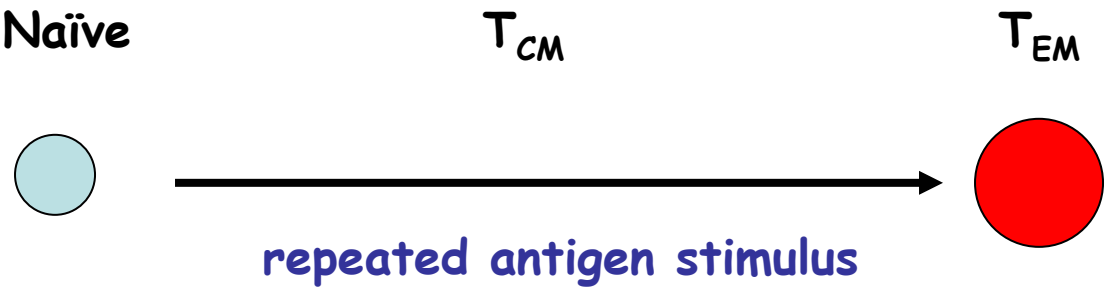
peptide toxins block the pore





Péter et al., BBRC, 1998, 242:621-625;
Péter et al, J. Membr.Biol., 2001, 179:13-25;
Péter et al., BBRC, 2000, 278:34-37;
Batista et al., Biochim. Biophys. Acta, 2002, 1601:123-131.

Why is important to selectively block K^+ channels of T cells?



