PHYSIOLOGY

Synthetic Physiology

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

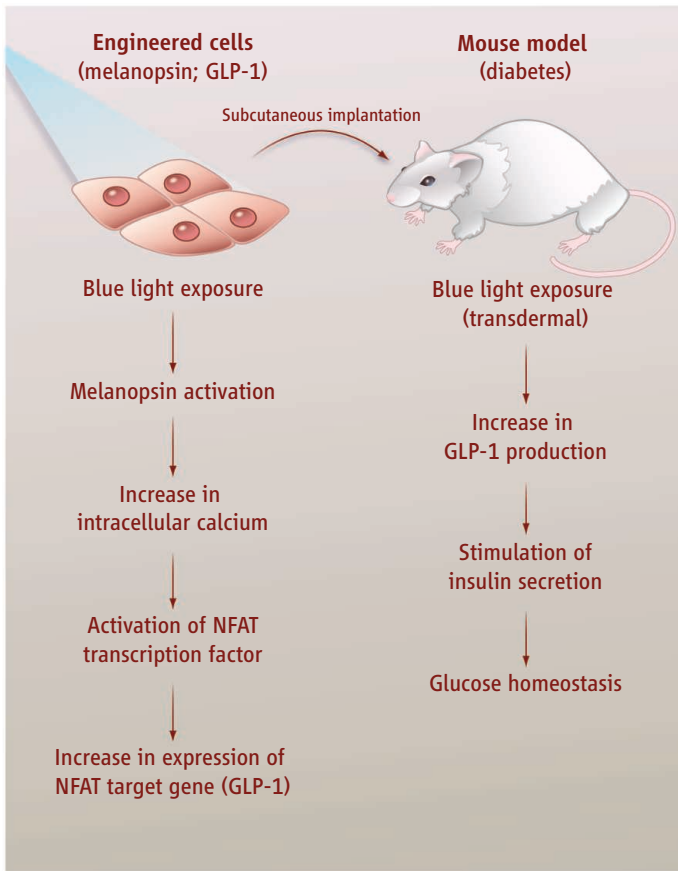
Brian Y. Chow and Edward S. Boyden

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 domain. 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 as 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 1565 of this issue, Ye *et al*. (*4*) explore such a hybrid approach to controlling a biological system, as well as the bioengineering and preclinical 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_q 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*. coexpressed the gene encoding melanopsin in cultured mammalian cells along with a DNA cassette encoding a reporter gene whose expression is controlled by NFAT (see the figure). Illuminating the cells for a few hours caused near-maximal expression of the reporter gene. The authors explored the 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,



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 implanted 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.

CREDIT: B. STRAUCH/*SCIENCE*

[1]Department of Bioengineering, University of Pennsylvania, 210 South 33rd Street, Philadelphia, PA 19104, USA. [2]The Media Laboratory, McGovern Institute, Department of Biological Engineering, and Department of Brain and Cognitive Sciences, Massachusetts Institute of Technology, 77 Massachusetts Avenue, Cambridge, MA 02139, USA. E-mail: esb@media.mit.edu

Published by AAAS

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.

This study by 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 such technologies in mammals in vivo with noninvasive 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*. 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 nonhuman primates may be of use in exploring such translational possibilities (*13*, *14*).

References

1. E. Andrianantoandro, S. Basu, D. K. Karig, R. Weiss, *Mol. Syst. Biol.* **2**, 0028 (2006).
2. A. S. Khalil, J. J. Collins, *Nat. Rev. Genet.* **11**, 367 (2010).
3. D. Endy, R. Brent, *Nature* **409**, 391 (2001).
4. H. Ye *et al., Science* **332**, 1565 (2011).
5. E. S. Boyden, *F1000 Biol. Rep.* **3** (3 May 2011).
6. G. Miesenböck, *Science* **326**, 395 (2009).
7. Y. I. Wu *et al*., *Nature* **461**, 104 (2009).
8. A. Möglich, K. Moffat, *Photochem. Photobiol. Sci.* **9**, 1286 (2010).
9. A. Levskaya *et al*., *Nature* **438**, 441 (2005).
10. M. Yazawa *et al.*, *Nat. Biotechnol.* **27**, 941 (2009).
11. M. J. Kennedy *et al*., *Nat. Methods* **7**, 973 (2010).
12. X. Li *et al*., *Proc. Natl. Acad. Sci. U.S.A.* **102**, 17816 (2005).
13. X. Han *et al*., *Neuron* **62**, 191 (2009).
14. X. Han *et al*., *Front. Syst. Neurosci.* **5**, 18 (2011).

10.1126/science.1208555

PLANETARY SCIENCE

The Earth and the Sun

Sample collection by the Genesis spacecraft reveals the isotopic composition of elements in the solar system.

Robert N. Clayton

For more than 2 years, NASA's Genesis mission collected atoms of the solar wind (charged particles ejected from the Sun's atmosphere). Positioned at the Sun-Earth L1 Lagrange point about 1.5 million km from Earth, the spacecraft was well beyond the complicating effects of Earth's atmosphere and magnetic field, which hinder accurate ground-based astronomical measurements. The balance of gravitational forces at the Lagrange point allowed the spacecraft to maintain a fixed relationship to the Earth and the Sun with minimal expenditure of propellant. The highest priority of the mission was to determine the abundances of the stable isotopes of oxygen (^{16}O, ^{17}O, and ^{18}O) and nitrogen (^{14}N and ^{15}N) in the Sun and, by inference, in the whole solar system (*1*). However, on returning to Earth with its payload, the capsule suffered an unplanned hard landing in Utah in 2004, shattering most of the collector materials and thereby greatly complicating the initial sample analysis. After years of developing analytical techniques, McKeegan *et al*. and Marty *et al*., on pages 1528 and 1533 of this issue (*2*, *3*), reveal that these goals have now been accomplished.

Variations in stable isotope abundances have been studied in solar system samples (Earth, Moon, and meteorites), but interpreting this information has been thwarted by the lack of precise knowledge about the isotopic abundances of the initial material from which the elements evolved. It may be surprising that these initial isotopic abundances were not already known for such abundant elements (oxygen ranks third and nitrogen sixth in solar system abundance). Earlier attempts were made to use lunar surface minerals as collectors of the solar wind (metal grains for oxygen, oxide grains for nitrogen), but the results were ambiguous and lacked adequate precision.

The solar wind is very dilute. The small number of atoms implanted in the collector material presents an analytical challenge, as illustrated by mass spectrometer count rates of the key rare isotopes ($^{17}O^{2+}$ and $^{12}C^{15}N^-$) of only 10 to 40 ions per second. In addition, the relatively low velocity of solar wind ions

CREDIT: NASA/JPL-CALTECH

From space to lab. The photograph shows the MegaSIMS facility at the University of California–Los Angeles used for oxygen isotope analysis of the Genesis samples (*2*, *3*). The initial sputtering source for oxygen ions is in the far background; the cream-colored cylindrical structure at right is the tandem accelerator; in the right foreground is the electrostatic sector of the double-focusing mass spectrometer; in the left foreground is the magnetic sector; the large silver-colored cylindrical structure at the left contains the ion detectors.

Enrico Fermi Institute, Department of Chemistry and Department of the Geophysical Sciences, University of Chicago, Chicago, IL 60637, USA. E-mail: r-clayton@uchicago.edu

Published by AAAS