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Presentation Abstract

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Presentation Title: Projection targeting and network assays in squirrel monkey optogenetics

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Abstract: In recent years, work in rhesus demonstrated neural modulation using both excitatory and inhibitory microbial opsin genes, as well as preliminary evidence of small but significant behavioral effects (O'Shea, et al, current volume). However, overall development of nonhuman primate opsins remains limited, in part due to long timescales of rhesus research. Primate optogenetics may be advanced by use of other primate models more closely matched to the rapid timescale of opsin development. New World monkeys, while an important model in neuroscience, have yet to be established in optogenetics, despite potential advantages compared to rhesus; for example, problems of scale (e.g., volume of light delivery) are less acute in these smaller primates. We previously reported histologically-assessed expression of ChR2 and eNpHR3.0 under the calmodulin dependent kinase II alpha (CamKIIa) promoter using AAV2/5 (Kalanithi, et al, SfN 2011). Here we report in squirrel monkey expression of a broader slate of opsins and promoters, including ChR2(H134R), eNpHR3.0, and C1V1(t/t), under control of several promoters, including human synapsin (hSyn), human thymocyte antigen (hThy1), and CamKIIa. This panel of opsins and promoters may allow versatile selection and control of neural targets; however, highly specific circuit selection in primates will likely require projection-targeting and transcellular tracer techniques. We first

tested a transcellular tracer protein, wheat germ agglutinin fused to Cre recombinase (WGA-Cre), along with a Cre-dependent opsin; we found that this strategy works well to selectively transduce M1 to PMd axons, without transducing M1 to thalamus axons. Next, to provide a functional assay of network activity, we intraoperatively stimulated opsin-expressing cells (hSyn-ChR2 in M1 in 3 animals and CamKIIa-C1V1 in PMd in 1 animal) and subsequently stained for the immediate-early gene product (and marker of neuronal activation) c-fos. In this anesthetized preparation, optogenetic activation appeared to recruit certain areas of cortex outside of the area of illumination, but did not recruit M1 projections to spinal cord, which is consistent with the ability to modulate rhesus behavior without evoking motor twitches. Optogenetic modulation in squirrel monkeys may allow important translational studies requiring larger numbers of animals than feasible in rhesus, and may aid the development of tools for rhesus research. In addition, optogenetic modulation appears to be a viable and reliable tool for use in squirrel monkey neuroscience.

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