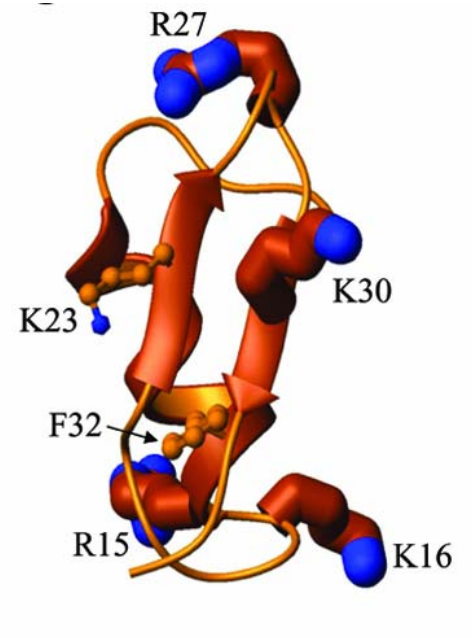
IKCa1: 5-35/cell ~50/cell

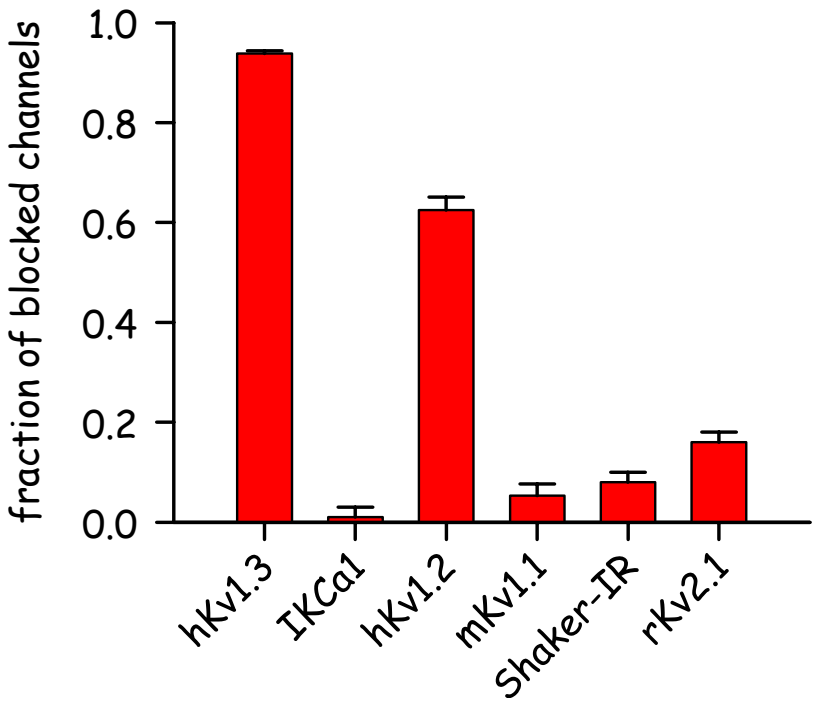
Kv1.3: ~200/cell ~1500/cell

-Multiple Sclerosis
-Type-I (autoimmune) diabetes
-Rheumatoid Arthritis

proliferation of T_{EM} in autoimmune diseases is selectively inhibited by Kv1.3 blockers

Wulff et al., J.Clin.Invest., 2003, 111:1703-1713 (Chandy lab., UCLA)





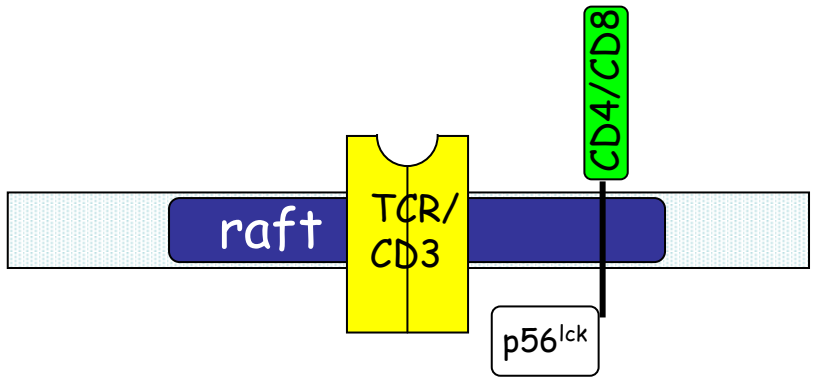
Anuroctoxin is a selective, high affinity blocker of Kv1.3

Bagdány et al., Mol. Pharmacol. 2005, 67:1034-1044; Olamendi-Portugal et al,., Toxicon, 2005, in press

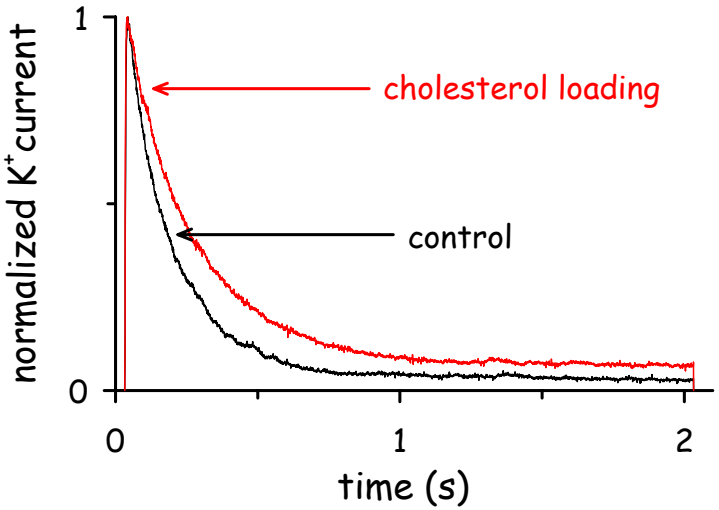
Can the microenvironment of the membrane alter the channels' behavior?

Does gating of Kv1.3 depend on the cholesterol content of the membrane?

