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Roger Tsien Wins 2008 Nobel Prize in Chemistry

The Royal Swedish Academy of Sciences announced this morning that the 2008 Nobel Prize in Chemistry was awarded to Roger Y. Tsien, a Howard Hughes Medical Institute investigator at the University of California, San Diego (UCSD), Osamu Shimomura of the Marine Biological Laboratory, and Martin Chalfie of Columbia University. The three were honored for the discovery and development of the green fluorescent protein, GFP.

According to the Royal Swedish Academy, this year's Nobel Prize in Chemistry rewards the initial discovery of GFP and a series of important developments that have led to its use as a tagging tool in bioscience. By using DNA technology, researchers can now connect GFP to other interesting, but otherwise invisible, proteins. This glowing marker allows them to watch the movements, positions and interactions of the tagged proteins.

Researchers can also follow the fate of various cells with the help of GFP: nerve cell damage during Alzheimer's disease or how insulin-producing beta cells are created in the pancreas of a growing embryo. In one spectacular experiment, researchers succeeded in tagging different nerve cells in the brain of a mouse with a kaleidoscope of colors.

Commenting on Tsien's work, HHMI President Thomas R. Cech, said, "Roger is an excellent scientist and he has provided key tools for researchers around the world to light up proteins in living cells. This work is both beautiful and important." Tsien has been an HHMI investigator at UCSD since 1989.

Tsien's fascination with colors has revolutionized the fields of cell biology and neurobiology by allowing scientists to peer inside living cells and watch the behavior of molecules in real time.

He is renowned for developing colorful dyes to track the movement of calcium within cells and has genetically modified molecules that make jellyfish and corals glow, creating fluorescent colors in a dazzling variety of hues. Scientists worldwide use these multicolored fluorescent proteins to track where and when certain genes are expressed in cells or in whole organisms.

Tsien has always been drawn to pretty colors. "Your science should ideally feed the deeper parts of your personality, to provide some intrinsic pleasure to tide you over the inevitable periods of discouragement," he says.

He grew up in Livingston, New Jersey, among a number of engineers in his extended family, and even from a young age he seemed destined for a career in science. Tsien's father was a mechanical engineer. His mother's brothers were engineering professors at the Massachusetts Institute of Technology. Tsien, who calls his own work *molecular* engineering, says, I'm doomed by heredity to do this kind of work.

Childhood asthma often kept Tsien indoors, where he spent hours conducting chemistry experiments in his basement laboratory and was first exposed to the chemistry of pretty colors. At 16, he won the top prize in the nationwide Westinghouse Talent Search. He later attended Harvard College on a National Merit Scholarship, graduating at age 20 with a degree in chemistry and physics.

As a graduate student at the University of Cambridge, Tsien worked to develop a better dye to track the levels of calcium inside cells. Calcium plays a critical role in numerous physiological processes, including the regulation of nerve impulses, muscle contraction, and fertilization. At that time, measuring intracellular calcium was a laborious process and typically involved injecting a calcium-binding protein through the cell membrane, a technique that often damaged the very cells being studied. Using techniques of chemistry, Tsien developed organic dyes that twist when they bind calcium, dramatically changing the dyes' fluorescence. He found a way to masquerade the dyes so they could pass through the cell membrane without having to be injected.

In the early 1990s, Tsien borrowed from jellyfish a molecule that glows, green fluorescent protein, and reengineered it to emit colors ranging from blue to yellow. The fluorescent proteins can be tagged to certain genes or to specific proteins of interest. Using a light microscope, scientists can easily determine by their glow when and where the genes are activated or the proteins are expressed.

Over the years, Tsien has expanded the color palette of fluorescent proteins - adding a dazzling array of hues, including cherry, strawberry, tangerine, tomato, orange, banana and honeydew. He has also developed a way to monitor the interactions of two proteins, each tagged with different hues of fluorescent proteins. As a whole, fluorescent proteins have had a huge impact on many areas of biological sciences because they gave [scientists] a direct link from genes and DNA to something you can see inside a cell or inside any organism, Tsien says, while also acknowledging that other scientists initially discovered and cloned fluorescent proteins.

In 2004, Tsien's group, fascinated by the efficient way the human immune system generates a rapid response to create a near-infinite variety of antibodies, hijacked that machinery and used it to evolve a new type of fluorescent protein. The mutation process, called somatic hypermutation

(SHM), normally acts on immunoglobulin genes, producing a large array of antibodies necessary to attack microbes and other foreign substances that the immune system may never have encountered before.

By demonstrating that SHM can be widely adaptable for research use, Tsien and his colleagues opened the way for enormously faster mutation of genes to produce proteins with useful new properties, including research tools and disease therapeutics. For example, Tsien's team used SHM to evolve a red fluorescent protein — which is used to track molecules inside cells — with improved stability and color emission properties beyond that which the researchers could create on their own. The properties of the new fluorescent protein make it a useful indicator of gene activity or protein trafficking when protein is attached to a specific gene in a living cell.

Tsien has also set his sights on the imaging and treatment of cancer. He and his colleagues have built U-shaped peptide molecules to carry a payload—an imaging molecule or chemotherapy drug. The peptides are substrates for certain proteases, protein-cleaving enzymes that are exuded from tumor cells but rarely appear on normal cells. When the protease cleaves the bottom of the U, the two arms of the U are separated, unleashing one arm to drag the payload portion of the peptide into a neighboring cancer cell. "I've always wanted to do something clinically relevant in my career, if possible, and cancer is the ultimate challenge," Tsien says.