Mitchell Goldfarb

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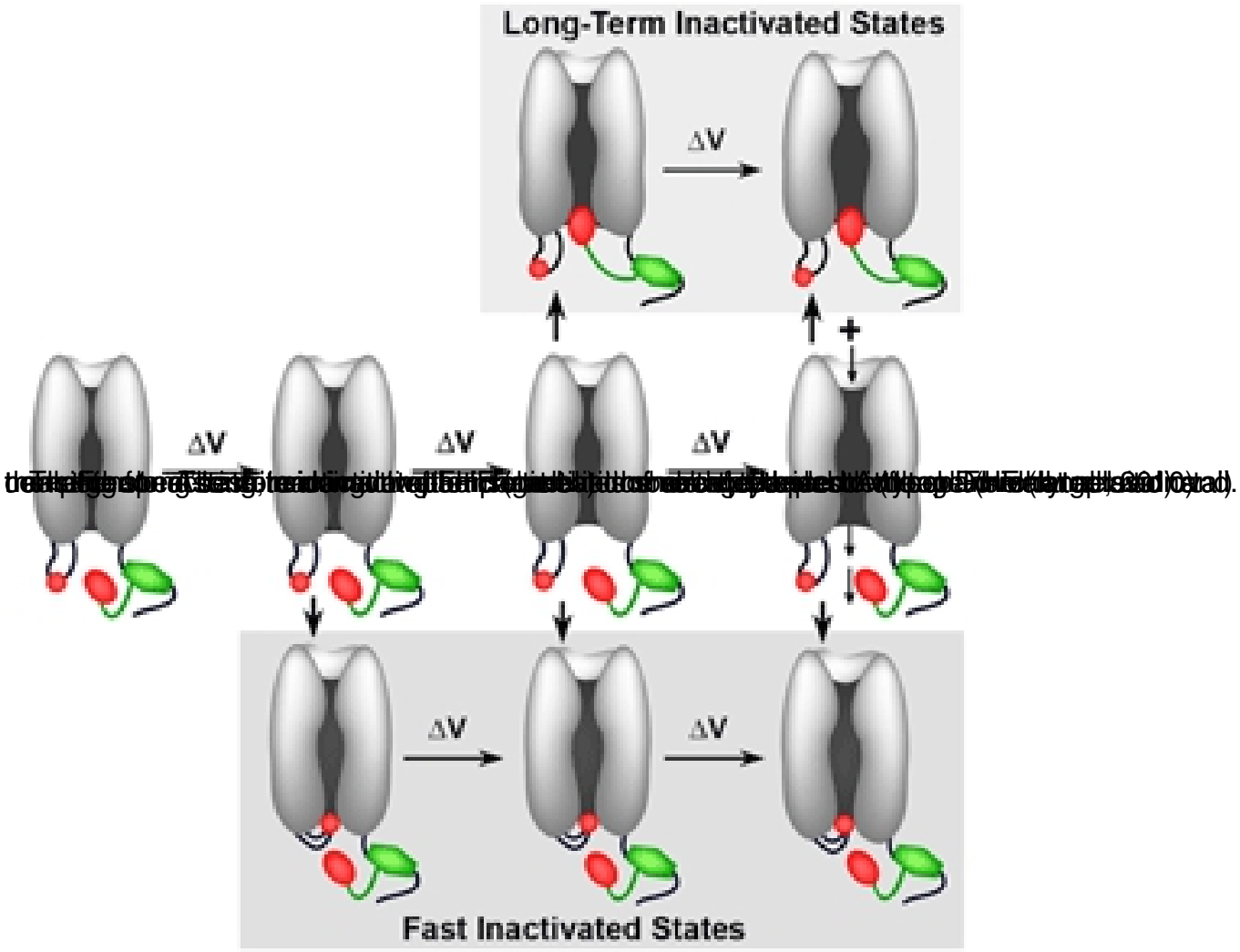
Education:

- B. S. 1974, Massachusetts Institute of Technology
- Ph. D. 1979, Massachusetts Institute of Technology

Current Research Projects

- **FGF Homologous Factors: Regulators of Sodium Channels Contolling Brain and Cardiac Function**

