of interest, we demonstrated a straightforward transfer to Rap1B. As understanding the precise functions of closely related family members is a current frontier in Ras research, this specific control over the activity of a given member is of particular interest. More importantly, successful sensitization of a different G protein to the compounds controlling the activity of the previously engineered H-Ras demonstrates the potential breadth of application of this approach.

2120-Symp
Protein Structure Prediction by Golbal Optimization and its Applications
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One of the fundamental goals of modern sciences is to understand the nature of life, and deciphering the protein structure and its working mechanism lies at the very heart of this agenda. Due to the tremendous success of many genome projects, the number of available protein sequences reached over 5.3 million as of 2007, but less than 1% of these protein structures are known. Reliable and accurate protein structure prediction using only the sequence information is greatly in demand, but it remains as an unsolved problem even after many years of efforts. We intend to establish a successful protein modeling method that is solely based on direct application of principles excluding human interference in modeling steps. This should be contrasted to the common conception in the field that human expertise accumulated by many years of protein modeling is the most important asset for accurate protein structure prediction. In this talk we will discuss recent progresses of our efforts in protein structure prediction. It appears that our newly proposed method, which is based on the direct and rigorous optimization of relevant score functions, can provide significantly improvement for 3D modeling of proteins in the category of High-Accuracy Template-Based Modeling. Applications of highly accurate proteins 3D models to various biological systems will be discussed.

2121-Symp
Finding Small Molecule Ligands for Protein-Protein Interactions and Other "undruggable" Targets
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The central tenant of chemical biology and small-molecule drug discovery is that biology can be manipulated using small, organic compounds. Nevertheless, the known drugs act on only ~1% of the proteome, and the realm of undrugged targets is vast. Protein complexes occupy much of this realm, yet are widely considered ''undruggable'' or, at best, ''challenging.'' Thus, there is an opportunity to greatly expand the range of chemical tools and drugs if we can identify which protein-protein interactions are most amenable to small-molecule interference, and what small-molecule discovery approaches are most likely to yield potent and selective modulators. This presentation will describe some of the outstanding issues and promising advances in tackling protein-protein interactions. For example, we note that many protein interfaces are structurally adaptive, and therefore could have low-energy conformations that are amenable to binding small ligands. Additionally, many enzymes are allosterically regulated by protein complexation, and these protein-protein interfaces are also targets for unconventional enzyme inhibitors.

Platform AC: Cardiac Electrophysiology

2122-Plat
Diverse Effects of a Familial Atrial Fibrillation (FAF)-Related KCNE2 Mutation, R27C, on Cardiac Voltage-Gated Potassium (Kv) Channels
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Background: KCNE2 (E2) is expressed in human heart and can potentially associate with all major cardiac Kv channels to modulate their current amplitude and/or gating kinetics. An E2-R27C mutation was identified in fAF patients, and shown to have a gain-of-function effect on E2/(KCN)Q1 channel complex. However, it is not clear whether/how E2-R27C affects E2 modulation of other cardiac Kv channels, and the biophysical nature of its gain-of-function phenotype when associated with Q1. **Methods**: We express E2-WT or E2-R27C with partner Kv channel α-subunits (E2:α-subunit = 3:1), and record currents using TEVC. **Results**: Coexpressing E2-WT with Kv4.3 (pore-forming subunit of I_{to} channels) reduces peak current amplitude and induces a depolarizing shift in $V_{0.5}$ of inactivation (from −45+5 to −37+5 mV). Relative to E2-WT/Kv4.3, E2-R27C reduces the current-suppressing effect and shifts $V_{0.5}$ of inactivation in the hyperpolarizing direction (to −41+5 mV). Relative to E2-WT/hERG (pore-forming subunit of I_{Kr} channels), E2-R27C induces a modest current suppressing effect along with a hyperpolarizing shift in $V_{0.5}$ of activation (from 10+4 to −8+1 mV). Relative to E2-WT/Q1 (pore-forming subunit of I_{Ks} channels), E2-R27C markedly increases the estimated fully-available current amplitude and induces a hyperpolarizing shift in $V_{0.5}$ of activation (from −7+2 to to −41+5 mV). **Conclusion**: E2-R27C affects how E2 modulates the current amplitude and voltage-dependence of gating of Kv4.3 and hERG channels. The net results can be gain-of-function or loss-of-function, depending on the resting membrane potential (RMP, depolarizing RMP exacerbates Kv4.3 inactivation by E2-R27C) and action potential plateau voltage (APPV, loss of APPV favors currents through E2-R27C/hERG channels). E2-R27C exerts a strong gain-of-function effect on E2/Q1 channels by 2 mechanisms: increasing the fully-available current amplitude and shifting the voltage range of activation in the hyperpolarizing direction.

