

Novel approaches for screening sodium channel function in drug discovery

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Sodium channels are vital constituents of excitatory cells and participate in a myriad of normal physiological functions. Voltage gated sodium channels are the molecular components that enable action potential generation in these cells and are comprised of a principal alpha subunit and accessory beta subunits. Ten alpha subunits have been identified each with a unique tissue and cellular distribution, and important differences in voltage dependent and kinetic properties. Congenital diseases such as long QT syndrome and epilepsy can be caused by mutations in voltage gated sodium channels and, therefore, they are validated “disease” genes. Modulation of sodium channel function by drugs is a strategy used to treat disease such as epilepsy, cardiac arrhythmia and chronic pain disorders as well as achieving local anaesthesia. As such they are attractive drug targets, yet many challenges remain. Because of the unique tissue distribution profile, achieving desired efficacy without adverse action demands subunit or functional selectivity. Current drug discovery efforts typically rely on high throughput low content screening based on fluorescence assays or on low throughput high content screening based on electrophysiological assays. An added complication is that *in vitro* efficacy and drug sensitivity do not necessarily predict desired *in vivo* efficacy and sensitivity. Here, we describe new approaches designed to address these issues and to provide a new screening method that should be able to meet the practical demands of the drug discovery cycle as well as increase the translation of drug effects from *in vitro* to *in vivo*.