We have discovered and are studying proteins called fibroblast growth factor homologous factors (FHFs). FHF gene mutations engineered in mice or occurring naturally in humans are associated with a range of neurological disorders. FHFs were discovered by virtue of their sequence homology to fibroblast growth factors (FGFs). While FGFs exert pleiotropic biological effects through interactions with their cell surface FGF receptors, we have demonstrated that FHFs are intracellular and bind to specific neuronal protein targets. A principal set of targets are the alpha subunits for voltage-gated sodium channels. Using FHF knockout mice, we have shown that FHFs are required for neurons to fire robustly, and this is accomplished by FHF modulation of sodium channel fast inactivation (Goldfarb et al., 2007). We have also shown that some FHFs induce a rapid onset long-term inactivation of sodium channels, which is mediated by an inactivation particle in the effector N-terminus of these FHF isoforms (Dover et al., 2010). Long-term inactivation progressively slows the firing rate of neurons, a process call accommodation or frequency adaptation (Venkatesan et al., 2014). Ongoing studies are defining the physical mechanisms of FHF actions and the functional significance of neuron-type-specific and neuron-compartment-specific distribution of FHF protein isoforms. Some of these studies entail the use of fast-responsive voltage sensitive dyes to visualize action potentials along axons and dendrites. An example on this technique applied to cultured cerebellar granule cells is shown in Figure 2 and has led to discovery that spike conduction occurs in an FHF-independent manner (Dover et al., 2016) We have also shown mechanistically how FHF dysfunction can lead to severe epilepsy (Siekierska et al., 2016) and temperature-dependent cardiac arrhythmia (Park et al., 2016).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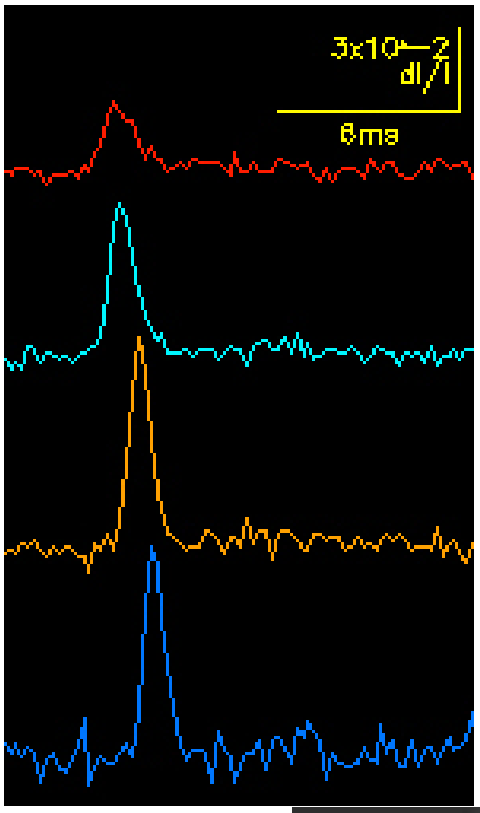
Fast Inactivated States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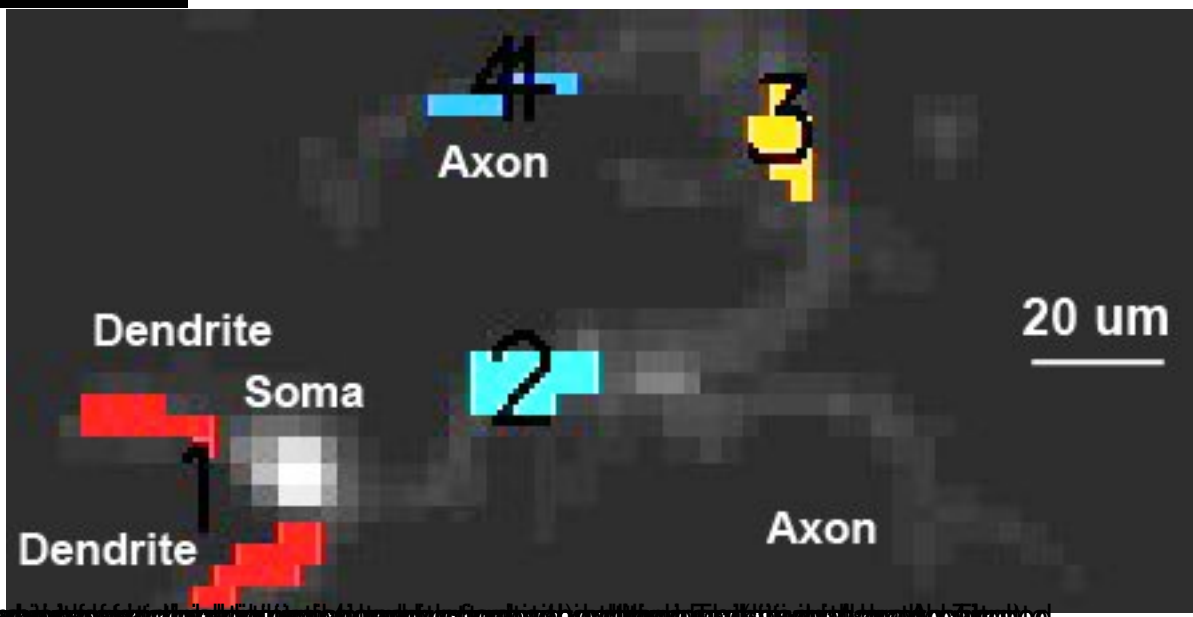
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