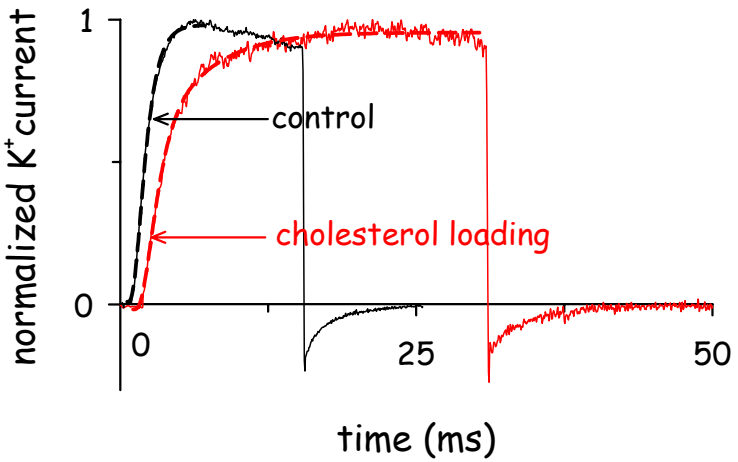
Are Kv1.3 channels localized in specific microdomains of the membrane?



Can cholesterol modulate channel kinetics?



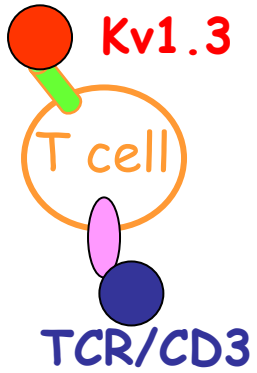
slower inactivation

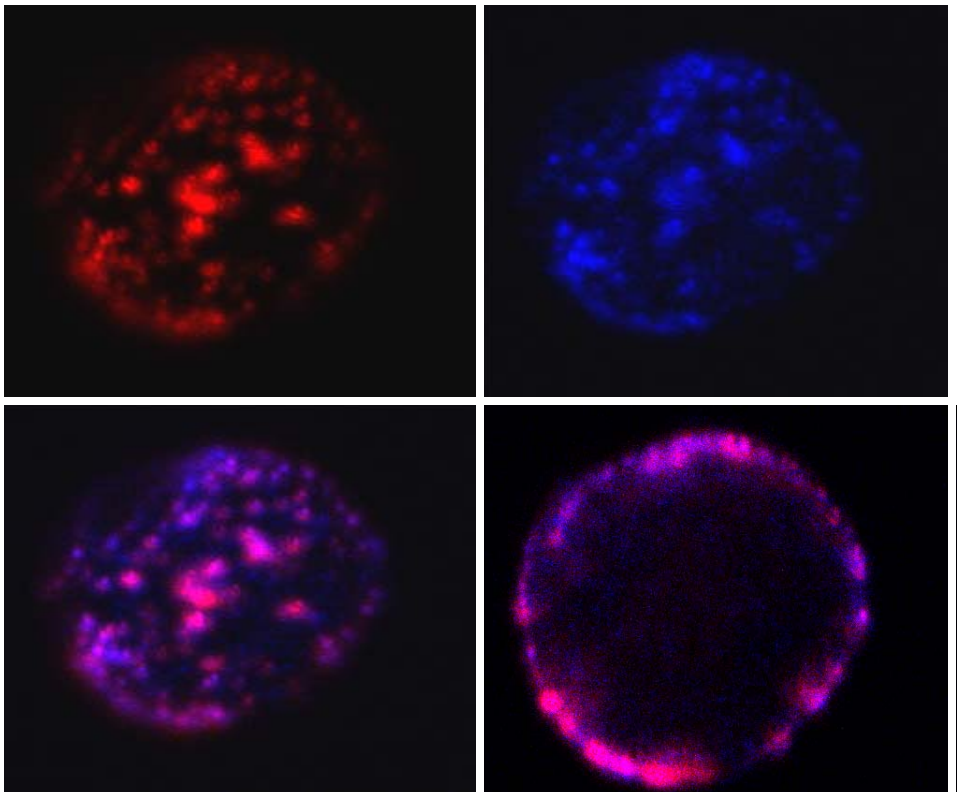


slower and biphasic activation

Hajdu et al., Pflugers Archives, 2003, 445:674-682.

