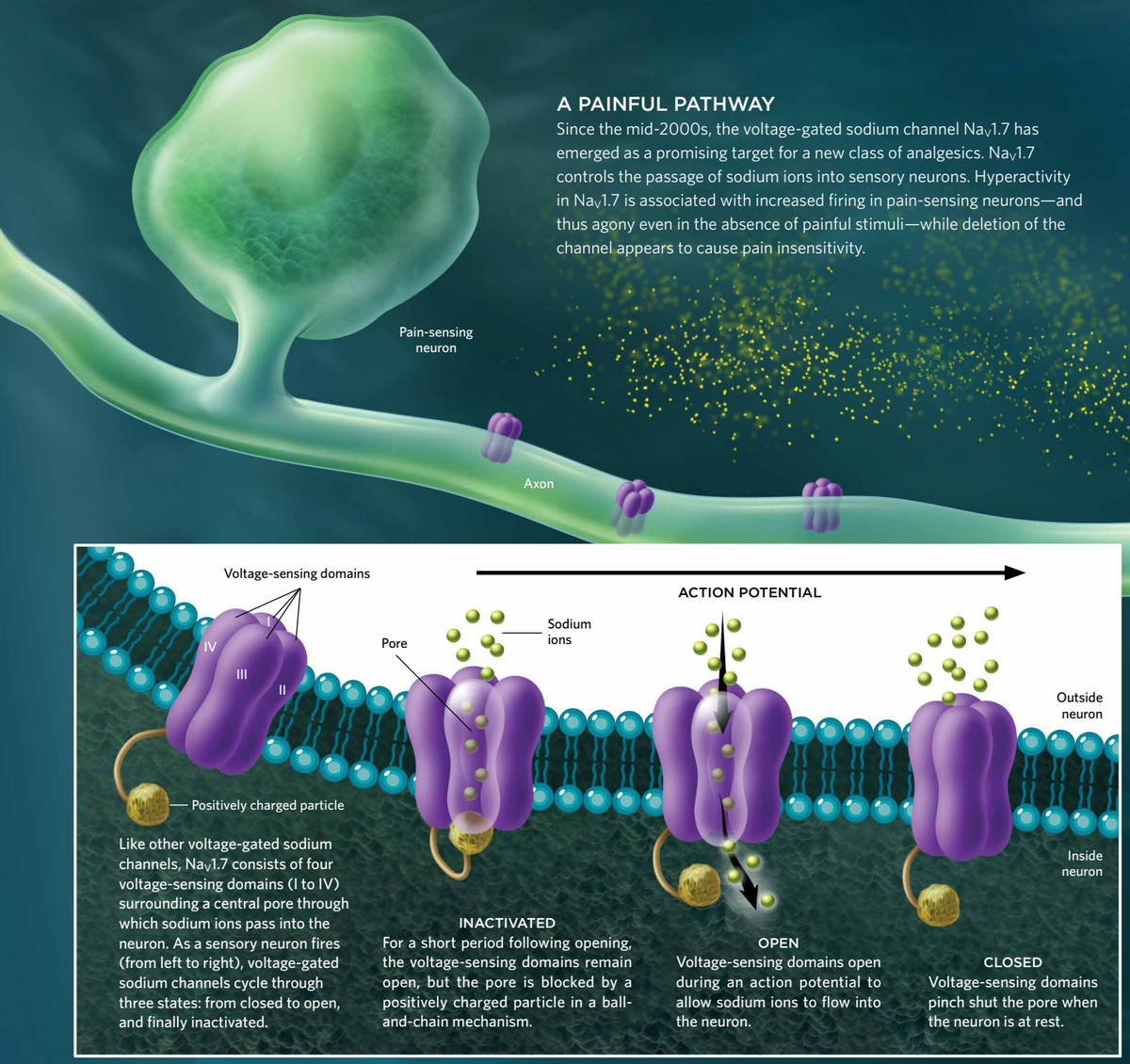
A PAINFUL PATHWAY

Since the mid-2000s, the voltage-gated sodium channel $Na_V1.7$ has emerged as a promising target for a new class of analgesics. $Na_V1.7$ controls the passage of sodium ions into sensory neurons. Hyperactivity in $Na_V1.7$ is associated with increased firing in pain-sensing neurons—and thus agony even in the absence of painful stimuli—while deletion of the channel appears to cause pain insensitivity.

