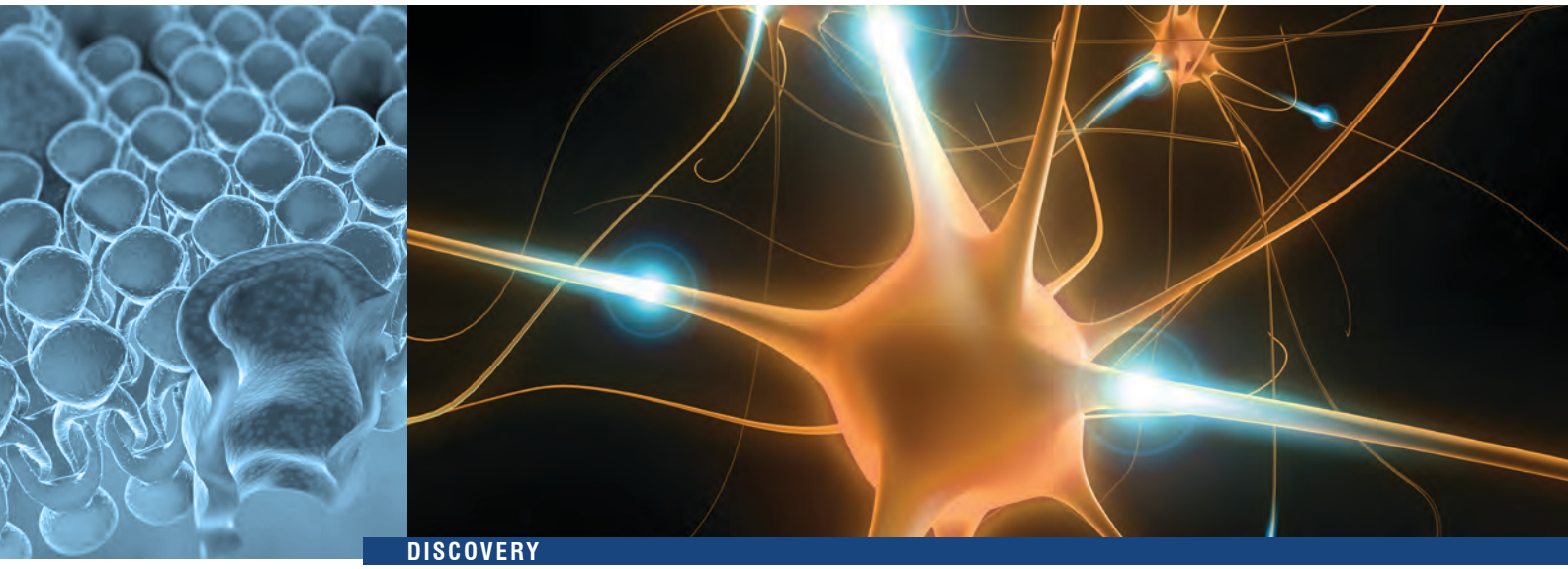
charles river



DISCOVERY

Ion Channel Selectivity Profiling: Seizure/Convulsion

Ion Channel Families:

- Chloride (CLC-2)
- Calcium, voltage-gated (Cav2.1/β_4/$\alpha_2\delta_1$ and Cav3.2)
- Hyperpolarization-gated (HCN1 and HCN2)
- Ligand-gated ($GABA_A$ ($\alpha_1\beta_2\gamma_2$, $\alpha_2\beta_2\gamma_2$, $\alpha_5\beta_2\gamma_2$) and NMDA (NR1/NR2A, NR1/NR2B))
- Potassium, calcium-activated (BK, IK, SK2 and SK3)
- Potassium, voltage-gated (Kv1.1, Kv4.2/KChiP2.2 and KCNQ (KCNQ2/3, KCNQ2/4 and KCNQ3/5))
- Sodium, voltage-gated (Nav1.1, Nav1.2, Nav1.3 and Nav1.6)

The Charles River ion channel portfolio includes over 120 targets which have been organized into Channel Panels® based on current scientific findings, proving a useful tool in guiding early screening and selectivity profiling. Our Seizure/Convulsion Channel Panel® includes ion channels expressed in the central nervous system (CNS) that have been linked to inherited forms of epilepsy.

Selectivity Profiling

Identification of a compound's target specificity and potential for off-target effects is a critical step in the drug discovery process and often includes assessments against specific target class families, critical safety targets or by therapeutic area. In addition to our therapeutic area-specific Channel Panels®, we offer screening on a number of electrophysiology platforms. When required, our scientists can design customized panels to meet a client's needs. As pioneers in the field of ion channels, we are able to provide expert consultation to facilitate interpretation of results.

Ion Channels and Seizures

Ion channels expressed in the CNS have been linked to inherited forms of epilepsy. Gain-of-function mutations in excitatory channels (e.g., voltage-gated sodium Nav1.1, Nav1.2 and Nav1.3, voltage-gated calcium Cav3.2, and hyperpolarization-gated HCN1 and HCN2 channels) have been shown to cause persistent, depolarizing currents leading to hyperexcitability that facilitates epileptic seizures and convulsions. Hyperexcitability also may result from loss-of-function mutations in inhibitory channels (e.g., voltage-gated potassium KCNQ, calcium-dependent potassium BK and ligand-gated chloride $GABA_A$). Adverse neurological events may be caused by drug side-effects that mimic mutation-induced alterations in channel function. Conversely, antiepileptic drugs can act as antagonists of excitatory channels or as agonists of inhibitory channels. Thus, the ion channels in our seizure-convulsion panel are potential therapeutic targets for treatment of hyper-excitability (e.g., seizure, pain, neurodegeneration, anxiety, migraine and psychosis) as well as targets for adverse events.