humans, and published the findings in the 15 January 2000 *Journal of Neuroscience*. Sensing paydirt, Provencio found the mammalian homolog was housed in a rare subtype of retinal ganglion cells, while David M. Berson, a professor of ophthalmology and visual sciences at Brown University, first determined the location of the melanopsin retinal ganglion cells within the eye. These cells, which are found in front of the retina, process signals from rods and cones, sending them on to the brain's visual centers. But the question remained: did melanopsin provide this light sensitivity?

In the December 2001 issue of *Nature Neuroscience*, Josh Gooley, then a first-year Harvard graduate student, showed in rats that melanopsin cells connect to the SCN. Berson, in an effort to prove these cells really are sensitive to light, disconnected the rods and cones from the melanopsin cells so the light sensitivity of the former would not affect his results. Then he plugged electrodes into the melanopsin cells. Under bright light, the electrodes signaled the melanopsin cells' reaction, as reported in the 8 February 2002 issue of *Science*.

In work published 3 July 2003 in *Nature*, King-Wai Yau and Samer Hattar of The Johns Hopkins University knocked out the melanopsin gene in a rodless, coneless mouse. The mice could not be entrained, "providing the last crucial bit of evidence linking melanopsin to circadian behavior," says Foster.

Meanwhile, other researchers explored the neural pathways that arise from the melanopsin cells. Roughly 40% of these cells' axons project to the SCN. Hattar, an assistant professor in the Solomon H. Snyder Department of Neuroscience, traced others to regions of the brain that are involved in, among other things, speed of circadian reentrainment, light's effects on activity levels, sleep regulation, and hormone regulation. Such connections project to the brainstem, to the limbic system (including the amygdala, from whence fear springs), and to the cerebral cortex (the mainspring of such cognitive functions as language, analytic thought, and long-term memory).

Blue Light Special

A parallel line of research, meanwhile, delved into the qualities unique to blue light. From 1995 until 2001, Brainard and his colleagues tested 72 healthy men and women in more than 700 experiments to determine the strongest wavelength for suppressing melatonin secretion. The result confirmed a slightly earlier Japanese study on mutant mice, showing that the blues are the most important wavelengths for entraining the circadian system. Cones, the color receptors, have a peak sensitivity in the greens, at 555 nm. For the rods, the peak comes at 507 nm. Across 10 published studies on humans, rodents, and monkeys, the peak sensitivity of the melanopsin receptors appears to span 459–485 nm, says Brainard.

Researchers have shown in humans that light influences hormone secretion, heart rate, alertness, sleep propensity, body temperature, and gene expression. Moreover, in such studies, blue wavelengths have been found to exert more powerful effects than green wavelengths. In experiments published in the September 2003 issue of *The Journal of Clinical Endocrinology and Metabolism*, Brainard, Czeisler, and Steven Lockley, an assistant professor of medicine at Harvard Medical School, compared suppression of melatonin in humans during 6.5 hours of nighttime exposure by monochromatic light at 460 nm, the peak sensitivity of melanopsin cells, with 555 nm, the peak sensitivity of the visual system. The blue wavelength suppressed melatonin for about twice as long as the green.

In other experiments, blue also proved more powerful in elevating body temperature and heart rate and in reducing sleepiness, according to Gilles Vandewalle, of the Center for the Study of Sleep and of Biological Rhythms at the University of Montréal. "[P]erformance improves acutely after the onset of light exposure, both at night and during the day," Vandewalle and colleagues wrote in a review in the October 2009 issue of *Trends in Cognitive Neuroscience*. Electroencephalography has shown that light exposure reduces alpha, theta, and low-frequency activity, which are correlates of sleepiness. And Vandewalle showed that blue light proved superior to other wavelengths in enhancing responses in the left frontal and parietal cortices during a working memory task.

Experimental subjects had quicker auditory reaction times and fewer lapses of attention under blue light than green, says Lockley. In

Blue light–emitting goggles, panels, and other devices are used to treat problems such as sleep disorders, jet lag, seasonal affective disorder, and premenstrual syndrome. But blue light doesn't work solely through ocular stimulation; the shorter wavelengths can penetrate skin—this is how blue light is used to treat neonatal jaundice, in which the infant's liver is unable to clear the normal hemolysis by-product bilirubin. Bilirubin builds up in the blood and enters body tissues, making the eyes and skin appear yellow. Blue light penetrates the skin and converts bilirubin into forms that can dissolve into the blood and be excreted in urine. The process repeats as untreated bilirubin continues to deposit into tissues from the blood, until most or all the bilirubin is converted.