

[Print this Page](#)

## Presentation Abstract

Program#/Poster#: 388.2/GG97

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

Location: South Hall A

Presentation Time: Monday, Oct 19, 2009, 9:00 AM -10:00 AM

Authors: **B. Y. CHOW**<sup>1</sup>, \***X. HAN**<sup>1</sup>, **X. QIAN**<sup>1</sup>, **M. LI**<sup>1</sup>, **A. S. CHUONG**<sup>1</sup>, **P. E. MONAHAN**<sup>1</sup>, **A. S. DOBRY**<sup>1</sup>, **E. S. BOYDEN**<sup>2</sup>;  
<sup>1</sup>Media Lab., <sup>2</sup>Media Lab, Bioengineering Dept., McGovern Inst., MIT, Cambridge, MA

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  $911 \pm 82$  pA at an effective yellow light illumination power of 65.8 mW/mm<sup>2</sup> (n = 6 cells); at 14.3 mW/mm<sup>2</sup>, silencing currents were  $329 \pm 31$  pA (n = 22). Arch is maximally sensitive to green light ( $566 \pm 66$  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  $0.174 \pm 0.001$  (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.

Disclosures: **B.Y. Chow**, None; **X. Han**, None; **X. Qian**, None; **M. Li**, None; **A.S. Chuong**, None; **P.E. Monahan**, None; **A.S. Dobry**, None; **E.S. Boyden**, None.

Keyword(s):  
optogenetic  
channelrhodopsin  
opsin

Support: XH: HHWF and NHI 1K99MH085944

ESB: NIH Director's New Innovator Award (DP2 OD002002-01), NSF (0835878 and 0848804), McGovern Institute Neurotechnology Award, Department of Defense, NARSAD, Alfred P. Sloan Foundation, Jerry Burnett Foundation

ESB:SFN Research Award for Innovation in Neuroscience, MIT Media Lab, Benesse Foundation, and Wallace H. Coulter Foundation

[Authors]. [Abstract Title]. Program No. XXX.XX. 2009 Neuroscience Meeting Planner. Chicago, IL: Society for Neuroscience, 2009. Online.

2009 Copyright by the Society for Neuroscience all rights reserved. Permission to republish any abstract or part of any abstract in any form must be obtained in writing by SfN office prior to publication.