



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



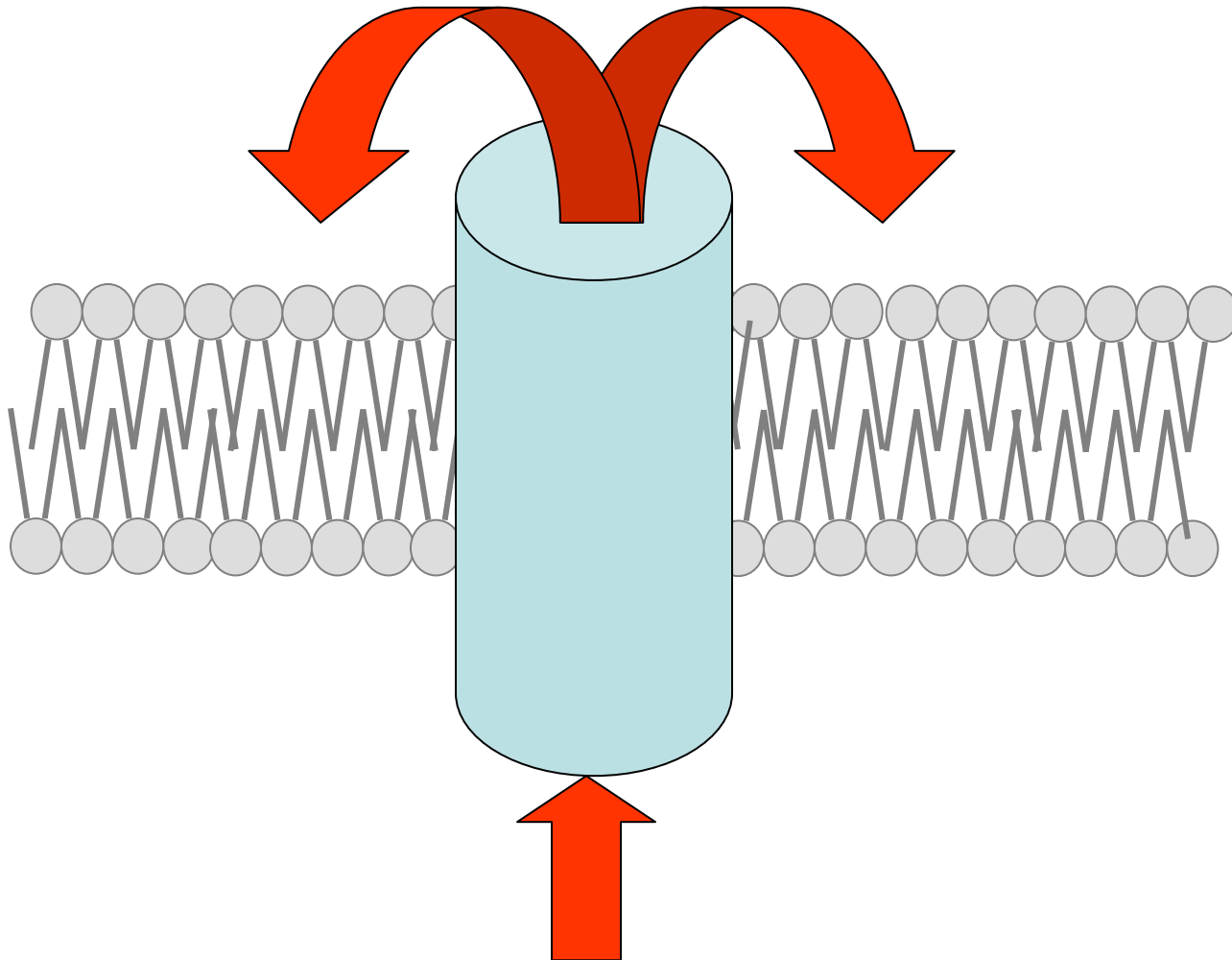
Regulation of Kv1.3 activity in human T lymphocytes: peptide blockers and molecular interactions

