of antibiotics through porins (OmpF, OmpC) was done to elucidate the uptake kinetics of antibiotics through porins.
One main set of experimental data to be presented is on connexins proteins. Connexins are widely distributed in mammalian tissues and serve to join cells together into larger, functional units. We investigated the properties of hemichannels from Cx26 and Cx43 which were isolated biochemically and reconstituted into synthetic lipid membranes. In this study, preliminary data suggest the formation of gap junctions between cells and synthetic bilayer membranes. This opens possibilities to access the cytoplasm of living cells for biochemical or electrical studies, and especially to develop novel automated techniques for electrophysiological studies.

3688-Pos
Viral and Host Channels: A Comparison
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Viruses and their host cells have something in common they both need and encode ion channels. Whilst for the host the role and the mechanism of function of these membrane proteins is straight forward, knowledge about the viral channels seems just to unroll on the molecular level. Experimental tools are gradually delivering low and high resolution structures with computational methods as another source for structural information on the atomic level.
The viral membrane proteins identified as channels are becoming increasingly more complex in respect to their topology. Most of the channels are still very much smaller than the channels of the host. This triggers an intrigued discussion about (i) when is a membrane protein a channel and (ii) what do the smaller viral channels have in common with their bigger class mates, the host channels. Data from computational modeling will be presented along these lines.

3689-Pos
Channelrhodopsin-2 Variants with Accelerated and Decelerated Channel Kinetics
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The light-activated cation channel Channelrhodopsin-2 (ChR2) is a powerful tool for controlling neuronal activity. Its genetic information is carried into neurons which express the protein. Channel activation by blue light exposure causes membrane depolarizations that immediately trigger action potentials. We genetically modified ChR2 wildtype and created variants with decelerated and accelerated channel kinetics as well as changed ion selectivities. ChR2 mutations with new features broaden the toolbox for neuroscientists but the mechanisms of channel activation and ion translocation are still unclear. We use a combination of theoretical approaches like molecular and mathematical modeling as well as experimental techniques like UV/vis spectroscopy, flashlight photolysis and two electrode voltage clamp to reveal how mutations affect the channel properties.

3690-Pos
VSOP/Hv1 Proton Channels Sustain Superoxide Production, Calcium Entry, and Cell Migration by Limiting the Depolarization and Acidification of Activated Neutrophils
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Neutrophils kill microbes with superoxide radicals generated by the NADPH oxidase, an enzyme that moves electrons across membranes. Voltage-gated proton channels (VSOP/Hv1) are required for high-level superoxide production by phagocytes, but the mechanism of this effect is not clear. Using mice bearing a targeted disruption in the VSOP/Hv1 gene (VSOP/Hv1-/-), we show that neutrophils devoid of VSOP/Hv1 lack proton currents but have normal electron currents, indicating that these cells have a fully functional oxidase that cannot conduct protons. VSOP/Hv1-/- neutrophils were more acidic and more depolarized than neutrophils from wild-type mice, and consequently produced less superoxide. Loss of VSOP/Hv1 also aborted calcium responses to chemoattractants, increased neutrophil spreading, and decreased chemokinesis. Our findings indicate that proton channels extrude the acid and compensate the charge generated by the oxidase, thereby sustaining calcium entry signals that control the adhesion and motility of neutrophils. Loss of proton channels thus aborts superoxide production and causes a severe signalling defect in neutrophils.

3691-Pos
Design of a Potent and Selective Small Molecule Kv1.5 Blocker
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The voltage-gated potassium channel Kv1.5 is being studied extensively as a potential target for treating atrial fibrillation and other life-threatening arrhythmias. Since Kv1.5 is expressed selectively in the human atrium and not in the ventricle, a potent and selective Kv1.5 blocker should therefore significantly increase the action potential duration (APD) of the atrium without affecting that of the ventricle. Unlike the existing anti-arrhythmic drugs such as amiodarone, sotalol etc. that block the Kv11.1 channel (hERG), a potent and selective Kv1.5 blocker should not induce dangerous and fatal proventricular arrhythmia.
Phenoxyalkoxypsoralens (PAPs) are a class of compounds that has previously been described to block both the lymphocyte Kv1.3 and the cardiac Kv1.5 channel (*Mol. Pharmacol. 2005*). Through a combination of classical medicinal chemistry and traditional electrophysiology, we now studied the structure-activity relationship of PAPs with the aim of generating more selective Kv1.5 blockers. When the side chain phenyl ring of PAPs were decorated with a combination of electron-donating (methyl) and electron-withdrawing (nitro) groups as in PAP-22 {5-[3-(4-methyl-2-nitrophenoxy)-propoxy]psoralen}, the compounds exhibited a four to five fold increase in selectivity for Kv1.5 over Kv1.3. However, when we substituted the nitro group with a chloro group, as in PAP-25 {5-[2-chloro-4-methylphenoxy)propoxy]-psoralen}, more selective Kv1.3 blockers were generated. We are currently further investigating the effect of other strongly electron-withdrawing groups instead of the nitro group in order to increase the potency and selectivity of PAPs for Kv1.5 over Kv1.3. Other fused tricyclic rings containing 2-aminobenzothiazole are also being explored as a potential pharmacophore to design and develop Kv1.5 blockers.
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3692-Pos
Using Domain Based Discovery Methods to Identify Prokaryotic Counterparts to Eukaryotic Protein Ion Channels
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Our lab, in collaboration with the laboratory of I. Aravind, used domain based methods to discover the prokaryotic counterparts of Ach receptor channels (Tasneem et al), after whole-protein approaches such as BLAST had failed. Our identification was verified by functional studies and by x-ray crystallization of targets we identified. We have subsequently streamlined and formalized the domain search methods and applied them to a variety of ion channels and other membrane proteins. It has become clear that domain based methods are more powerful than whole-protein approaches, provided one has good domain definitions to start the search. The use of domain-based methods depends on a somewhat different model of evolution from BLAST. In BLAST, the operational model is the substitution of one amino acid for another, with gaps being treated as a particular type of substitution. Domain-based methods deal readily and directly with the phenomenon of large scale reorganization of domains, which is now recognized as an essential process for innovation in evolution. In this presentation we will provide an update on prokaryotic Ach receptor channels, a survey of prokaryotic glutamate receptor channels and their relationship to their eukaryotic counterparts, the discovery of a prokaryotic counterpart to HCN and CNG channels which appears likely to be closely related to their common ancestor, and searches on other families that are under way at the time of preparation of this abstract. We gratefully acknowledge support from NSF grants 0835718 and 0235792, from NIH grants 5PN2EY016570-06 and 5R01NS063405-02 from the Beckman Institute for Advanced Science and Technology, the National Center for Supercomputing Applications, and the Renaissance Computing Institute.

3693-Pos
A Novel Fluorescence Assay for Voltage-Gated Ion Channels Based upon Light Induced Voltage Clamp
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Ion channels are a key target class with a high therapeutic potential in virtually all possible disease indications. In addition, a potential side effect of pharmaceutical compounds is the blocking of hERG channels in heart cells making easy and cost effective hERG safety screening necessary for drug development today. Conventional screening techniques yield insufficient data quality particularly when assessing voltage-gated ion channels. Thus, the development of new reliable technologies is desirable to integrate ion channel screening into early lead generation stages of drug discovery.