2123-Plat
Simulation of the Impact of Elevated Cytosolic Na+ on Ca2+ Handling, Mitochondrial Energetics and Cellular Electrophysiology in Guinea Pig Myocytes
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Chronic heart failure is one of the leading causes of morbidity and mortality in the United States. One of the classical strategies for treating heart failure is to inhibit sarcolemmal Na+/K+-ATPase (NKA). Blocking NKA can result in dramatic elevation of [Na+]i, increasing the sarcoplasmic reticulum (SR) Ca2+ load by acting on the plasmalemmal Na+/Ca2+ exchanger (NCX). Whether and how change of [Na+]i affects mitochondrial Ca2+ dynamics and energetics is still under investigation. Since intracellular Na+ is regulated by a complex system involving multiple ions, channels, exchangers and membrane potentials, unraveling its effect on cell physiology and function requires an integrative view of cardiomyocyte physiology. In the present study we developed a mathematical model of cardiomyocyte that incorporates mitochondrial energetics, ion channels and exchangers, and E-C coupling. Using this model, we simulated the effect of elevated cytosolic Na+ on Ca2+ handling, mitochondrial energetics and reactive oxygen species (ROS) generation. Model simulations show that inhibition of NKA (50%) dramatically increased [Na+] in both the cytosol and mitochondria, which consequently caused Ca2+ overload in the cytoplasm during increased workload. Elevated Na+ also decreased ATP concentration and increased mitochondrial ROS production. Concomitant inhibition of mitochondrial Na+/Ca2+ exchanger (mNCE) ameliorated these effects by attenuating cellular Ca2+ overload and increasing [Ca2+]m. Furthermore, inhibiting mNCE also prevented the [ATP]i drop and decreased ROS production. The findings indicate that increasing cytosolic Na+ has an adverse effect on mitochondrial energetics that can be attenuated by simultaneous inhibition of mNCE.

2124-Plat
Biexcitability and Early Afterdepolarization-Mediated Cardiac Arrhythmias
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Under normal conditions in ventricular tissue, both planar wave propagation and spiral wave reentry are mediated by Na current (I_{Na})-mediated depolarization. Under diseased conditions in which repolarization reserve is reduced, however, secondary depolarizations can occur in the plateau or repolarizing phase of the action potential (AP) due to reactivation of the L-type calcium current ($I_{Ca,L}$), known as early afterdepolarizations (EADs). Under these conditions, we observed a novel behavior in which both I_{Na}-mediated spiral wave reentry and $I_{Ca,L}$-mediated spiral wave reentry coexisted in the same homogeneous tissue. I_{Na}-mediated spiral waves were similar to those observed under normal condition, with high rotation frequency (~10 Hz) and nearly full repolarization between beats. $I_{Ca,L}$-mediated spiral waves, however, rotated much slower (2-3 Hz) with membrane voltage remaining above −40 mV, at which I_{Na} is inactivated. We call this novel property of an excitable medium ***biexcitability***. In heterogeneous tissue with transmural AP gradients, pause-induced EADs initiated $I_{Ca,L}$-mediated rotors from the M-cell region. The resulting arrhythmia was characterized by co-existing $I_{Ca,L}$- and I_{Na}-mediated wavefronts, with a frequency and electrocardiographic appearance resembling Torsades de Pointes. The arrhythmia either terminated spontaneously or degenerated to ventricular fibrillation. We propose biexcitability as a novel mechanism of Torsades de Pointes in long QT syndromes.

2125-Plat
B-Type Natriuretic Peptide (BNP) Prolongs Action Potential Duration through Suppressing Transient Outward Potassium Current in Rat Hearts
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