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Presentation Abstract

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Title: Development of next-generation optical neural silencers through directed combinatorial optimization

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Abstract: An invaluable power in the study of the brain is the ability to rapidly and safely silence individual neurons or neuron types with high spatiotemporal precision. In past years, we and others have devised powerful optical neural silencers through strategies such as the identification of novel reagents through exploration of genomic diversity, and the optimization of existing reagents through enhancement of membrane trafficking. These ‘optogenetic’ technologies are in widespread use in neuroscience, and are freely available (e.g., see <http://syntheticneurobiology.org/protocols>). In order to continue the improvement of neural silencers, we have performed further optimization of neural silencing tools by directed mutagenesis of key residues. Here we present the results, revealing multiple point mutations in specific halorhodopsins that enhance light-driven chloride pumping performance by ~3x, as well as point mutations in specific light-driven proton pumps that enhance photocurrents by ~3x. Finally, we present the results of the combinatorial optimization of silencing opsins along all three axes - opsin type, mutation set, and trafficking strategy - thus yielding reagents that operate with maximum light sensitivity and photocurrent magnitude.

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