



Presentation Abstract

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Presentation Title: Cell-type manipulation of neuronal activity using Cre-responder and Cre-driver mice

Location: Hall A-C

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Authors: ***L. MADISEN**¹, T. MAO², H. KOCH³, J. ZHUO⁴, C. MONETTI⁵, T. HSU³, J. KIDNEY¹, H. GU¹, M. MILLS¹, E. BOYDEN⁶, A. JONES¹, N. RAMIREZ³, A. NAGY⁵, K. SVOBODA⁷, X. HAN⁴, E. TURNER³, H. ZENG¹;
¹Allen Inst. Brain Sci., SEATTLE, WA; ²Oregon Hlth. and Sci. Univ., Portland, OR; ³Seattle Children's Res. Inst., Seattle, WA; ⁴Boston Univ., Boston, MA; ⁵Samuel Lunenfeld Res. Inst. of Mount Sinai Hosp., Toronto, ON, Canada; ⁶MIT, Cambridge, MA; ⁷Howard Hughes Med. Institute, Janelia Farm Res. Campus, Ashburn, VA

Abstract: A major challenge in neuroscience is to understand how brain functions are mediated by particular cell types within neural networks. Dissection of such complex networks requires the ability to manipulate the activity of specific cell populations and to examine resulting changes in the output of interest. To this end, we have been working to create a set of Cre-responder and Cre-driver mice that will enable the activation or inactivation of neuronal activity in a cell-type selective manner. We previously found that, when targeted to the Rosa26 locus, floxed transgenes encoding fluorescent markers and genetic tools can be expressed at functionally high levels in cells that also express Cre. Using our transgenic strategy, we created 4 mouse lines that carry various light-activated channel proteins: channelrhodopsin-tdTomato (Ai27), channelrhodopsin-EYFP (Ai32), enhanced halorhodopsin eNpHR3.0 (Ai39), and the proton pump Arch (Ai35). We report here that, both in cortical slices and in awake, head-fixed mice, the opsins in all 4 lines are responsive to photoactivation in a Cre-dependent manner. Photostimulation of Ai27 and Ai32-expressing neurons evoked action potentials and increased firing, whereas stimulation of Ai35 and Ai39-expressing neurons resulted in cellular hyperpolarization and the

silencing of action potentials. Although the Rosa26 locus has proven useful for expressing Cre-responder transgenes, we are pursuing other ubiquitous genetic loci as alternative targets that may confer even higher levels of activator-dependent transgene expression.

As a second component of our transgenic effort, we continue to expand our collection of novel driver lines in which Cre expression is enriched in particular classes of neurons, cell layers, structures or nuclei. To further increase the specificity of this genetic component, we are developing intersectional strategies for transgene regulation that rely on the expression of inducible or multiple recombinases, and a variety of activators or split activators. By combining responder genes that require two activating events for expression with our growing collection of Cre and other activator-driver lines, we expect to develop more spatially and temporally precise tools to manipulate various neuronal cell types.

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