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Presentation Abstract

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Title:	Multiple-color optical silencing of distinct neural populations using novel classes of light-driven ion pumps
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Abstract:

In order to assess the causal contribution of two different kinds of neurons to neural dynamics within a single microcircuit, it would be helpful to be able to rapidly and reversibly silence each of the two populations of neurons, using two different colors of light. Recently we performed an unbiased and systematic screen of halorhodopsin homologs across multiple kingdoms, and discovered multiple relatively-uncharacterized classes of microbial opsins which possess significant neural silencing potential. Some of these opsins had spectral sensitivity significantly shifted to the blue, suggesting a potentiality for multiple-color silencing, in combination with yellow-light driven halorhodopsins. In particular, we discovered that one opsin, from the fungus Leptosphaeria maculans, here nicknamed Mac, has a spectral activation peak at 537 nm, blue-shifted relative to the N. pharaonis halorhodopsin, Halo/NpHR. Mac mediates currents of 308 $\pm$ 68 pA in response to 14.3 mW/mm^2 light through a standard 535 $\pm$ 25 nm bandpass filter. Importantly, the shape of the Mac action spectrum is also distorted to include additional blue regions of the spectrum. In addition, we have engineered a variant of halorhodopsin, ss-Prl-Halo (sPHalo), that boosts the performance of Halo by 2.5-fold when illuminated with yellow light. At 620 nm, illumination of spHalo results in currents approximately 6x higher than elicited from Mac, whereas at 488 nm, illumination of Mac results in currents approximately 2.5x higher than for spHalo. We are in the process of optimizing these results and assessing these functions in vivo. We anticipate that the natural diversity of genomic possibility across kingdoms of living organisms will continue to reveal novel reagents for enabling powerful and precise optical control of specific neural functions. 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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