We are interested in the molecular biology of sensory transduction and neurotransmitter action in the mammalian nervous system. One of our goals is to understand the molecular basis of somatosensation - the process whereby we experience touch and temperature - with an emphasis on identifying molecules that detect noxious (pain-producing) stimuli. We are also interested in understanding how somatosensation is altered in response to tissue or nerve injury.

Our approach has been to identify molecular targets for drugs or natural products that mimic the psychophysical effects of commonly encountered somatosensory stimuli, such as heat or cold. Thus, we have asked how capsaicin, the main pungent ingredient in "hot" chili peppers, elicits a sensation of burning pain. Using a combination of molecular genetic, electrophysiological, and histological methods, we have shown that capsaicin activates an excitatory ion channel (called TRPV1) on sensory nerve endings. Remarkably, TRPV1 is also activated by heat (>43°C), and we have used transgenic methods to demonstrate that this channel contributes to the detection of noxious heat in vivo and is essential for the development of thermal hypersensitivity following tissue injury. These findings have led us to ask how TRPV1 functions as a molecular integrator of physical and chemical signals that regulate sensory neuron excitation under normal and pathophysiological conditions.

On a related front, we have extended our molecular analysis of somatosensation by determining how we detect cold. Following the paradigm set forth by our work on the capsaicin receptor, we asked how cooling compounds, such as menthol, elicit a cool sensation. We have cloned a menthol receptor from primary sensory neurons and shown that it is also activated by cold thermal stimuli, proving that menthol elicits its familiar psychophysical sensation by activating a cold receptor. The structure of this menthol/cold receptor (TRPM8) resembles that of TRPV1, demonstrating that ion channels of this class serve as the principal sensors of thermal stimuli in the mammalian peripheral nervous system. Indeed, we have recently shown that mice deficient in TRPM8 display striking defects in cold and menthol sensitivity at the cellular and behavioral levels.

In more recent studies, we have identified another TRP channel (ANKTM1 or TRPA1) on sensory nerve fibers that is activated by allyl isothiocyanate, the pungent ingredient in wasabi and other mustards. Genetic and physiological evidence from our lab suggests that TRPA1 is an important component of the signaling mechanism through which certain pro-algesic agents depolarize sensory neurons to produce pain hypersensitivity and neurogenic inflammation.

In addition to our work on somatosensation and pain, we also study specific neurotransmitter receptor systems, such as those activated by serotonin or extracellular nucleotides. A recent example of our work in this area includes identification of the P2Y12 receptor, an ADP-
activated G protein-coupled receptor that contributes to platelet aggregation and serves as the molecular target for the widely prescribed antithrombotic drugs, clopidogrel and ticlopidine. P2Y12R is also expressed by microglial cells in the brain and we have recently shown that this receptor modulates microglial activity to regulate injury responses in the central nervous system.