charles river

DISCOVERY

# Ion Channel Selectivity Profiling:
# Cardiovascular

### Ion Channel Families:

- Calcium, voltage-gated ($Cav1.2/\beta_2/\alpha_2\delta_1$, $Cav1.3/\beta_3/\alpha_2\delta_1$ and Cav3.2)
- Exchanger (NCX1.1)
- Hyperpolarization-gated (HCN2 and HCN4)
- Ligand-gated ($nAChR\alpha_7$ and P2X4)
- Potassium, voltage-gated (Kv1.3, Kv1.5, Kv4.3, KvLQT1/mink (Kv7.1) and hERG (Kv11.1))
- Potassium, inward rectifier (Kir2.1, Kir3.1/3.4 and Kir6.2/SUR2A)
- Potassium, calcium-activated (BK, IK and SK3)
- Sodium, epithelial (ENaC)
- Sodium, voltage-gated (Nav1.5)
- Transient receptor potential (TRPC1, TRPC4, TRPC6, TRPM4, TRPV1 and TRPV4)

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 Cardiovascular Channel Panel® includes ion channels which regulate blood flow primarily by vasodilation and constriction of blood vessels.

### 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 Vasodilation

Physiological regulation of vascular resistance relies on the control of $Ca^{2+}$-dependent contraction of the smooth muscle that surrounds the endothelial cell lining of the vessel lumen. Control of smooth muscle tension involves a variety of $Ca^{2+}$-permeable channels (e.g., Cav1.2, P2X4, nAChRα7 and most TRP channels), as well as channels that regulate release of vasoactive substances, and channels that regulate arterial tone via control of membrane potential ($K^+$-selective channels BK, SK3, IK, Kir2.1, Kir6.1, Kir6.2, Kv1.5 and Kv7.1; and a non-selective channel TRPM4). Under pathological conditions (e.g., vascular inflammation, chronic hypertension, heart failure or hypoxia) decreased vascular integrity, increased endothelial permeability, and hyperplasia may compromise vascular function. Ion channels involved in pathological mechanisms include Kv7.1, nAChRα7 and several TRP channels. Thus, the Cardiovascular Channel Panel® represents a selection of channels that are potential therapeutic targets for conditions such as hypertension, atherosclerosis, and heart failure. Moreover, drug-induced channel dysfunction may be responsible for adverse effects.

EVERY STEP OF THE WAY