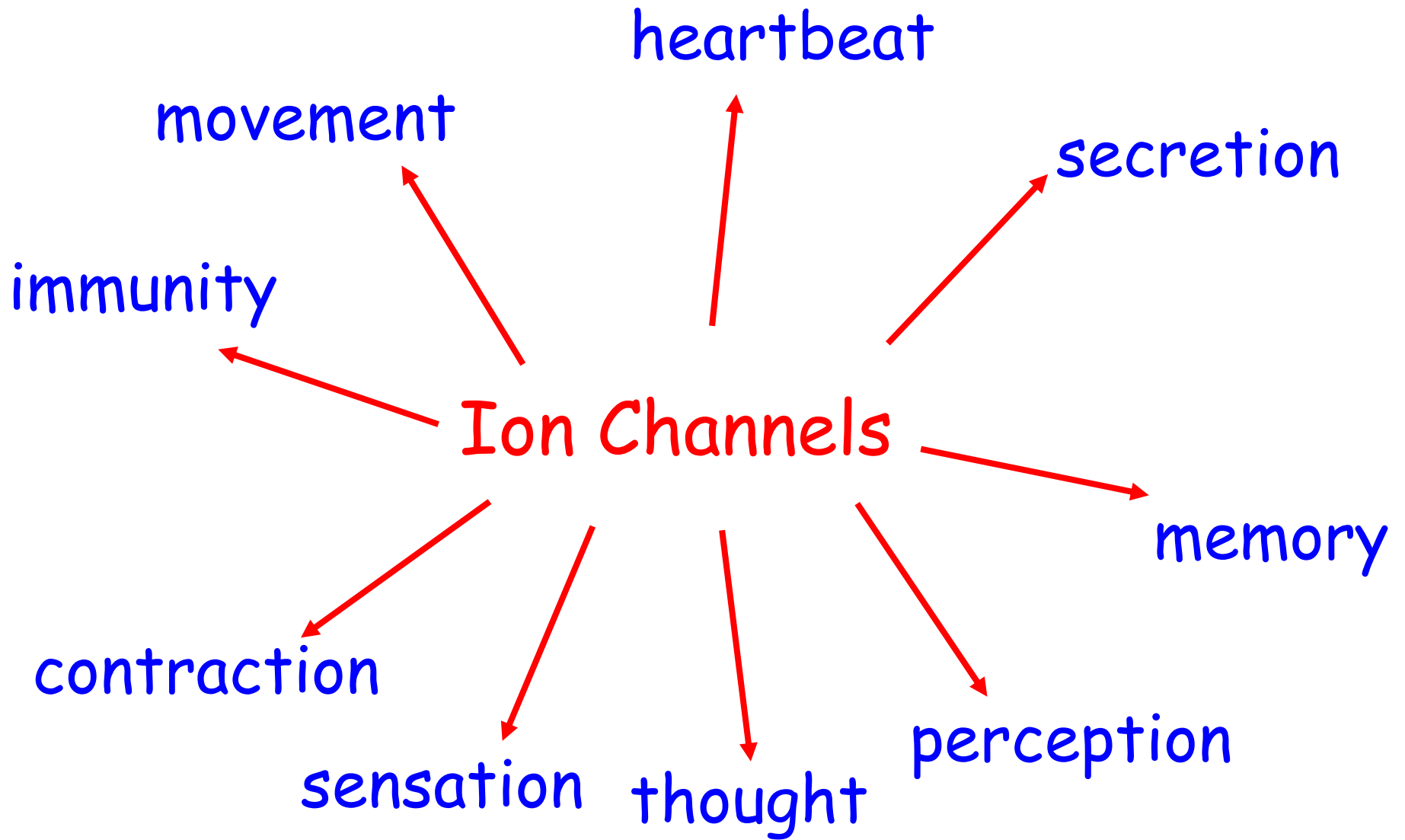
György Panyi

August 27, 2005, Montpellier

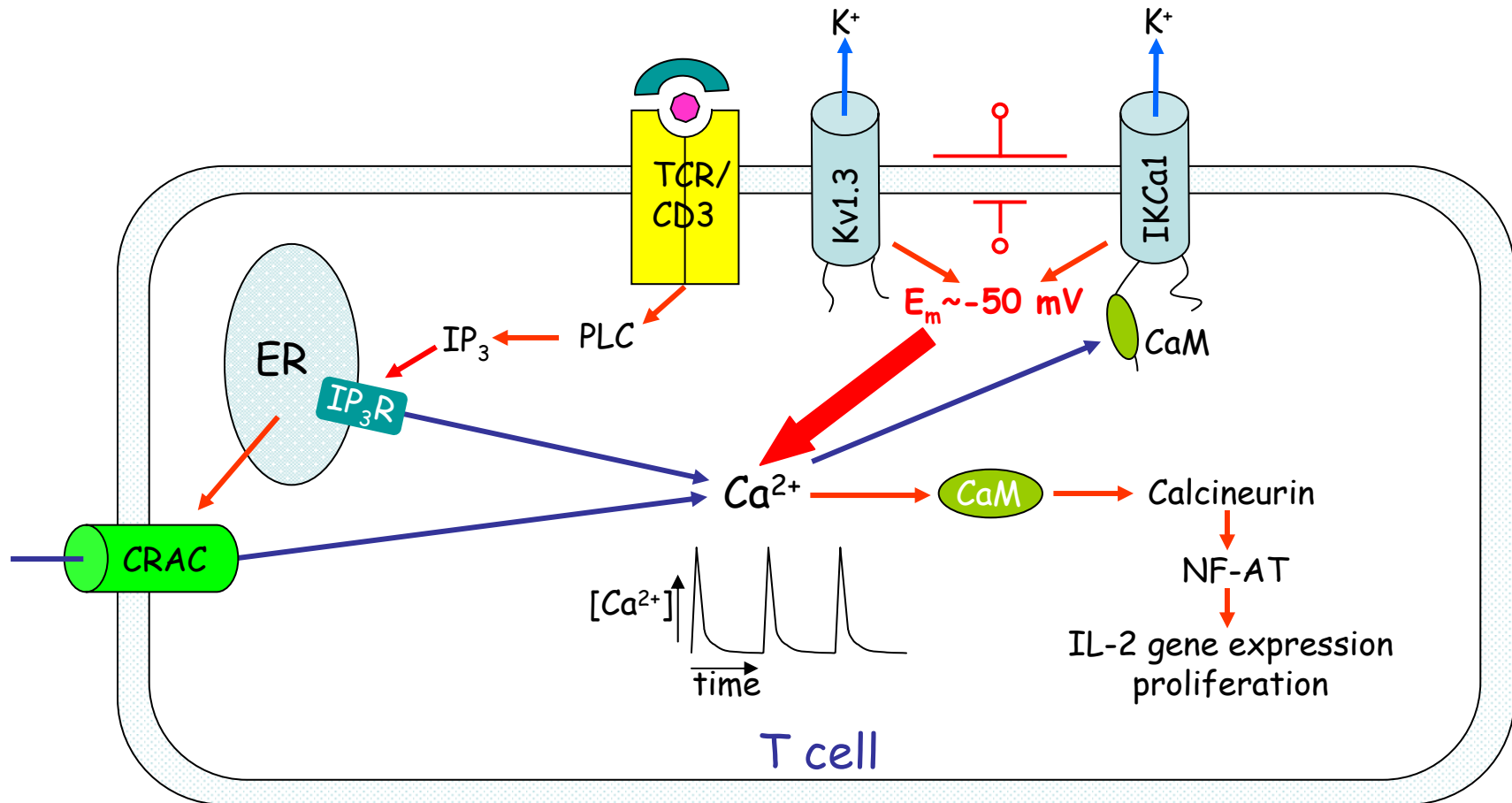
Simple view of an ion channel:

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

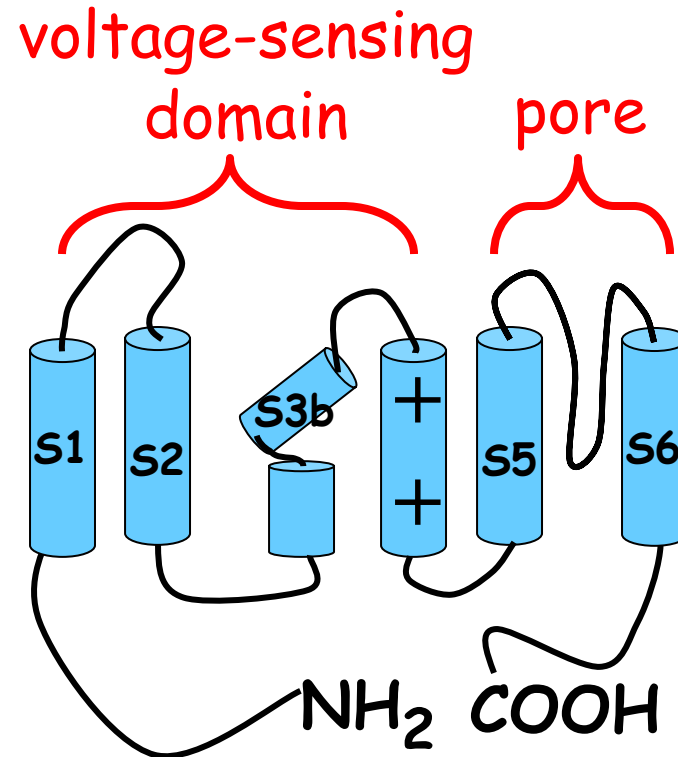
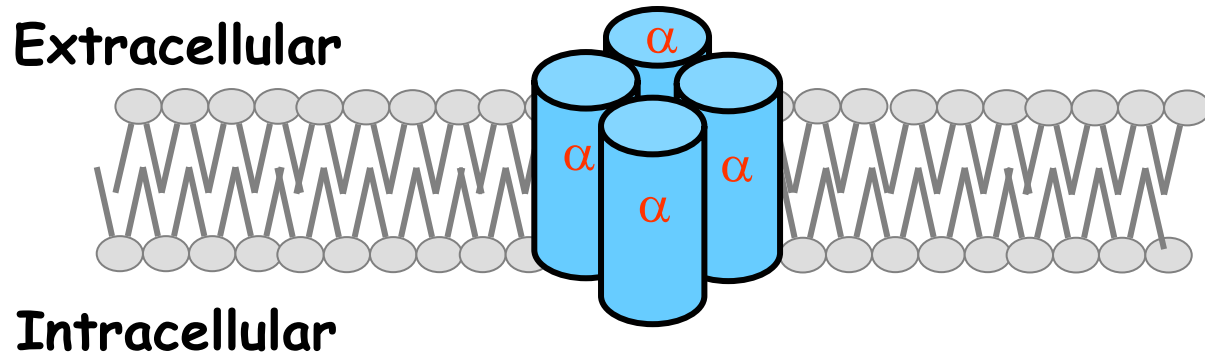




How do ion channels regulate the immune functions?