Let's see where the channels are!

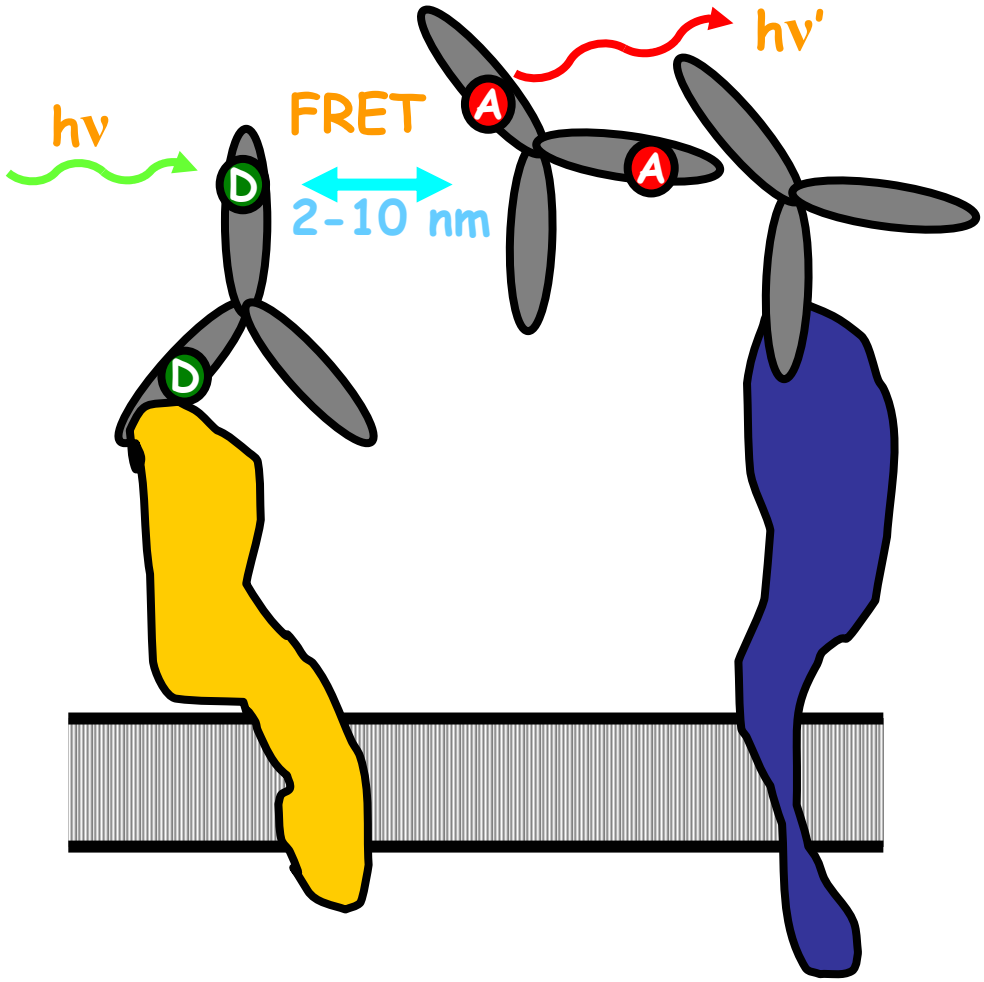




Kv1.3 and CD3 are highly co-localized

Panyi et al., Proc. Natl. Acad. Sci. USA, 2003, 100:2592-2597.

Can we determine this relationship more precisely?



