**Molecular Scale Prediction of Lidocaine Interaction with the Pore Domain of Human NaV1.5**

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A primary hindrance to ion channel based drug discovery and design is that no experimental technique exists for identifying drug-target interactions at the molecular scale. In the case of the dominant cardiac Na+ channel isoform Na**V**1.5, the persistent lack of approaches to investigate drug-channel interactions means that there is no way to differentiate between potentially useful and harmful drugs. For example, no method exists to distinguish between drugs that slow conduction or widen the QRS like flecainide, and those that have a strong safety profile in the clinic, such as lidocaine.

To address this problem, we have begun to probe the interaction of the local anesthetic molecule lidocaine with closed and open states of Na**V**1.5 using a computational approach that combines homology modeling with all-atom molecular dynamics (MD) simulation. Models of the pore domain of Na**V**1.5 in putative open and closed conformational states based on the crystallographic bacterial orthologs Na**V**Rh and Na**V**Ms were developed using Rosetta protocols. The lidocaine molecule was parameterized according to CHARMM standards, and MD simulations were run in order to identify the molecular determinants of interaction of the drug within each pore model.

Free energy surface projections from the MD simulations suggested binding sites for lidocaine within our channel models. Preliminary structural analysis suggests that the aromatic group of lidocaine interacts with phenylalanine (F1759) on the S6 helix of domain IV via π-interactions in both open and closed states. In addition, the carbonyl oxygen of lidocaine was predicted to interact with lysine (K1418) of domain III in the open state, indicating a stabilized configuration in which its amide tail physically occludes the pore.