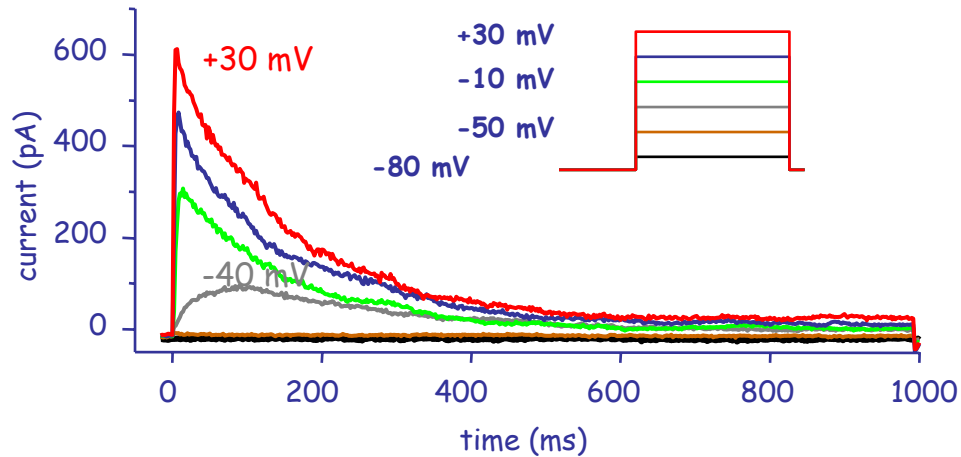
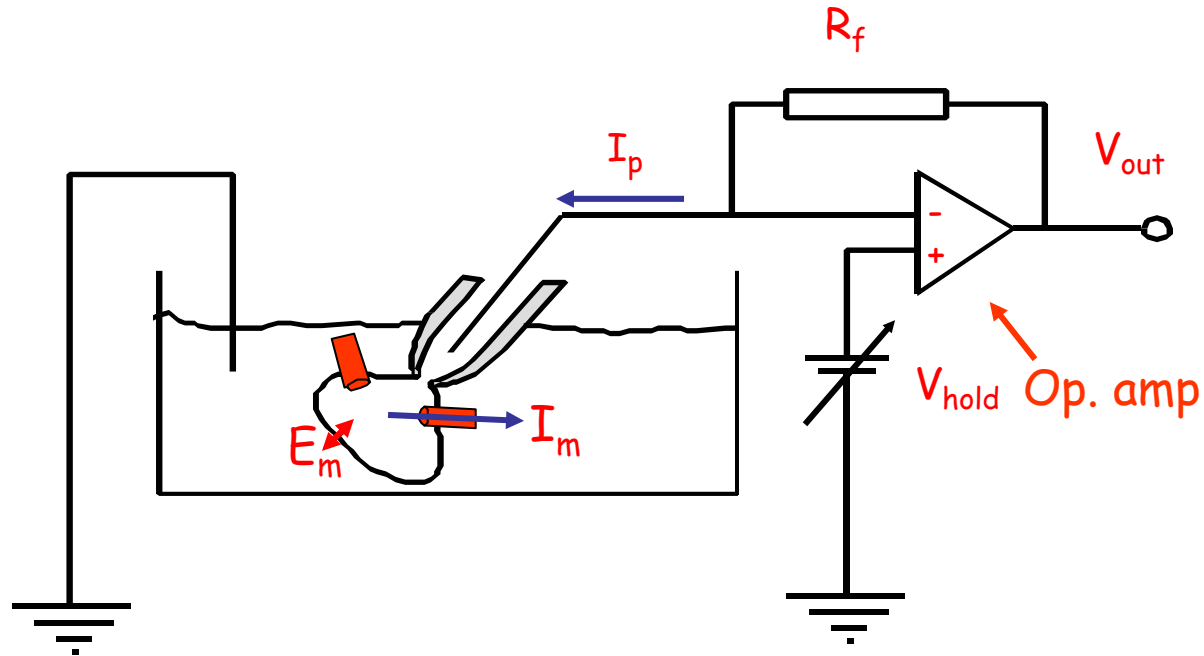


Ion channels are oligomeric transmembrane proteins

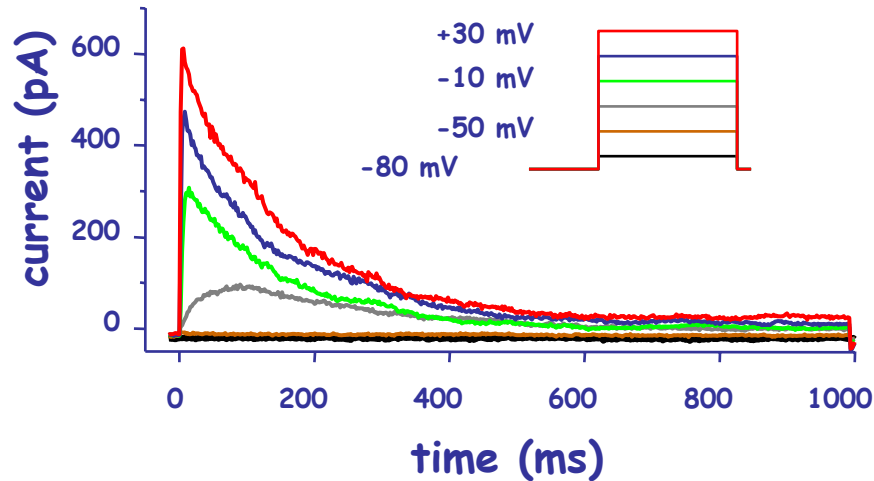


How do we study the channels?

By measuring ionic currents using the patch-clamp technique



How do K^+ channels of T cells compare?



Kv1.3

Gating:

voltage-gated

Single channel
conductance

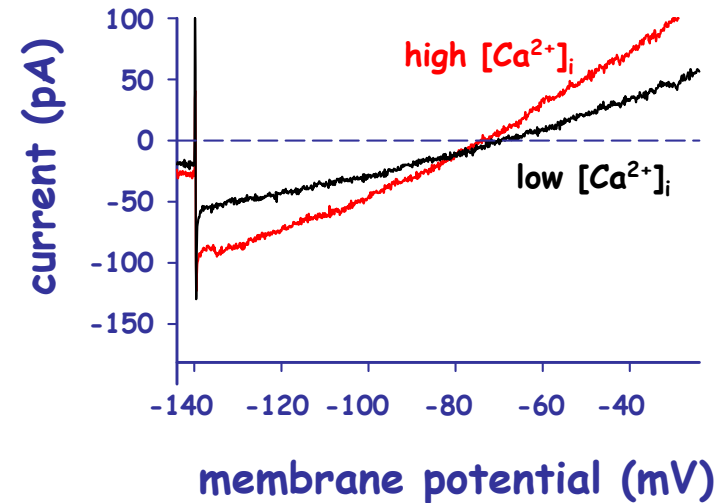
similar (~10 pS)

Selectivity

K^+ selective

Block

different sensitivity to organic and inorganic compounds



IKCa1

Ca^{2+} -activated

similar (~10 pS)

K^+ selective

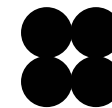
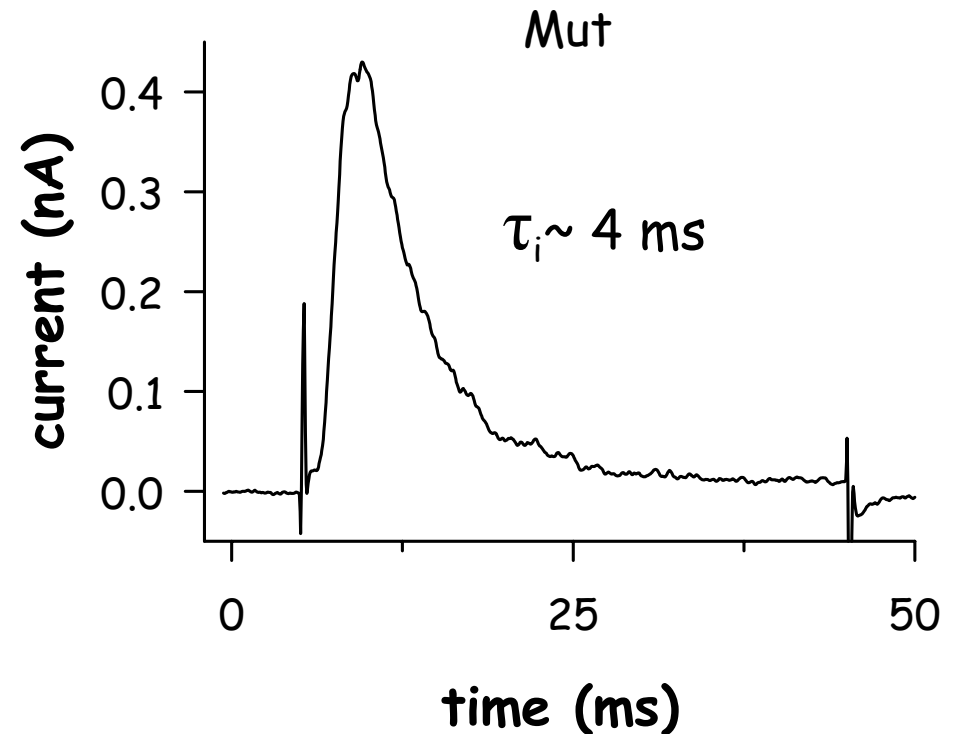
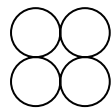
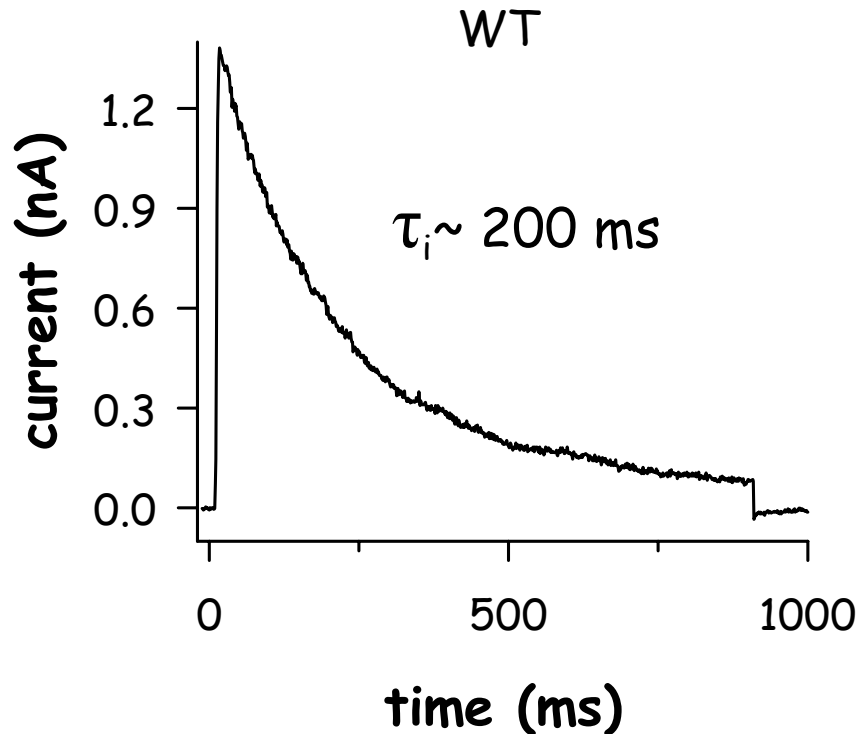
three important problems