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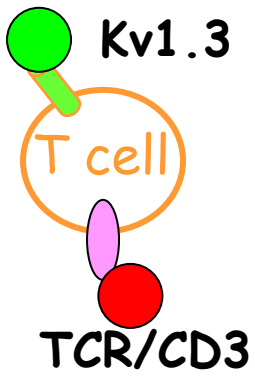
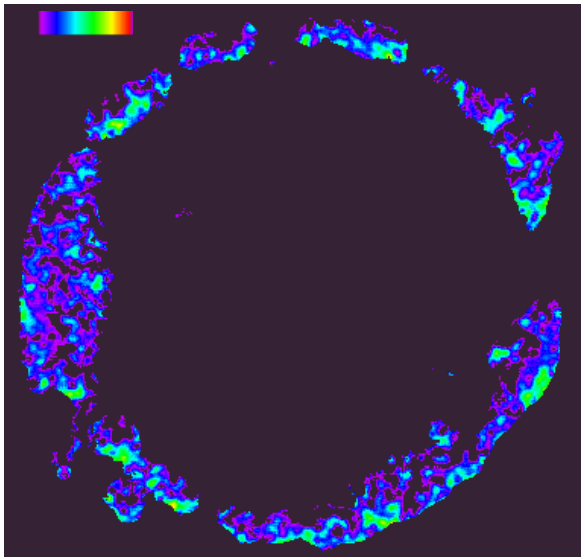
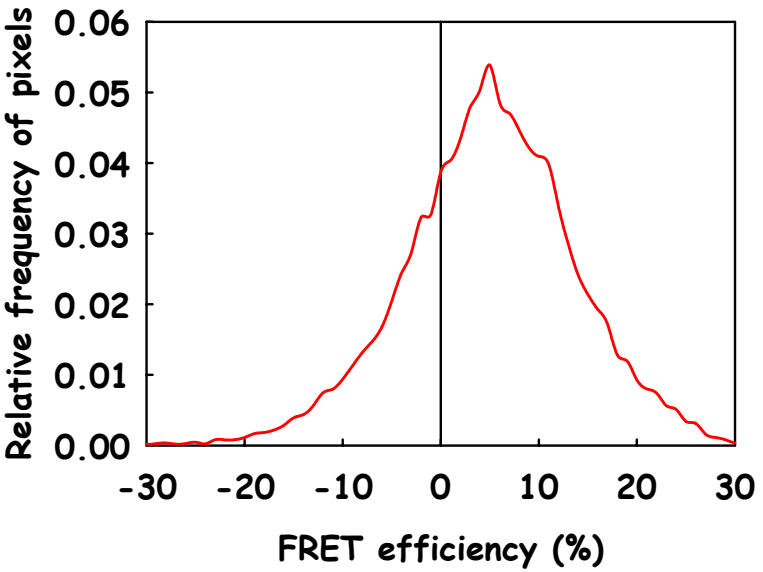


