Profile of King-Wai Yau

Jennifer Viegas, *Science Writer*

Neuroscientist King-Wai Yau of Johns Hopkins University has made fundamental discoveries concerning the mechanisms underlying sensory transduction. His research over the past four decades has focused primarily on vision. "Vision is one of our most precious senses from which come art, science, humanity, beauty, and practically all aspects of life," says Yau. His findings concerning phototransduction—the process by which light is converted into a neural signal—have led to a sophisticated understanding of many hereditary diseases causing blindness. Additionally, Yau has elucidated the process of olfaction transduction that, like vision, relies on a G protein-coupled cellular signaling pathway. His Inaugural Article, signifying his 2010 election to the National Academy of Sciences, advances understanding of the electrical response of olfactory neurons to odorants.

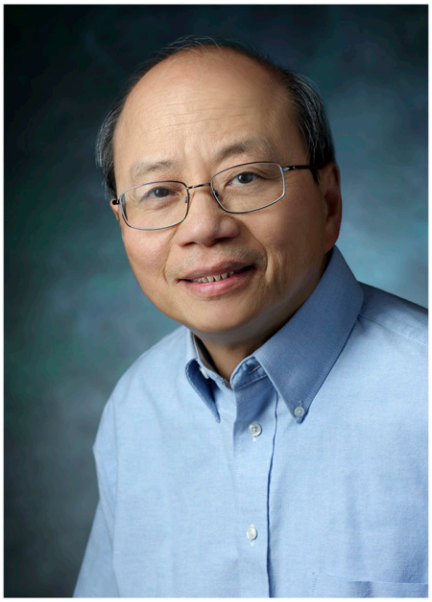
Mentors at Harvard, Stanford, and Cambridge

Yau was born in China in 1948, the sixth of seven children. His family relocated to Hong Kong within months of his birth. His father died 5 years later. Dedicating himself to scholarship and science, Yau excelled in high school. He entered the University of Hong Kong Faculty of Medicine in 1967. After a year, he set out for the United States, studying at the University of Minnesota before transferring to Princeton University on a full scholarship to study physics and eventually graduating in 1971. "The best decision that I ever made was to leave medical school," Yau says. "I determined that I did not wish to be a clinician."

Yau then entered Harvard Medical School, where he earned a PhD in neurobiology in 1975. At Harvard, he studied invertebrate neurobiology under John Nicholls in the university's small but influential neurobiology department. There, he became strongly influenced by the seminal vision-related work of prominent neurophysiologists Stephen Kuffler, David Hubel, and Torsten Wiesel.

From 1976 to 1979, Yau did postdoctoral work at the Stanford University School of Medicine in neurobiologist Denis Baylor's laboratory. With Baylor and neuroscientist Trevor Lamb, Yau developed a method to detect and record the response of rod photoreceptors, which are found in the retina, to single photons (1). The method revolutionized the study of phototransduction and continues to be used today. Soon afterward, Yau, Baylor, and neurobiologist Gary Matthews detected the spontaneous thermal activity of a single in situ molecule of rhodopsin, which is a photosensitive G protein-coupled receptor (GPCR) found in retinal rods (2).

In 1979 Yau became a research fellow at Cambridge University, where he studied rod photoreception under the guidance of Nobel Prize-winning physiologist and biophysicist Sir Alan Hodgkin. Yau says, "I greatly admired Hodgkin's unique thinking, creative approaches, and analytical skills."



King-Wai Yau. Image courtesy of Johns Hopkins Medicine (Baltimore, MD).

Discovery of Phototransduction Mechanism

Yau returned to the United States in 1980, having accepted an assistant professorship in physiology and biophysics at the University of Texas Medical Branch in Galveston. The same year, Yau, Baylor, and Lamb received England's Rank Prize in Optoelectronics. Yau's studies on phototransduction came to fruition over the next 6 years, when he served as associate (1982–1985) and full professor (1985–1986).

