Optogenetic Control of Ca^{2+} channels *in vivo*

In the year 2040, exposure to light is all that is needed to treat diseases linked to intracellular Ca^{2+} dysfunction, especially neurological diseases such as Alzheimer's disease. It takes only 10 minutes of exposure to lukewarm red light to restore a patient's priceless memories with their family.

Department of Biological Sciences
Won Do Heo,
Daesoo Kim, and
Yong-Mahn Han

Calcium (Ca^{2+}) signals are a crucial part of diverse cellular functions, including contraction, excitation, growth, differentiation, and death. In this study, a light-responsive plant protein was conjugated with a Ca^{2+} channel activator to induce an influx of Ca^{2+} into cells through exposure to light. This protein, called OptoSTIM1, has proven its broad utility by making it possible to modulate Ca^{2+} levels in various cell lines, including human embryonic stem cells, and animal models, such as zebrafish embryos and mice.

Recent evidence suggests that abnormal Ca^{2+} channel activity is involved in various human diseases, and severe Ca^{2+} deficiency has been linked to cardiac arrhythmia, cognitive impairment, and ataxia. Also, there is a great need for the development of non-invasive means of manipulating intracellular Ca^{2+} levels for therapeutic purposes, such as via light exposure, instead of utilizing toxic chemicals or electrical shocks.

In this study, a light-responsive oligomerized plant protein was conjugated with a Ca^{2+} channel activator, which binds to Ca^{2+} channels only when oligomerized by themselves . Depending on the power and exposure time of the blue light used, Ca^{2+} levels in the cell can be controlled quantitatively, and varied levels of Ca^{2+} could be decoded into different functional outcomes, such as actin cytoskeleton remodeling or gene expression.
The broad utility of OptoSTIM1 has been proven through the modulation of Ca^{2+} levels in various human and mouse cell lines, including human embryonic stem cells, potentially leading to advances in stem cell engineering. Additionally, Ca^{2+} levels could be manipulated in live animals, such as zebrafish embryos, or in the brains of mice, where increases in Ca^{2+} levels in neurons resulted in elevated learning capacity, suggesting that Ca^{2+} plays a significant role in the memory formation process.

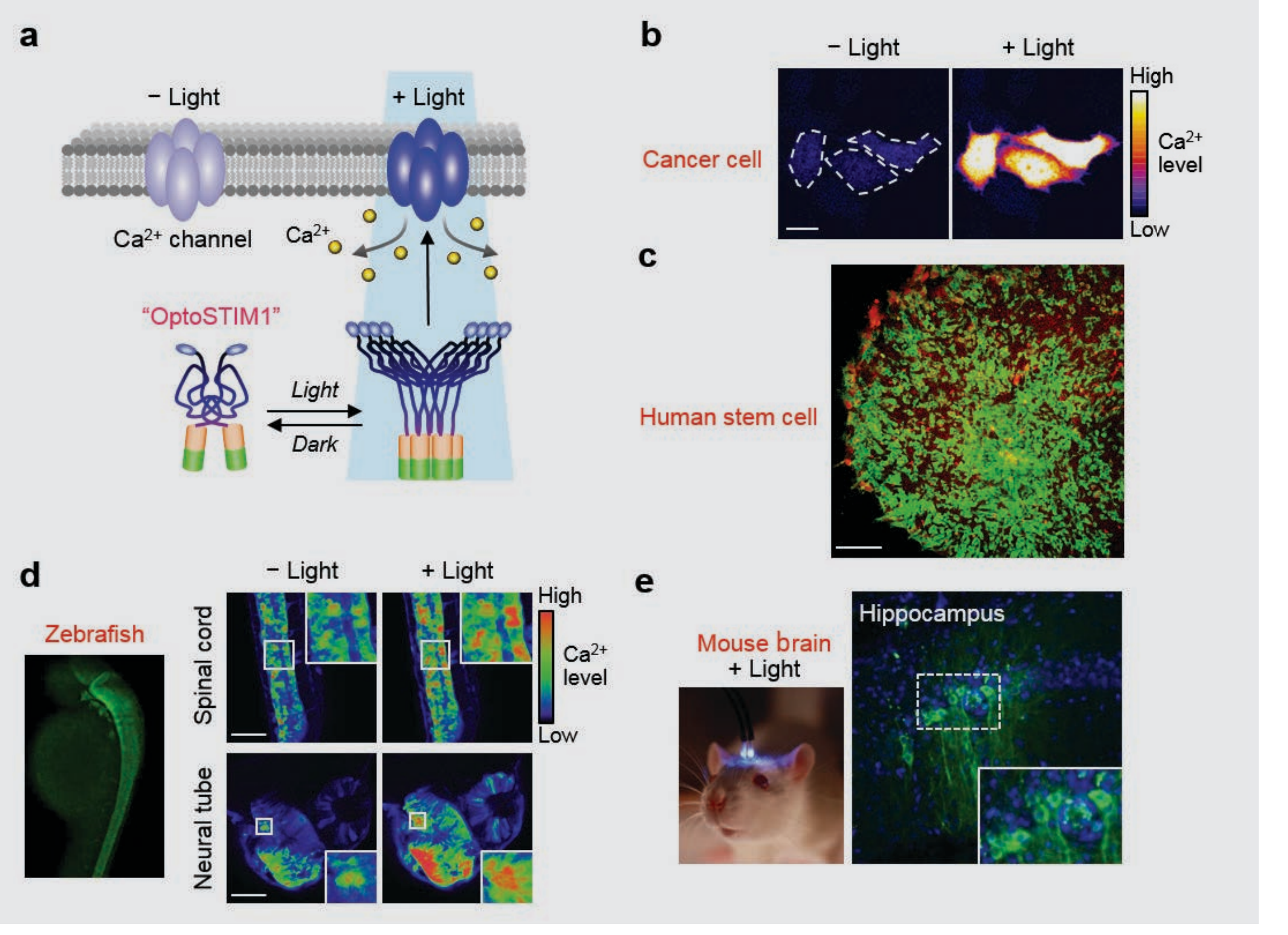

Figure 1.
a) Schematics of Ca^{2+} channel activator (OptoSTIM1); b) Increase of Ca^{2+} level in human cancer cells; c) Expression of OptoSTIM1 (green) in human embryonic stem cells (hESCs); d) Elevation of Ca^{2+} in the central nervous system of a zebrafish embryo; e) Selective expression of OptoSTIM1 (green) in the hippocampal region of a mouse brain.

The precise control of Ca^{2+} channels through the use of OptoSTIM1 will provide a robust cell- or animal-based screening platform for identifying drug candidates that target Ca^{2+} channels. OptoSTIM1 also offers potential optogenetic therapeutic means of treating diseases associated with Ca^{2+} deficiency.

Research Funding
This research was supported by the Institute for Basic Science (IBS-R001-G1), KAIST Institute for the BioCentury, the National Leading Research Laboratory Program of the Ministry of Science, ICT and Future Planning (MSIP) (2011-0028772 to Daesoo K.), and the NRF Stem Cell Program (2011-0019509), which is funded by the MSIP.

Research Outcomes
Optogenetic control of endogenous Ca^{2+} channels *in vivo*. Nature Biotechnology, 23, 1092-1096 (2015).