Docket #: S06-398

New Light Control Mechanism (NpHR) That Inhibits Neural Activity

The inventors have identified and developed an archaeal light-driven chloride pump (NpHR) from Natronomonas pharaonis for temporally precise optical inhibition of neural activity. NpHR allows either knockout of single action potentials, or sustained blockade of spiking. NpHR is compatible with ChR2, the previous optical excitation technology from their laboratory (Stanford Docket S05-170), in that the two opposing probes operate at similar light powers but with well-separated action spectra. NpHR, like ChR2, functions in mammals without exogenous cofactors, and the two probes can be integrated with calcium imaging in mammalian brain tissue for bidirectional optical modulation and readout of neural activity. Likewise, NpHR and ChR2 can be targeted together to Caenorhabditis elegans muscle and cholinergic motor neurons to control locomotion bidirectionally. NpHR and ChR2 form a complete system for multimodal, high-speed, genetically targeted, all-optical interrogation of living neural circuits.

Additional optical control of neural circuitry using NpHR is described in Stanford Docket S06-398A.

Stage of Research
The inventors have developed eNpHR (enhanced NpHR), an improved version of NpHR for safe expression at high levels under strong promoters and with augmented inhibitory function *in vitro* and *in vivo*.

Applications

- Optical inhibition of neural activity for therapeutic and research purposes

Advantages

- When combined with the engineered Channelrhodopsin ChR2, the NpHR/ChR2 system enables rapid bidirectional control of neurons on the timescale of milliseconds, thus enabling emulation or alteration of the neural code. These fast genetically based, neural-spike-controlling technologies powerfully augment existing tools for interrogating neural systems.

Publications

- US Patent Application: 12/041,628
- Feng Zhang, Li-Ping Wang, Martin Brauner, Jana F. Liewald, Kenneth Kay, Natalie Watzke, Phillip G. Wood, Ernst Bamberg, Georg Nagel, Alexander Gottschalk & Karl Deisseroth. "Multimodal fast optical interrogation of neural circuitry" *Nature* 446, 633-639 (5 April 2007)
- Gradinaru V, Thompson KR, Deisseroth K. "eNpHR: a Natronomonas halorhodopsin enhanced for optogenetic applications.", *Brain Cell Biol.* 2008 Aug;36(1-4):129-39. Epub 2008 Aug 2.
- PCT Application: "Systems, Methods and Compositions for Optical Stimulation of Target Cells" (W0/2008/106694)

Patents

- Published Application: 20090093403
- Published Application: 20110301529
- Published Application: 20140113367
- Published Application: 20160175607
- Published Application: 20180050219
- Published Application: 20190224493
- Issued: 9,284,353 (USA)
- Issued: 10,589,123 (USA)

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