PRECISION TARGETING

Many companies are working to develop molecules that inhibit the $Na_V1.7$ channel. But while the basics of the protein complex's function are well established, researchers are still learning how best to target $Na_V1.7$ in order to achieve analgesia. Early attempts to inhibit the channel used small molecules to block the pore region, but because this pore is well-conserved among the Na_V family, these drugs generally showed low selectivity for $Na_V1.7$. Recent efforts have targeted the less-conserved voltage-sensing domains of $Na_V1.7$ to lock the channel in a closed or inactivated state. Hitting the right part of the protein is not the only challenge—even with the development of apparently highly potent $Na_V1.7$ blockers, researchers are now questioning just where along a sensory neuron a drug needs to act in order to be maximally analgesic.



Like other voltage-gated sodium channels, $Na_V1.7$ consists of four voltage-sensing domains (I to IV) surrounding a central pore through which sodium ions pass into the neuron. As a sensory neuron fires (from left to right), voltage-gated sodium channels cycle through three states: from closed to open, and finally inactivated.

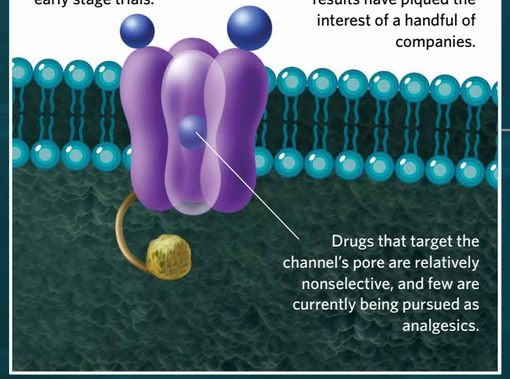
INACTIVATED
For a short period following opening, the voltage-sensing domains remain open, but the pore is blocked by a positively charged particle in a ball-and-chain mechanism.

OPEN
Voltage-sensing domains open during an action potential to allow sodium ions to flow into the neuron.

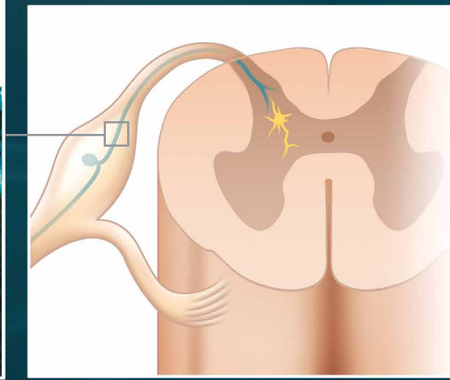
CLOSED
Voltage-sensing domains pinch shut the pore when the neuron is at rest.

Small molecules that target $Na_V1.7$'s voltage-sensing domains show high specificity for the receptor, and have shown promise in early stage trials.

Toxin-derived peptides also show high specificity for $Na_V1.7$'s voltage-sensing domains, and promising preclinical results have piqued the interest of a handful of companies.



Drugs that target the channel's pore are relatively nonselective, and few are currently being pursued as analgesics.



The failure of many supposed $Na_V1.7$ blockers to effectively blunt pain has some researchers questioning the assumption that inhibiting $Na_V1.7$ in the periphery is sufficient. Because sensory neurons often have axons that terminate inside the central nervous system, drugs targeting $Na_V1.7$ may need to cross the blood-brain barrier to boost their painkilling effect.