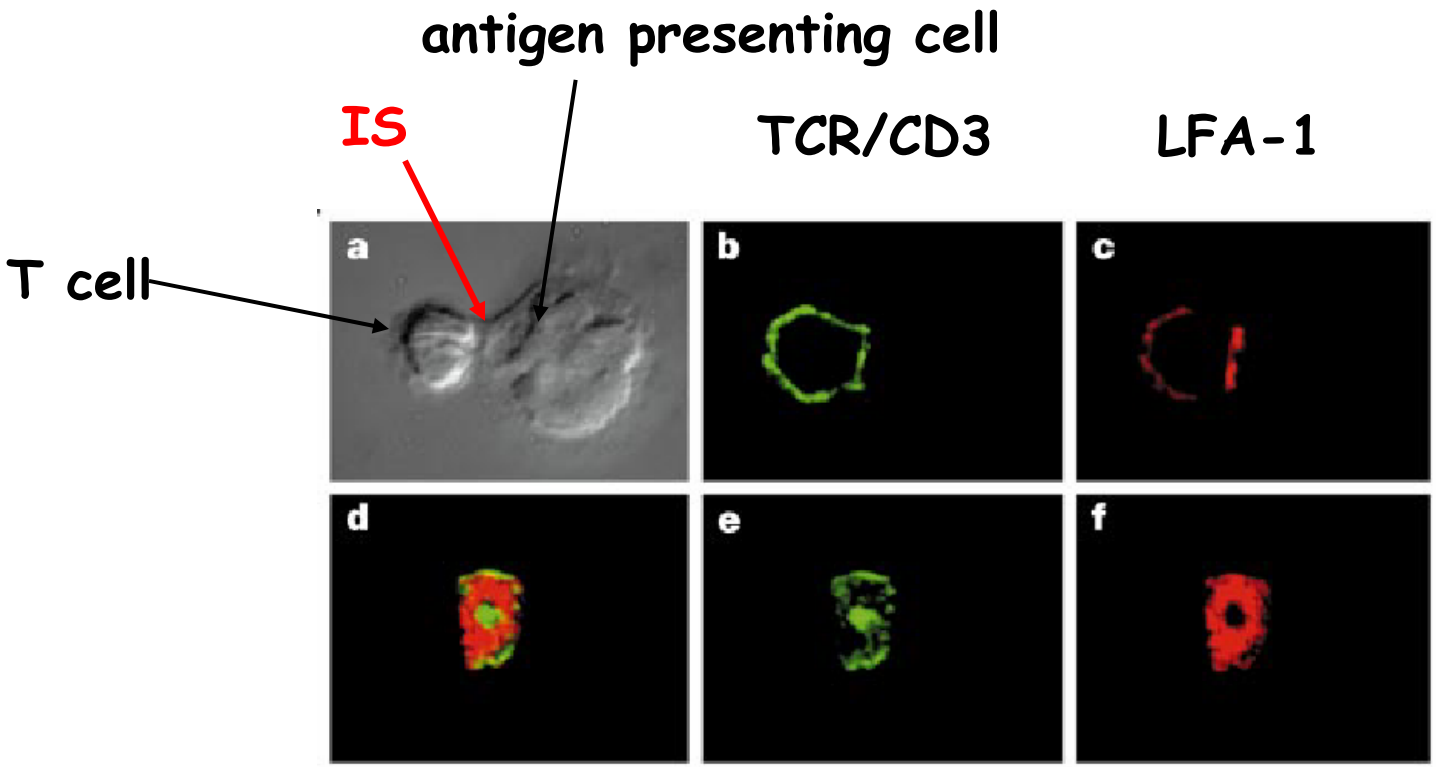




Kv1.3 and TCR/CD3 are closely associated

Panyi et al., Proc. Natl. Acad. Sci. USA, 2003, 100:2592-2597.