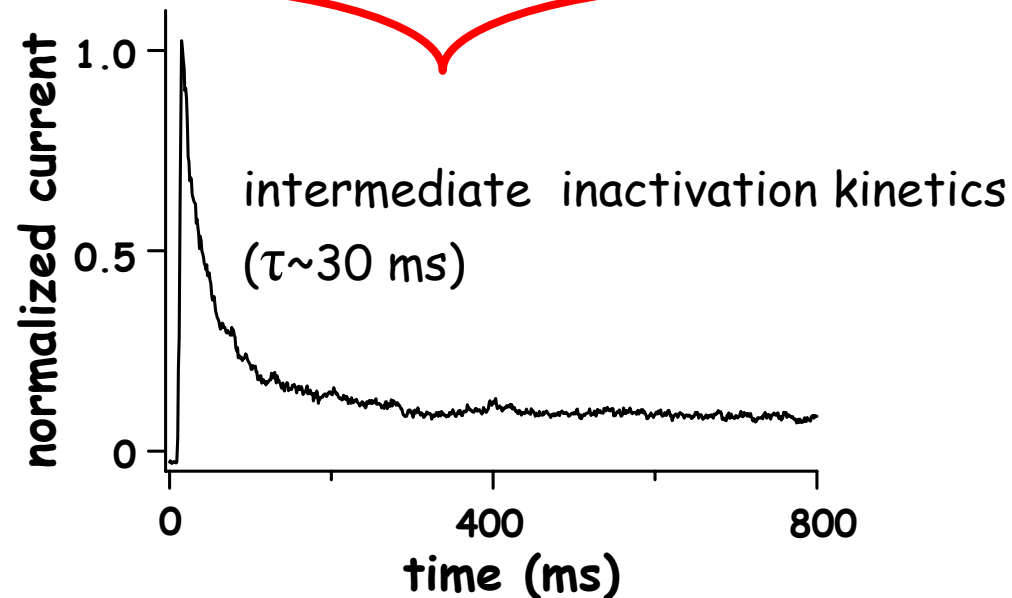
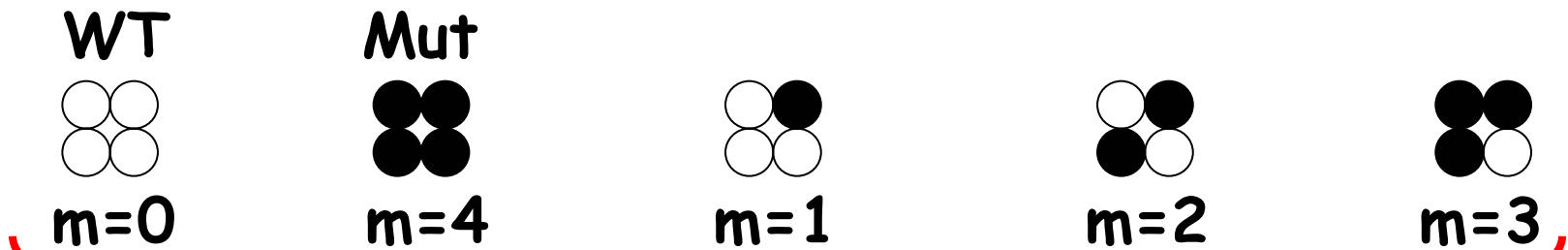
How does each subunit contribute to gating, specifically slow inactivation?

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?



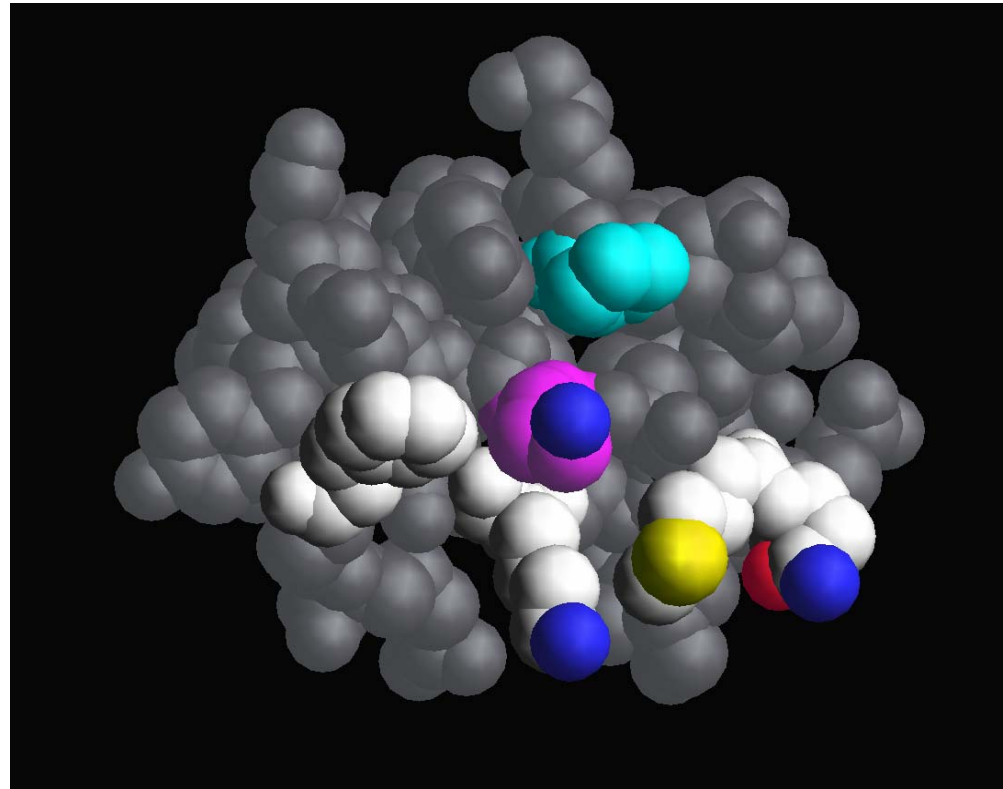
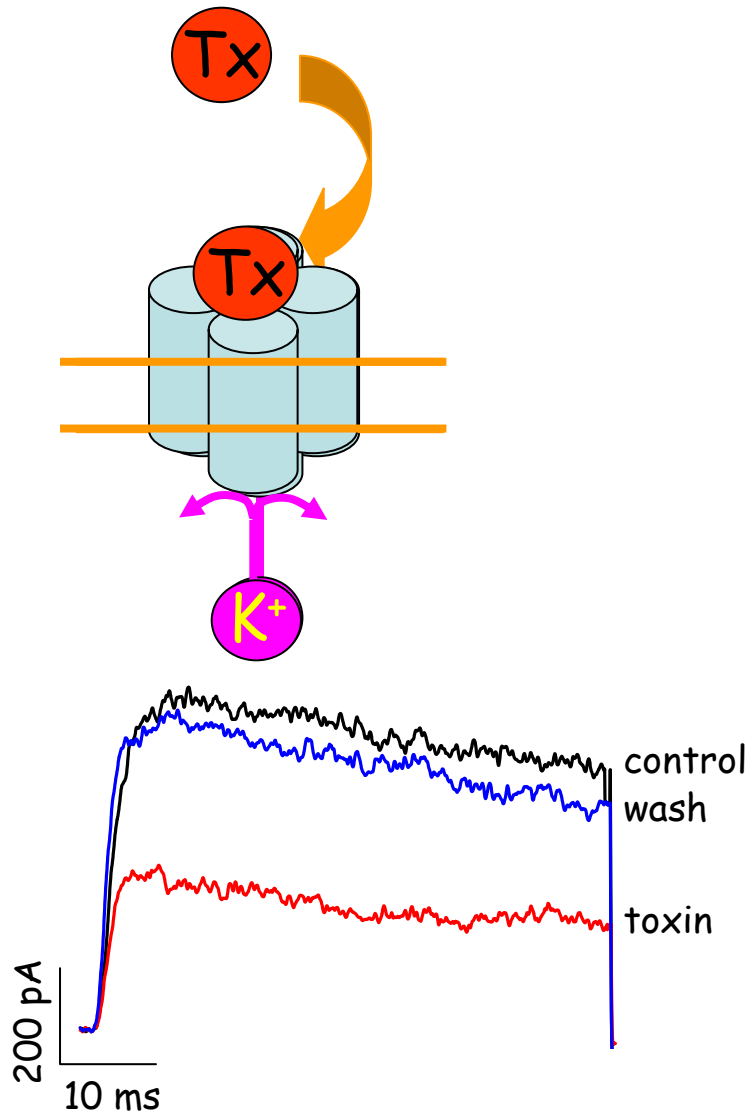