In a series of articles (3–6), Yau and coauthor Kei Nakatani, in parallel with biophysicist Evgeny Fesenko's group in the former Soviet Union, detailed the cellular mechanisms by which light triggers vision. Yau later summarized these and related findings upon receiving the Friedenwald Award in 1993 from the Association of Research in Vision and Ophthalmology (7) and in an overview article published in PNAS in 2008 (8). The studies established the roles of signaling molecules—calcium (Ca^{2+}) ions and cGMP—in rod photoexcitation (when a rhodopsin molecule experiences an increase in energy after absorption of a

This is a Profile of a recently elected member of the National Academy of Sciences to accompany the member's Inaugural Article on page 11078 in issue 40 of volume 113.

www.pnas.org/cgi/doi/10.1073/pnas.1707649114

photon) and photoadaptation (the negative-feedback adaptation of the eye to light), respectively. The researchers further discovered a ubiquitous membrane current associated with the transport of Ca^{2+} ions across cell membranes. The same phototransduction mechanism operates in cones.

A defining feature of rod phototransduction concerns the relatively large number of G protein molecules that are activated by a single light-stimulated rhodopsin molecule and, consequently, the large number of cGMP molecules turned over. The GPCR substantially amplifies the incoming light signal; this amplification helps explain why rods produce a large signal in response to a single photon. The mechanism has since become a focus of increasingly precise study.

Discovery of Photoreceptors Involved in Circadian Rhythm

In 1986 Yau became an investigator at the Howard Hughes Medical Institute and a professor of neuroscience and ophthalmology at Johns Hopkins University School of Medicine. There, in the late 1990s, Yau solved the phototransduction mechanism of the parietal eye of lizards (9). He found that this eye uses a more elaborate phototransduction mechanism for detecting light than that used by rod or cone cells in the two lateral eyes.

He and his team followed up on the work of neurobiologists Russell Foster, Robert Lucas, and Ignacio Provencio. This line of research suggested the existence of additional ocular photoreceptors and culminated with a discovery by neuroscientist David Berson that certain retinal ganglion cells are intrinsically photosensitive. Yau established that the photosensitivity of these cells involves the photopigment melanopsin and that the cells project to brain nuclei for various functions (10). Yau characterized these cells in detail (11) and solved their phototransduction mechanism (12), which is distinct from rod/cone phototransduction. "Unlike rods and cones, these other photosensing cells are designed primarily for purposes such as telling us the time of day based on the cycle of light and darkness around us, not for recognizing visual images," explains Yau. The existence of the melanopsin-containing retinal cells overturned a century of dogma that rods and cones are the retina's only photoreceptors.

Source of Visual False Alarms, Translational Work

Photoreceptor cells in the eye are known to misfire occasionally in darkness and signal to the brain as if they had captured photons. The basis of this phenomenon largely remained a mystery until Yau and his team determined that high temperatures can cause misfiring (13). The researchers also found that red-sensing pigment (i.e., pigment that is sensitive to long-wavelength light) triggers false alarms most frequently. The discovery, together with a theory first reintroduced by neuroscientist Petri Ala-Laurila, emphasized that biomolecules have more thermal energy than sometimes thought. The finding also helped explain why humans and other animals do not have infrared vision via opsin-based pigments.

In addition to basic research, Yau has been engaged in translational work on ocular diseases in collaborations, such as with his close colleagues Jeremy Nathans (14) and Maria Canto Soler (15). Yau received Portugal's António Champalimaud Vision Award in 2008 and the National Academy of Sciences Alexander Hollaender Award in Biophysics in 2013, among other honors. He is a Fellow of the American Academy of Arts and Sciences.

Identifying Similarities and Differences Between Vision and Olfaction

Yau began collaborating with Randall Reed, codirector of the Center for Sensory Biology at Johns Hopkins University School of Medicine, on olfaction 15 years ago. "While working with Randy, I became intrigued by the commonality between vision and olfaction," says Yau.

He explains that both vision and olfaction rely upon GPCRs to convert stimuli into brain signals. GPCRs are involved in innumerable biological processes. It was generally assumed that, as in vision, other GPCRs also greatly amplified stimulus signals. Yau, however, showed that olfactory transduction does not have such high amplification (16), which could be the norm for most chemical-triggered G-protein pathways.