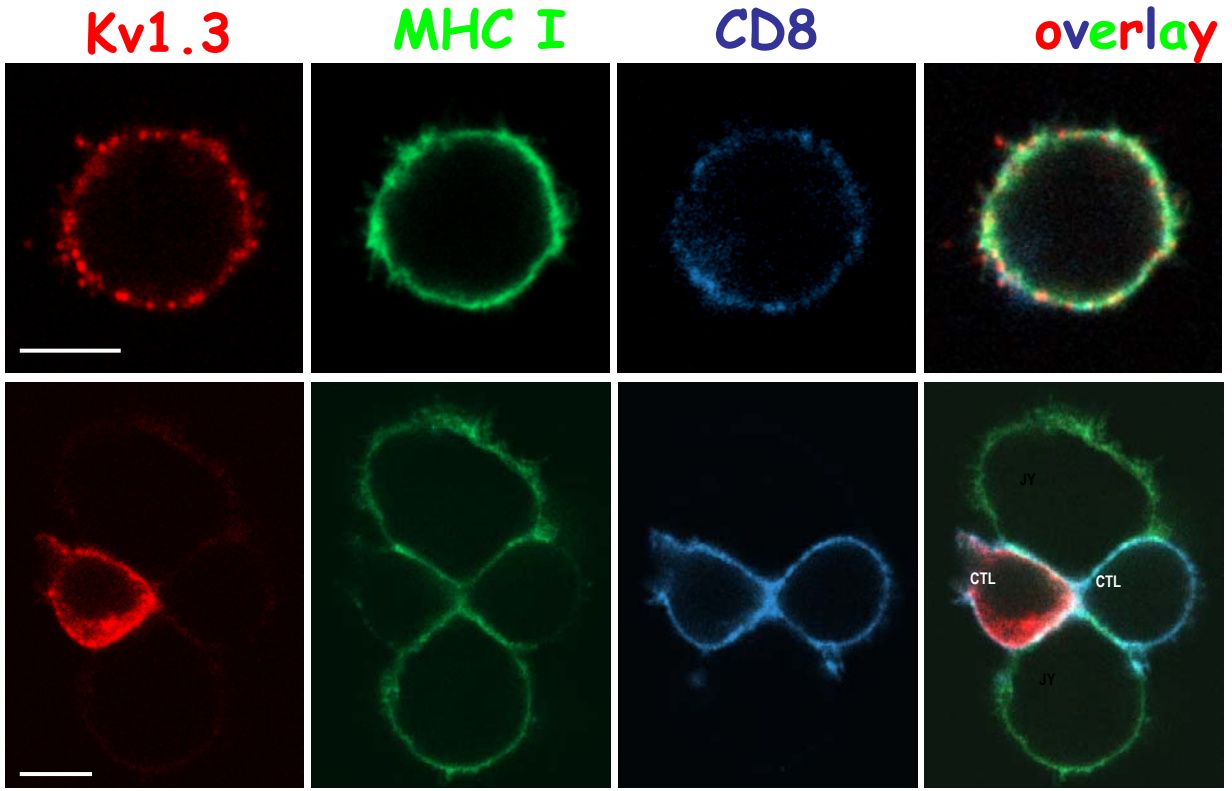
Does this co-localization occur during a physiological immune response?



Structured recruitment of molecules in the immunological synapse

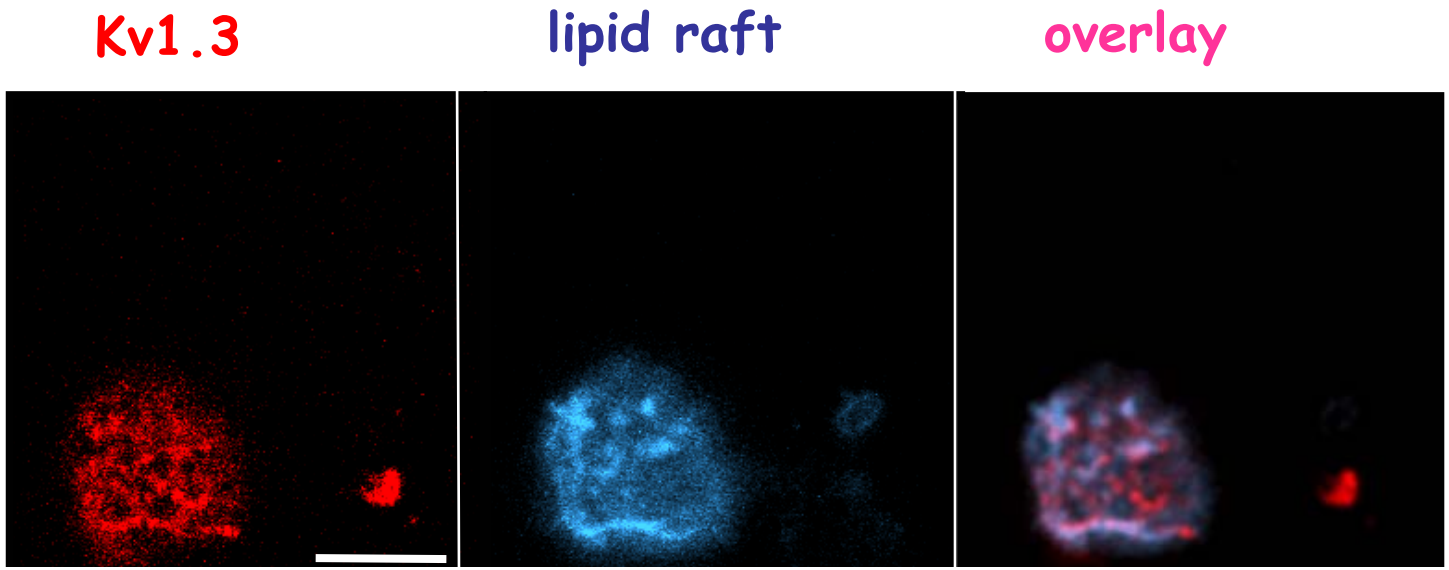
Monks et al., Nature, 1998, 395:82-86 (Kupfer lab.)

