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Author Manuscript

*Science*. Author manuscript; available in PMC 2013 January 24.

Published in final edited form as:

*Science*. 2011 June 24; 332(6037): 1508–1509. doi:10.1126/science.1208555.

## Synthetic Physiology

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Optogenetic tools are DNA-encoded molecules that, when genetically targeted to cells, enable the control of specific physiological processes within those cells through exposure to light. These tools can pinpoint how these specific processes affect the emergent properties of a complex biological system, such as a mammalian organ or even an entire animal. They can also allow control of a biological system for therapeutic or bioengineering purposes. Many of the optical control tools explored to date are single-component reagents containing a photoactive signaling protein. An interesting question is raised by comparing optogenetics to synthetic biology. In the latter, interchangeable and modular DNA-encoded parts are assembled into complex biological circuits, thus enabling sophisticated logic and computation as well the production of biologics and reagents (1, 2). Is it possible to devise strategies for the temporally precise cell-targeted optical control of complex engineered biological computational or chemical-synthetic pathways? Such a marriage of optogenetics and synthetic biology--which one might call synthetic physiology--would open up the ability to use optogenetics to trigger and regulate engineered synthetic biology systems, which in turn could execute computational and biological programs of great complexity (3). On page xxxx in this issue, Ye *et al.* (4) explore such a hybrid approach to controlling a biological system, and the bioengineering and pre-clinical capabilities opened up by such an approach.

Single component optical control tools have been successfully devised, such as those based on naturally occurring light-gated ion channels and pumps that organisms use to sense light. When genetically expressed in specific neurons within the mammalian brain, these tools enable the electrical activity of the targeted neurons to be driven or silenced by pulses of light (5, 6), thus revealing the causal roles that the targeted neurons play in behaviors and pathologies. As another example, a photoactivatable version of an intracellular signaling protein—the small guanosine triphosphatase (GTPase) Rac1--has recently been designed (7) in which a photosensor domain [the light oxygen voltage (LOV) domain] is fused to a mutated form of Rac1 such that the GTPase can be activated by light.

Ye *et al.* began with melanopsin, a heterotrimeric GTP-binding protein (G-protein)-coupled light-sensitive molecule that, upon illumination, signals through the G protein subunit G<sub>q</sub> to downstream effectors such as phospholipase C, protein kinase C, and calcium signaling. One of the outcomes of calcium signaling is the activation of gene expression driven by a transcription factor called nuclear factor of activated T cells (NFAT). Ye *et al.* co-expressed the gene encoding melanopsin in cultured mammalian cells along with a DNA cassette encoding a reporter gene whose expression is controlled by NFAT. Illuminating the cells for a few hours caused near-maximal expression of the reporter gene. The authors explored the

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application of this finding in a number of bioengineering and preclinical domains, including light-controlled bioreactors in which the cellular production of a genetically encoded payload placed under control of the NFAT-dependent promoter can be driven by illumination. This allowed production of the payload to be regulated over time simply by modulating the patterns of light over periods of hours to days.

Ye *et al.* also show that this light-responsive melanopsin-NFAT signaling cascade can be induced in mice, placing, for example, the gene encoding glucagon-like peptide 1 (GLP-1) into the NFAT reporter cassette. Mammalian cells containing this cassette and the gene for melanopsin were generated and subcutaneously implanted into mice. Such mice, when exposed to blue light (transdermally), showed an increase in insulin production, as would be expected from the administration of GLP-1 (which stimulates glucose-dependent insulin secretion), and a concomitant decrease in blood glucose concentration as well. This demonstration shows that synthetic physiology tools can control organism states relevant to the understanding and treatment of conditions such as diabetes. Indeed, the authors performed this experiment in a mouse model of type 2 diabetes and show that beneficial changes in blood insulin and glucose concentrations arise when the diabetic mice, implanted with these engineered cells, are illuminated.

A marriage of optogenetics and synthetic biology could open the door to diverse applications, from animal models of disease to diagnostics and therapies.

This study of Ye *et al.* shows that coupling an optogenetic driver to a downstream system can result in biologically meaningful changes. It also extends previous synthetic physiology results to use of this technology in mammals *in vivo* with non-invasive stimulation (8). Relevant past work includes coupling a light sensor to transcription in bacteria (9), driving the heterodimerization of a DNA binding domain and a transcriptional activation domain by light to control gene expression (10, 11), and using the G-protein-coupled light-sensitive molecule rhodopsin to actuate potassium currents in neurons in response to light, thereby enabling optical neural silencing (12). Ye *et al.* demonstrate that one of the most difficult aspects of designing and implementing synthetic physiology is coupling the optogenetic tool to downstream signaling pathways. For example, using calcium to couple light reception by melanopsin to NFAT-driven transcription may result in unintended side effects of illumination, given the diverse cellular functions that calcium signaling controls. Clearly, synthetic physiology will need to devise more specific coupling strategies for connecting optogenetic tools to downstream synthetic biology processes.