Uncovering Mechanisms of Olfactory Transduction

Yau's Inaugural Article describes the two currents comprising the electrical response of olfactory receptor neurons to odors, a calcium-activated chloride (Cl) current and a cyclic-nucleotide–gated (CNG) current. (17) "These two currents are causally and tightly coupled, so they cannot be easily separated," Yau says. He and his team achieved the separation by carefully applying the antiinflammatory agent niflumic acid to olfactory tissue exposed to an odorant and then monitoring the currents. They found that the Cl current was dominant, suggesting its important role in olfaction.

Yau credits the collegiality at Johns Hopkins for his success in probing the basis of two separate senses, a rare feat in sensory neuroscience. Even after decades of intense research, his ardent curiosity about olfaction and vision is evident. "The picture of ocular photoreceptors consisting of rods, cones and ganglion-cell photoreceptors is likely incomplete," he says. "There are probably others in the eye, the brain, and elsewhere. Hopefully, before my time is up, we will find them."

1 Yau K-W, Lamb TD, Baylor DA (1977) Light-induced fluctuations in membrane current of single toad rod outer segments. *Nature* 269:78–80.

2 Yau K-W, Matthews G, Baylor DA (1979) Thermal activation of the visual transduction mechanism in retinal rods. *Nature* 279:806–807.

3 Yau K-W, Nakatani K (1984) Cation selectivity of light-sensitive conductance in retinal rods. *Nature* 309:352–354.
4 Yau K-W, Nakatani K (1984) Electrogenic Na-Ca exchange in retinal rod outer segment. *Nature* 311:661–663.
5 Yau K-W, Nakatani K (1985) Light-induced reduction of cytoplasmic free calcium in retinal rod outer segment. *Nature* 313:579–582.
6 Yau KW, Nakatani K (1985) Light-suppressible, cyclic GMP-sensitive conductance in the plasma membrane of a truncated rod outer segment. *Nature* 317:252–255.
7 Yau KW (1994) Phototransduction mechanism in retinal rods and cones. The Friedenwald Lecture. *Invest Ophthalmol Vis Sci* 35:9–32.
8 Luo D-G, Xue T, Yau K-W (2008) How vision begins: An odyssey. *Proc Natl Acad Sci USA* 105:9855–9862.
9 Xiong WH, Solessio EC, Yau K-W (1998) An unusual cGMP pathway underlying depolarizing light response of the vertebrate parietal-eye photoreceptor. *Nat Neurosci* 1:359–365.
10 Hattar S, Liao H-W, Takao M, Berson DM, Yau K-W (2002) Melanopsin-containing retinal ganglion cells: Architecture, projections, and intrinsic photosensitivity. *Science* 295:1065–1070.
11 Do MTH, et al. (2009) Photon capture and signalling by melanopsin retinal ganglion cells. *Nature* 457:281–287.
12 Xue T, et al. (2011) Melanopsin signalling in mammalian iris and retina. *Nature* 479:67–73.
13 Luo D-G, Yue WWS, Ala-Laurila P, Yau K-W (2011) Activation of visual pigments by light and heat. *Science* 332:1307–1312.
14 Sun H, Tsunenari T, Yau KW, Nathans J (2002) The vitelliform macular dystrophy protein defines a new family of chloride channels. *Proc Natl Acad Sci USA* 99:4008–4013.
15 Zhong X, et al. (2014) Generation of three-dimensional retinal tissue with functional photoreceptors from human iPSCs. *Nat Commun* 5:4047.
16 Bhandawat V, Reisert J, Yau K-W (2005) Elementary response of olfactory receptor neurons to odorants. *Science* 308:1931–1934.
17 Li R-C, Ben-Chaim Y, Yau K-W, Lin C-C (2016) Cyclic-nucleotide-gated cation current and Ca^{2+}-activated Cl current elicited by odorant in vertebrate olfactory receptor neurons. *Proc Natl Acad Sci USA* 113:11078–11087.