**UKE Paper of the Month April 2014**

Science 344(6182):409-412.

## Conversion of Channelrhodopsin into a Light-Gated Chloride Channel

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**ABSTRACT:** The field of optogenetics uses channelrhodopsins (ChRs) for light-induced neuronal activation. However, optimized tools for cellular inhibition at moderate light levels are lacking. We found that replacement of E90 in the central gate of ChR with positively charged residues produces chloride-conducting ChRs (ChloCs) with only negligible cation conductance. Molecular dynamics modeling unveiled that a high-affinity Cl–-binding site had been generated near the gate. Stabilizing the open state dramatically increased the operational light sensitivity of expressing cells (slow ChloC). In CA1 pyramidal cells, ChloCs completely inhibited action potentials triggered by depolarizing current injections or synaptic stimulation. Thus, by inverting the charge of the selectivity filter, we have created a class of directly light-gated anion channels that can be used to block neuronal output in a fully reversible fashion.

**STATEMENT:** *Chloride-conducting channelrhodopsins are the first directly light-gated ion channels that block neuronal firing in response to blue light. They are up to 10000 times more sensitive than light-driven ion pumps that were previously used for optogenetic inhibition. Our new tool will enable researchers to switch off well-defined groups of neurons and to study the effects on perception, cognition, learning and memory in reversible lesion experiments. in the future, ChloCs might provide new possibilities to dampen pathological hyperexcitable states on demand. One month after the UKE publication, a group from Stanford University announced a similarly engineered channelrhodopsin which they termed SwiChR.*

**BACKGROUND:** All experiments on neurons were performed by Simon Wiegert at the Institute of Synaptic Physiology, headed by Thomas Oertner, Professor at the UKE since 2011. Both authors use optogenetic methods to study the function of synapses in intact brain tissue. Critical mutations were identified by Jonas Wietek in the Group of Peter Hegemann at the Humboldt University in Berlin. Molecular simulations were performed at the KIT in Karlsruhe. The project has been supported by the DFG Priority Program 1665 “Resolving and manipulating neuronal networks in the mammalian brain – from correlative to causal analysis