Is Kv1.3 also in the immune synapse?



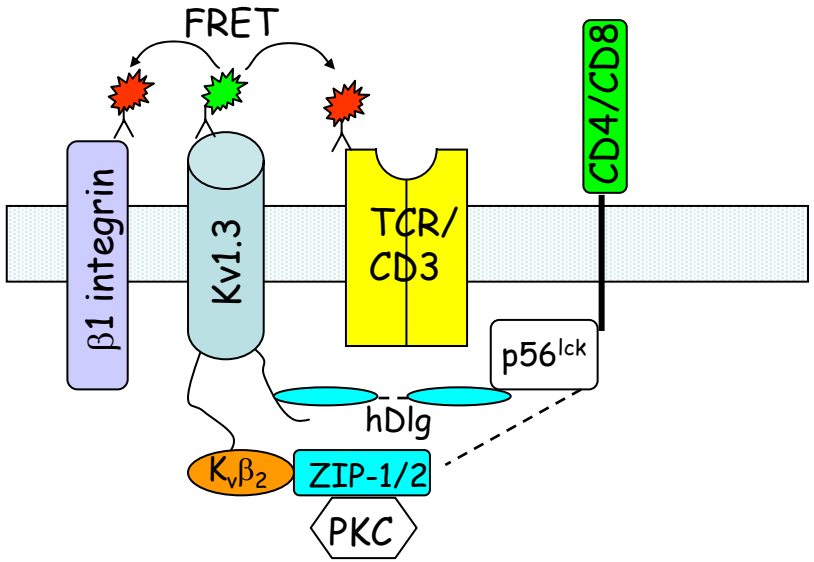
Panyi et al, Proc. Natl. Acad. Sci. USA, 2004, 101:1285-1290.

Are Kv1.3 channels in lipid rafts?



Panyi et al, Proc. Natl. Acad. Sci. USA, 2004, 101:1285-1290.

What is our model for the molecular interactions of Kv1.3 in the immune synapse?



Panyi et al., Trends Immunol., 2004, 25: 565-569; Panyi et al., Imm. Lett., 2004, 92:55-66.

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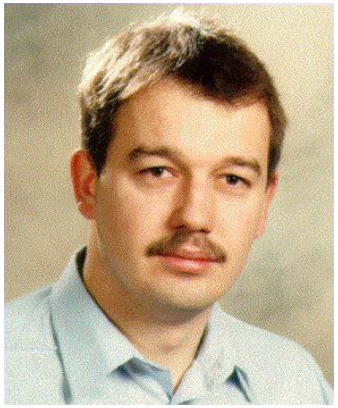

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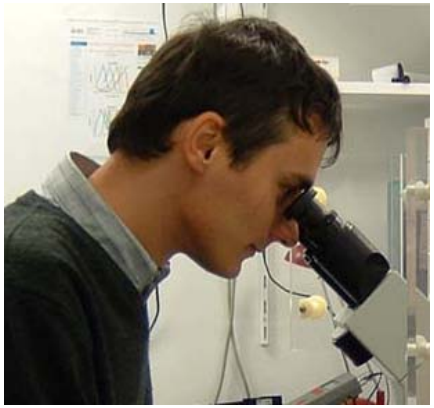

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