The power of synthetic physiology approaches – leveraging the high speed and dynamic control of optogenetics and the computational power and biological richness of synthetic biology – may open up new applications, ranging from animal models of disease that are modulated by light, to personalized medicine applications in which cells from patients can be probed *in vitro* using causal tools to assess which pathways are involved in a given disease state. A tantalizing possibility also explored by Ye *et al.* paper is whether these tools may be useful as components of a new generation of prosthetics, allowing ultraprecise correction of dysfunctional biological processes. Assessing optogenetic methods in non-human primates may be of use in exploring such translational possibilities (13, 14).

## References

1. Andrianantoandro E, Basu S, Karig DK, Weiss R. 2006; 2:0028. 2006.
2. Khalil AS, Collins JJ. *Nat. Rev. Genet.* 2010; 11:367. [PubMed: 20395970]
3. Endy D, Brent R. *Nature.* 2001; 409:391. [PubMed: 11201753]
4. Ye H, Daoud-El Baba M, Peng R-W, Fussenegger M. *Science.* 2011; 332:xxx.
5. Boyden ES. *F1000 Biol. Rep.* May 3.2011 3

6. Miesenbock G. *Science*. 2009; 326:395. [PubMed: 19833960]
7. Wu YI, et al. *Nature*. 2009; 461:104. [PubMed: 19693014]
8. Moglich A, Moffat K. *Photochem. Photobiol. Sci.* 2010; 9:1286. [PubMed: 20835487]
9. Levskaia A, et al. *Nature*. 2005; 438:441. [PubMed: 16306980]
10. Yazawa M, Sadaghiani AM, Hsueh B, Dolmetsch RE. *Nat. Biotechnol.* 2009; 27:941. [PubMed: 19801976]
11. Kennedy MJ, et al. *Nat. Methods*. 2010
12. Li X, et al. *Proc. Natl. Acad. Sci. U.S.A.* 2005; 102:17816. [PubMed: 16306259]
13. Han X, et al. *Neuron*. 2009; 62:191. [PubMed: 19409264]
14. Han X, et al. *Front. Syst. Neurosci.* 2011; 5:18. [PubMed: 21811444]

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### **Optogenetic control of mammalian physiology**

Mammalian cells are engineered to express light-responsive melanopsin. Melanopsin activates a signaling cascade that activates the transcription factor NFAT, which drives the expression of a target transgene (GLP-1). When cells are transplanted into mice and the animals are exposed to pulses of light, GLP-1 is produced. GLP-1 affects the production of insulin and can restore glucose homeostasis.

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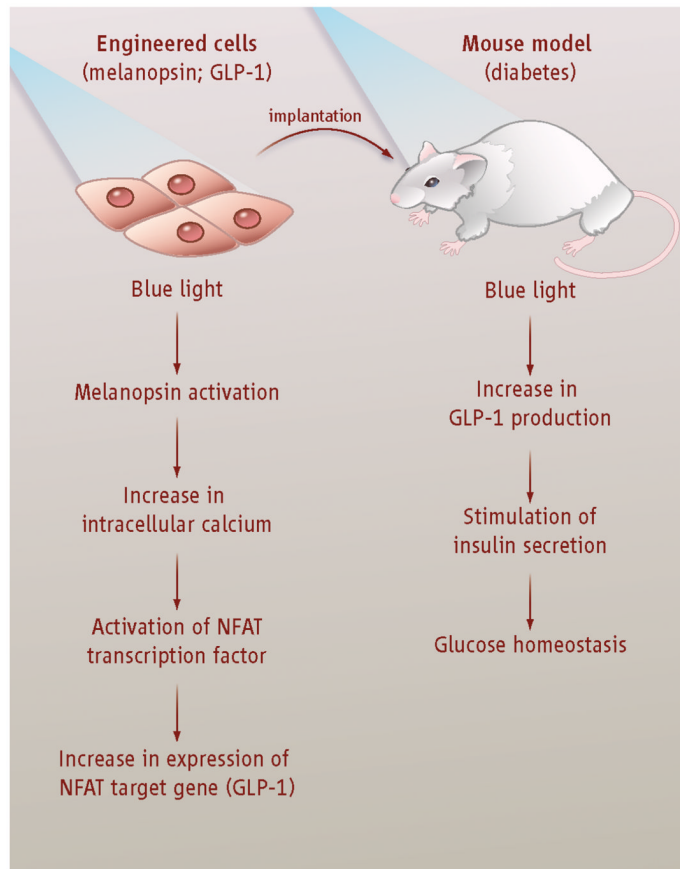


Figure 1.