- cooperative interaction between subunits
- each subunit contributes equal free energy to inactivation
- constraints the possible physical models of inactivation

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



peptide toxins block the pore



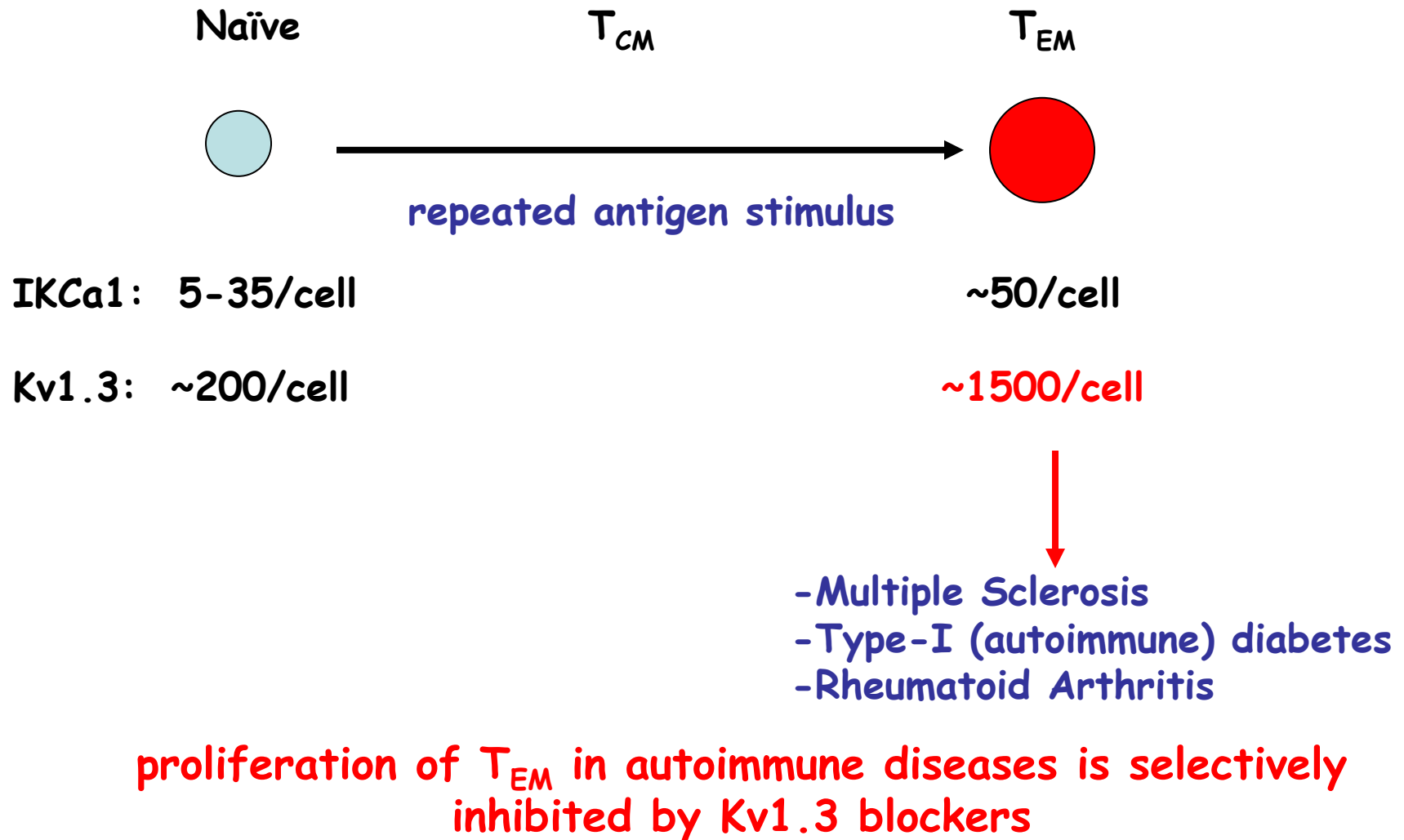
Péter et al., BBRC, 1998, 242:621-625;

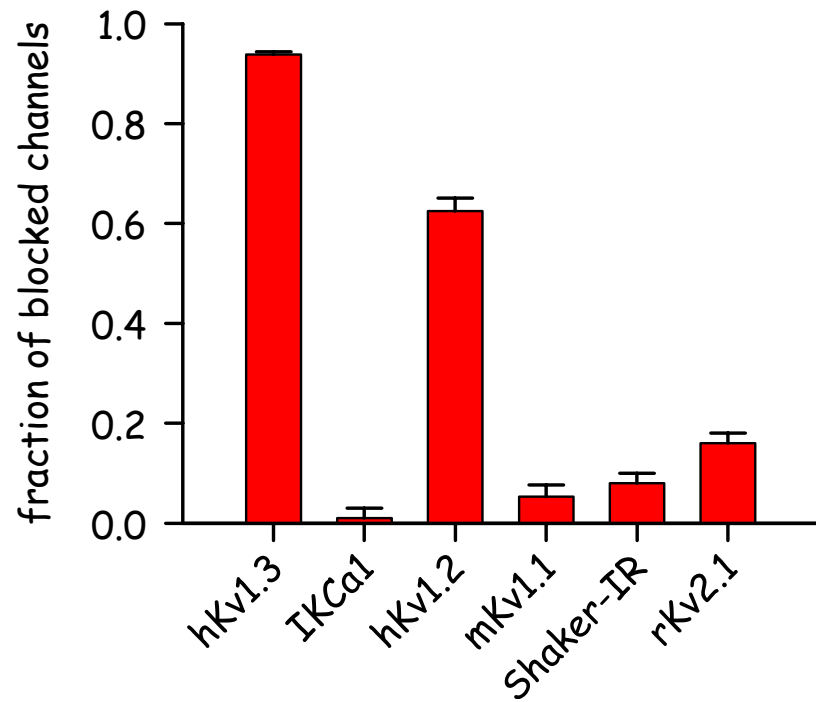
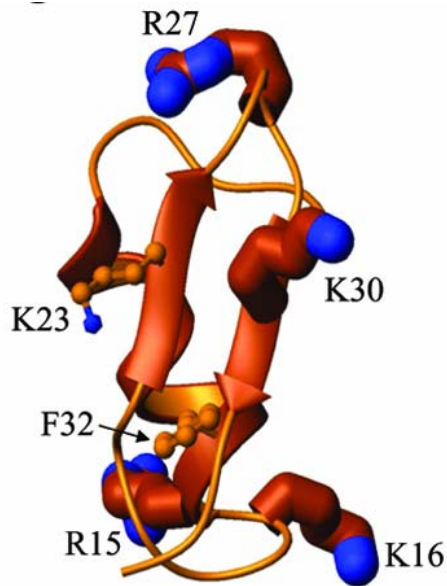
Péter et al., J. Membr. Biol., 2001, 179:13-25;

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?



