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Presentation Abstract

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Title: High-efficacy, temporally-precise, in vivo neural silencing via light-driven proton pumping

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Abstract: The ability to silence neurons in vivo in a temporally-precise fashion requires the ability to hyperpolarize neurons strongly, safely, and in a rapidly-reversible fashion. While *N. pharaonis* halorhodopsin (Halo/NpHR) and derivatives thereof (eNpHR) have been reported to mediate inhibitory currents of 40-100 pA in response to yellow light, such currents are small compared to the drive currents to many neurons in the awake behaving mammalian brain. Accordingly, we performed an unbiased, systematic screen of halorhodopsin homologs across species from multiple kingdoms, revealing that a novel neural silencer, an archaerhodopsin proton pump, can mediate currents up to 6x higher than the initially-reported halorhodopsin. The molecule Arch (*H. sodomense* archaerhodopsin-3, also referred to as aR-3), when delivered to neurons in vitro, can mediate peak currents of 911 ± 82 pA at an effective yellow light illumination power of 65.8 mW/mm² (n = 6 cells); at 14.3 mW/mm², silencing currents were 329 ± 31 pA (n = 22). Arch is maximally sensitive to green light (566 ± 66 nm peak excitation), useful given the low cost of green lasers, but Arch is also effectively stimulated by yellow/orange light, and thus is compatible with existing Halo-driving equipment. Indeed, Arch can mediate $90 \pm 4\%$ reductions in firing rate in cortical neurons in awake behaving mice (n = 13 neurons). In Arch-expressing cells, 60 seconds of illumination results in a slight, but significant increase of pH by 0.174 ± 0.001 (n = 10 neurons). No cell damage was observed. Arch also demonstrates significantly improved kinetics for increased temporal

precision, with an onset time half the duration of Halo ($\tau_{\text{on}} = 8.3 \pm 1.4$ ms, $n = 20$ cells). Finally, Arch spontaneously recovers in the dark after light exposure, unlike Halo, which requires a second wavelength of light to accelerate recovery. Thus, Arch may enable simpler optical devices for systematic probing of circuits in neurological and psychiatric animal models.

The plentifulness of protons in the brain, combined with the efficiency of Arch, reveals a new and powerful reagent for safe, effective, *in vivo* neural silencing in response to light. The characterization of a third class of microbial-type opsins capable of optical control of neural activity reveals the power inherent to genomic diversity in revealing highly-optimized reagents for neural control. Also, given our recent work demonstrating channelrhodopsin-2 safety and efficacy in non-human primates (Han et al., 2009), it is possible that some of these novel reagents may find a translational path, enabling new therapies for improving human health.

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