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Presentation Abstract

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Title: Molecular toolboxes for quantitatively precise, genetically-targeted optical control of normal and pathological neural network dynamics

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Abstract: The use of genetically-targetable molecules such as channelrhodopsin-2 (ChR2) and halorhodopsin (Halo/NpHR) to make neurons optically activatable and silenceable for milliseconds at a time is beginning to open up new frontiers in the investigation of how the brain computes. These optical molecular sensitizers also may enable novel therapies to remedy neurological and psychiatric disorders. However, viral and transgenic gene delivery is not usually considered at the quantitative level of gene expression required for precise optical control of neural network dynamics. Here we present multiple synergistic technologies that together enable multiple cell types to be targeted with equal levels of channelrhodopsin-2 and halorhodopsin, thus opening up quantitative and analytical control of neural circuits. First, we have generated a single gene that encodes a fusion protein between channelrhodopsin-2 and halorhodopsin, which cleaves between the two opsins. This gene results in the two opsins being expressed in stoichiometry to one another, enabling precise bi-directional control of neuronal activity in any cell expressing the gene. Second, we have developed a large-cassette lentiviral delivery system, containing this self-cleaving fusion protein in the antisense orientation (and thus silent) and flanked by loxP sites that allow Cre-mediated inversion to the sense orientation and thus expression. When this virus is injected into the brains of mice from any of the many transgenic lines expressing Cre recombinase in specific cell types, the specific cells then become bi-directionally controllable by different colors of light. We demonstrate cell-specific manipulation of neural dynamics using these novel technologies.

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