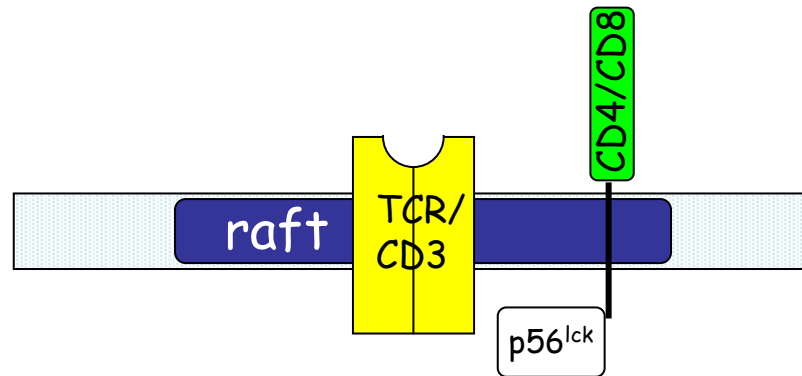


Anuroctoxin is a selective, high affinity blocker of Kv1.3

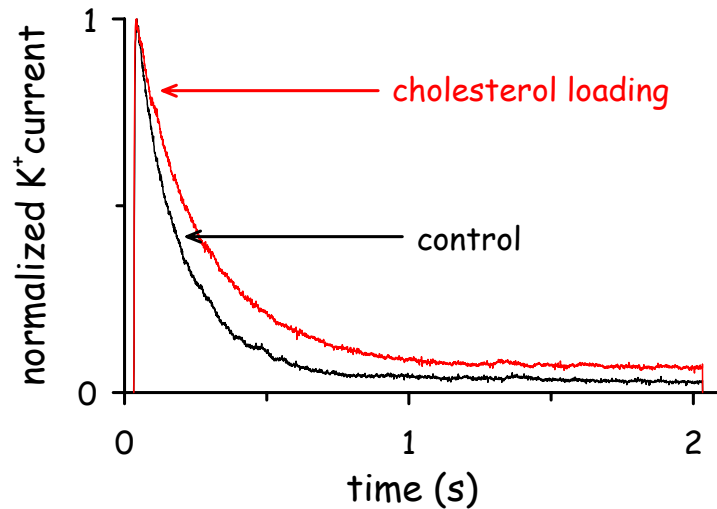
Can the microenvironment of the membrane alter the channels' behavior?

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

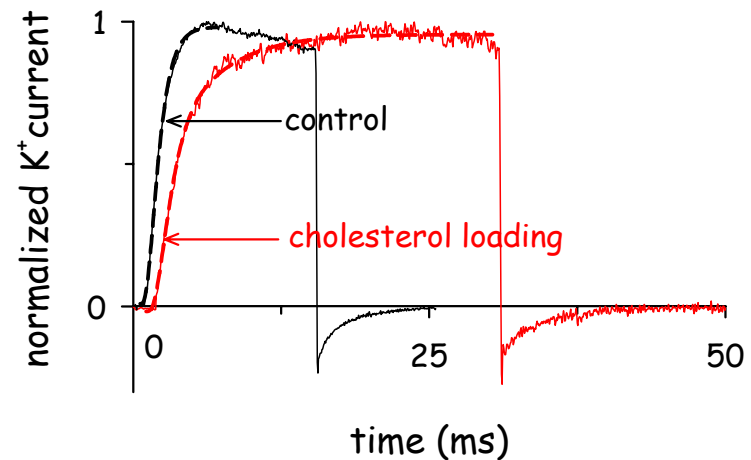
Are Kv1.3 channels localized in specific microdomains of the membrane?



Can cholesterol modulate channel kinetics?

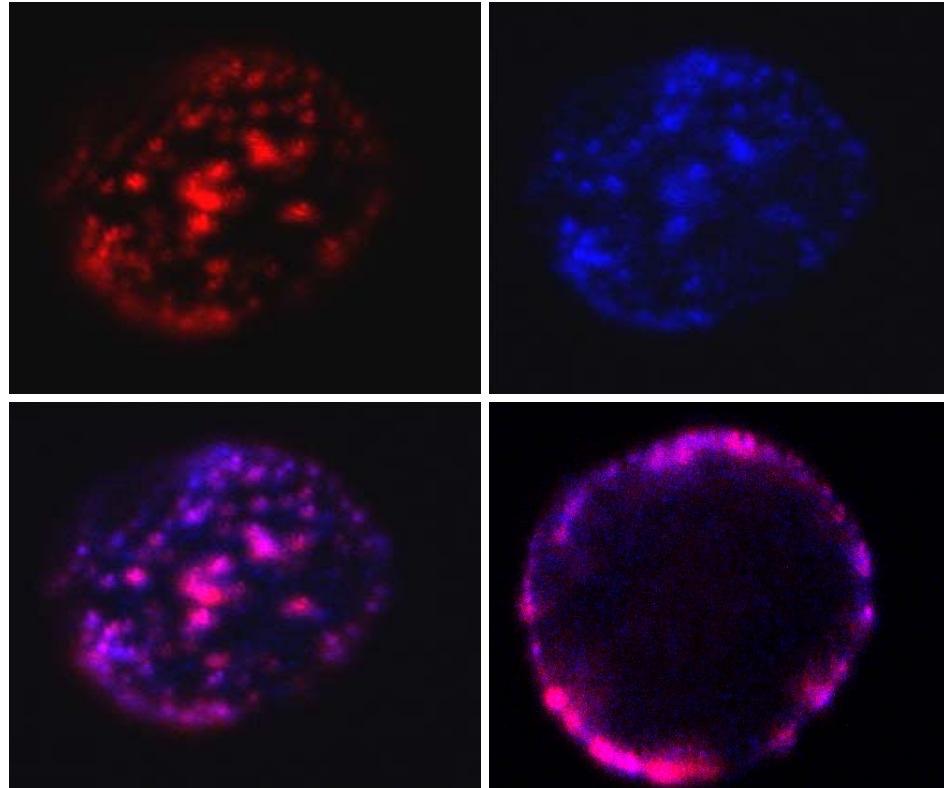
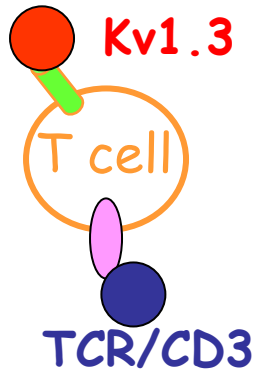


