# The light fantastic

Chemical biologists are advancing our understanding of light's role in the natural world and expanding its applications in the research lab.

Solar radiation has been a constant feature on Earth, and organisms have evolved to detect and respond to light in numerous ways, ranging from photosynthesis to circadian rhythms and vision. Understanding how these and other systems convert photons into energy or biological signals is increasingly a focus of chemical biology research as we seek to define the mechanistic details of these processes and strive to more closely imitate them. Building on their chemical heritage, chemical biologists are also leading the way in using light to enable research by creating new methods that use light as an orthogonal and selective reagent. In this themed issue, we offer a collection of pieces that focuses on light as a messenger, trigger and tool.

Photosynthesis is the most fundamental connection between light and living organisms. The photosynthetic machinery of plants, algae and cyanobacteria has been characterized in molecular and structural terms, which has furthered our understanding of how light is converted into energy-rich biomolecules. Yet important intellectual challenges remain in defining these complex systems with mechanistic clarity and applying this knowledge in practical areas. Research into light-harvesting complexes, which capture photons and shunt their energy to photosynthetic reaction centers, has revealed how natural systems harness light energy and, by extension, how chemical biologists might design artificial light-harvesting antennae for practical applications such as sustainable energy production (Perspective, p. 492).

Biofluorescence and bioluminescence, observed in animals such as jellyfish and fireflies, have similarly served as archetypical examples linking light and biology where the emitted light requires both protein scaffolds and environmentally sensitive small molecules within these scaffolds. Applying previous knowledge of the photophysical properties of small-molecule dyes to the rational dissection of fluorescent protein behavior led to demonstrations that these proteins could be manipulated to serve more broadly as tools in biological research (*Curr. Biol.* **6**, 178–182, 1996). Since then, scientists have studied a wide range of natural and engineered fluorescent proteins, seeking variants with improved stability, brightness and excitation and emission wavelengths across the visible spectrum and beyond (Review, p. 512).

Though fluorescent proteins have become indispensable for tracking target proteins within a cell or organism, scientists have also sought alternative ways to use light to control or interrogate biological systems. Physical organic chemistry and photochemistry have led to a wealth of information about photoactive compounds and light-triggered chemical reactions. Application of these reactions to create inactive 'caged' biomolecules that are activated by a pulse of light (Review, p. 533) has allowed temporal precision in turning on (or off) a particular biological process, whereas advances in laser technology have enabled increasingly precise spatial regulation. The development of optogenetics—defined broadly as the engineering of light-regulated systems into cells and organisms—has similarly allowed the defined manipulation of biomolecules, including efforts to turn natural photoreceptors such as rhodopsin into genetically encodable effectors of *in vivo* function (Review, p. 533) or the creation of tethered, light-sensitive ligands to examine glutamate receptor desensitization (*Nat. Chem. Biol.* **10**, 273–280, 2014). Renewed interest in organic photochemistry may also yield new opportunities to create light-sensitive tools (Research Highlights, p. 484; *Science* **343**, 1239176, 2014).

The discovery of other light-sensitive proteins such as cryptochromes and phytochromes offered an alternative entrée into the control of protein function with light. Defining conformational changes induced by light (Research Highlights, p. 485) improves our understanding of these proteins and provides important insights for creating engineered variants that can, for example, control gene expression (*Nat. Chem. Biol.* **10**, 196–202, 2014). These studies should also inspire efforts to create methods for the cellular imaging of biomolecules such as RNA, for which few options are currently available (Review, p. 512).

Of course, applications of light-based tools have benefited from parallel advances in microscopy, ranging from fluorescence readouts of ensemble properties to finely optimized single-particle tracking (Review, p. 524). For example, *in vivo* multicolor flow cytometry of photoswitchable proteins can report on the fate of circulating tumor cells (Research Highlights, p. 485), whereas far-red fluorogenic probes monitored by stimulated emission depletion microscopy can reveal unprecedented details of the cytoskeleton (*Nat. Methods* doi:10.1038/nmeth.2972). Chemical biologists have set a high standard for translating microscopy images into biological meaning through careful and quantitative analysis, which itself can be enabled by light (Perspective, p. 502). However, it is important to remember that the complexity of a chosen method should be appropriate for the question at hand; sometimes simple solutions offer important advantages, as highlighted in the development of a luminescence-based drug monitoring system that can be read out with a digital camera (Article, p. 598; News & Views, p. 490).

As our tools and techniques continue to expand, chemical biologists should seek out biological systems where converting existing observations to molecular details would be particularly valuable. For example, prolonged exposure of skin to ultraviolet radiation can lead to oxidative damage and disease (Review, p. 542). To counter this, the body has developed a complex defense system to restore skin homeostasis, but many molecular details remain unknown. Similarly, the brain relies on a carefully regulated circadian clock to dictate sleep and wake cycles dependent on light entrainment (Research Highlights, p. 484). Disruptions to this clock can have drastic effects on the overall physiology and behavior of an organism. Recent initiatives focused on the brain, which have called for new technology development for imaging neurons and brain circuitry (*Nat. Chem. Biol.* **10**, 85, 2014), may help reveal the exact relay of communication between the clock and the body and the myriad molecular details of brain function.

We hope this collection provides a glimpse into the interplay of light and biology and how our understanding of these processes can be exploited to create tools for the further interrogation of biological systems. And just as the human visual system is only one of many perspectives on the world (http://nautil.us/issue/11/light/how-animals-see-the-world), we look forward to seeing how chemical biologists, with their diverse backgrounds and interests, will shape how we use light to illuminate future research. ■