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RED-SHIFTED CHROMOPHORE SUBSTITUTION FOR OPTOGENETIC APPLICATIONS

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Optogenetics is one of the most important technological breakthroughs in neuroscience during the past decade, and holds tremendous promise for dissecting the mechanisms of neurologic disease and for treating a range of disorders. Optogenetic actuators are ion channels or pumps that can be regulated by light, thus permitting the investigator to turn neuronal activity on and off with high spatial and temporal precision. The most commonly used optogenetic actuators operate in the 450-600 nm range, presenting two challenges to the investigator: (1) light in this range is strongly scattered and absorbed by brain tissue and blood, limiting the tissue depth at which actuators can be effectively utilized; and (2) many optogenetic sensors that report physiological states (e.g., calcium levels or voltage) have activation or emission spectra that strongly overlap the wavelength range of the optogenetic actuators, thus complicating their simultaneous use.

This invention represents a novel biomimetic strategy for red-shifting optogenetic actuators: red-shifted chromophore substitution. This approach is complementary to protein engineering and is based on a strategy used by migrating fish to enable better vision in turbid water. When salmon migrate from the open ocean (where incident light is in the 450-500 nm range) into inland streams (where incident light is significantly red-shifted), they switch from using retinal as their visual chromophore to 3,4-didehydroretinal which has red-shifted spectral properties. This chromophore switch causes a dramatic red-shift of the fish's opsin spectral sensitivity, thereby permitting the animal to peer more deeply into the shallow stream. We have identified the enzyme mediating the conversion of retinal into 3,4-didehydroretinal, and plan to co-express it with optogenetic actuators in mammalian neurons in vivo, thereby red-shifting their action spectra. A key feature of this approach is that chromophore substitution can be coupled to the use of any existing actuator in any part of the mammalian CNS. Thus, this strategy has the potential to broadly impact the field of optogenetics, with important basic and therapeutic applications. A recent study demonstrated that in vitro substitution of retinal with 3,4-didehydroretinal in optogenetic actuators can red-shift the actuator's action spectrum, thus confirming the validity of our approach.

In summary, this invention consists of the application of Cyp27c1 co-expression with optogenetic devices to red-shift their action spectra, thereby permitting the use of optogenetic devices at greater tissue depths and in conjuction with other actuators. This red-shifting approach has important basic and therapeutic implications.