slower inactivation



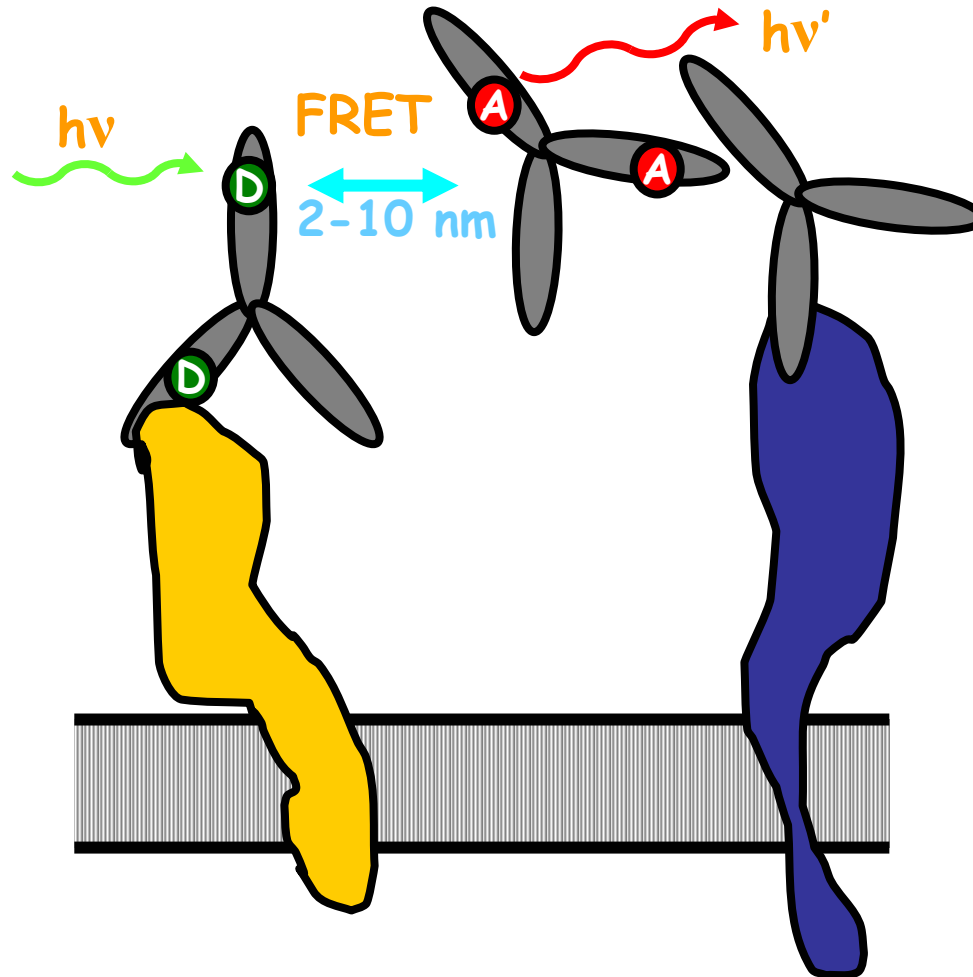
slower and biphasic activation

Let's see where the channels are!

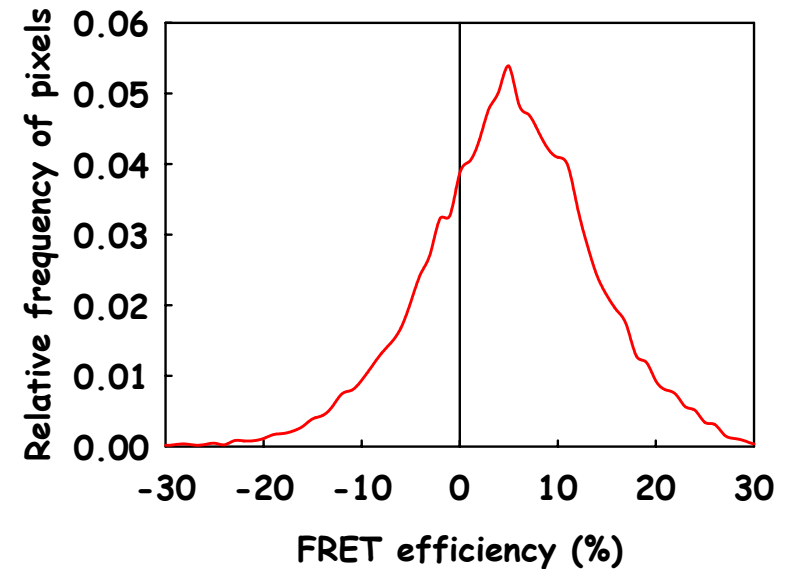
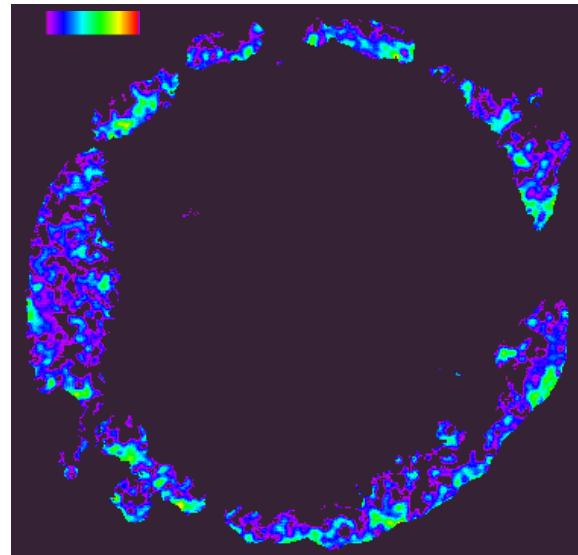
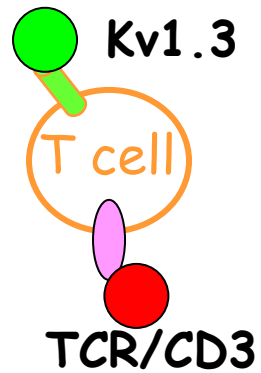


Kv1.3 and CD3 are highly co-localized

Can we determine this relationship more precisely?

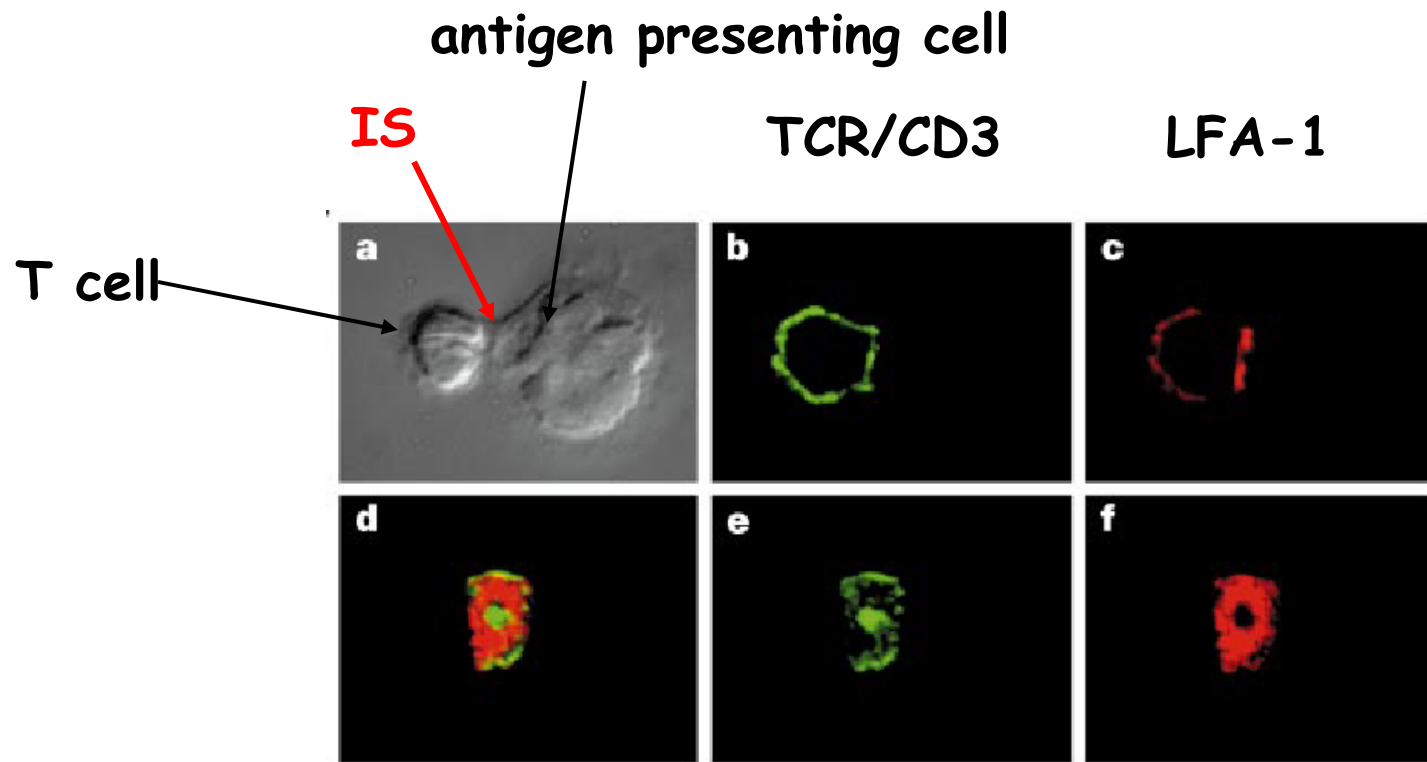


Can we determine this relationship more precisely?



Kv1.3 and TCR/CD3 are closely associated

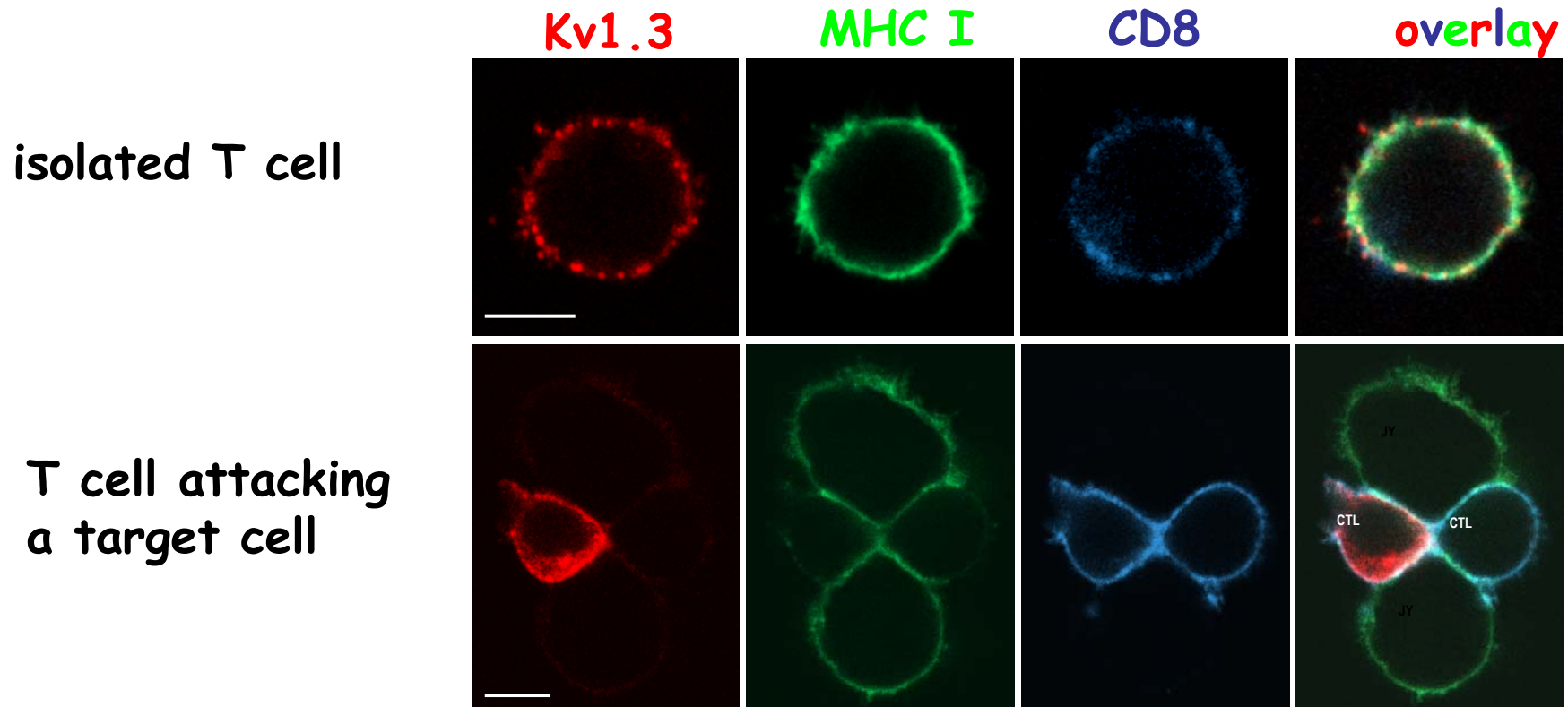
Does this co-localization occur during a physiological immune response?



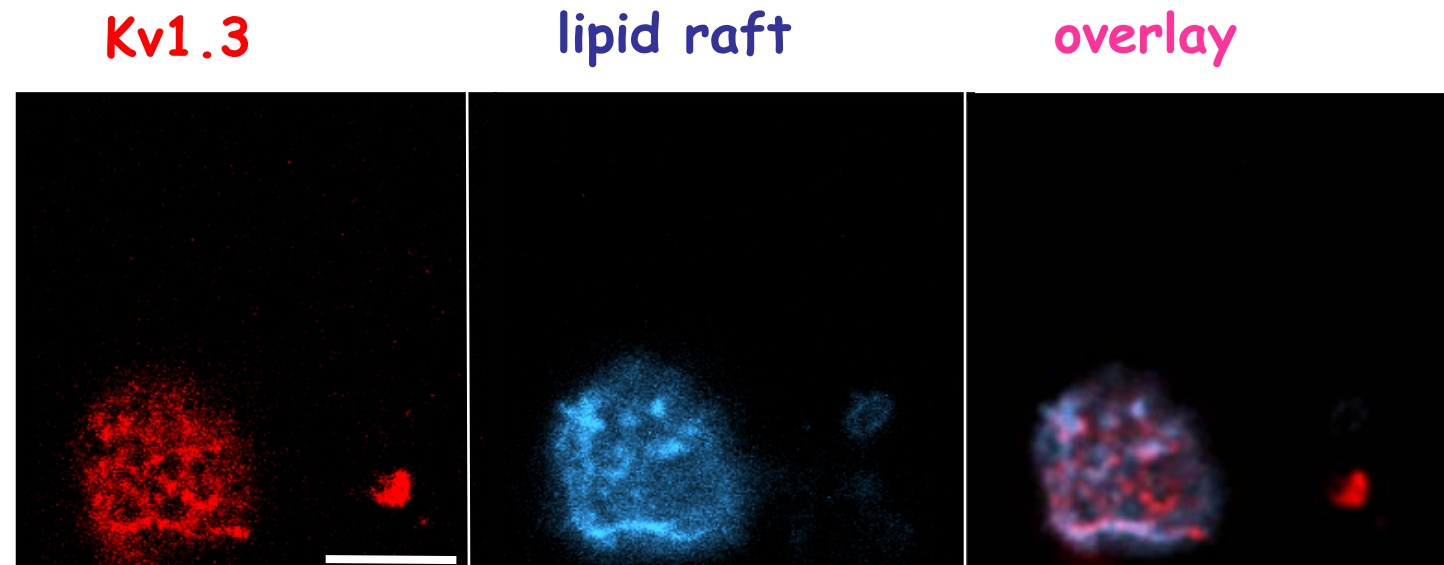
Structured recruitment of molecules in the immunological synapse

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

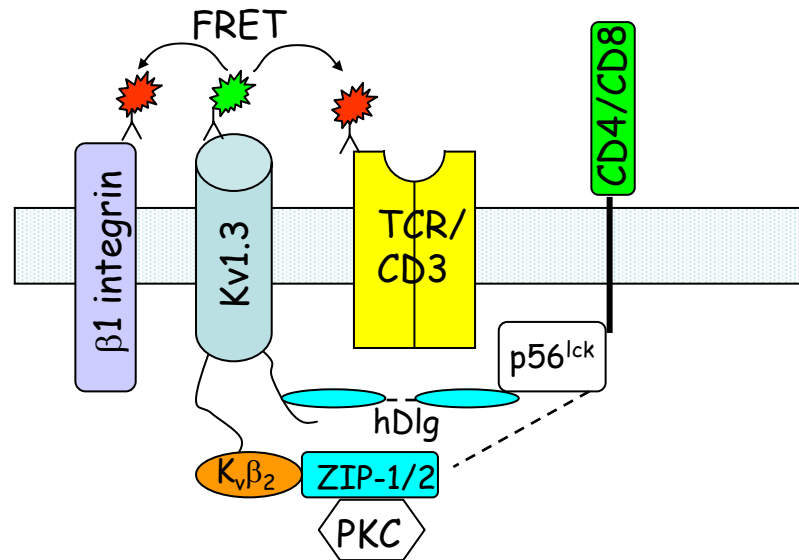
Is Kv1.3 also in the immune synapse?



Are Kv1.3 channels in lipid rafts?



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



Mentors, co-workers and students



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U. of Pennsylvania, USA



Lourival D. Possani
UNAM, Mexico



László Mátyus



Rezső Gáspár

Mentors, co-workers and students



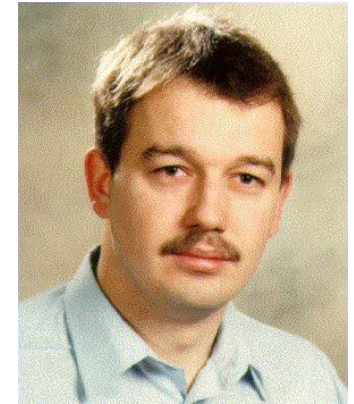
Zoltán Varga



Péter Hajdu



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Miklós Bagdány



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Sándor Somodi