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OMG Glowing Cats! Fluorescent Felines Illuminate Medical Mysteries

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The old proverb “All cats are grey in the dark” took a hard hit in September. That’s when biomedical researchers at the Mayo Clinic unveiled a clan of genetically engineered housecats that glow green under ultraviolet light, thanks to DNA from a fluorescent jellyfish spliced into their chromosomes.

The Mayo Clinic cats join a small menagerie of other glowing animals born in laboratories in recent years, including mice, pigs, rabbits, worms, fish, and even an earlier set of cats in Korea. Some were developed purely as novelties: an artist commissioned French scientists to create a fluorescent rabbit as a commentary on biotechnology, and Yorktown Technologies raises its GloFish line of fluorescent zebrafish for sale as pets.

But most, such as the Mayo Clinic’s glowing cats, serve more serious research purposes. And all are products of a technique—genetically encoded fluorescent labeling—that in barely a decade and a half has become one of the most important in modern bioscience. In 2008, Osamu Shimomura, Martin Chalfie, and Roger Y. Tsien were rewarded with a Nobel Prize in Chemistry for their roles in developing it.

The same cats in the light. Courtesy Mayo Clinic

For biomedical research, the technique is “incredibly useful,” according to Marc Zimmer, a chemist at Connecticut College and the author of Glowing Genes: A Revolution in Biotechnology (Prometheus Books, 2005). “It’s a bit like the microscope,” he notes. “It’s something that every lab is going to have and use to some extent.”

The key to the technique that created these creatures is the green fluorescent protein (GFP), which Shimomura at Princeton University extracted from the glowing jellyfish Aequoria victoria and began to study in 1962. Decades later, when Chalfie learned about GFP at Columbia University, he recognized its potential as a tool for fluorescently marking the proteins in other animals. In 1994, after the GFP gene was isolated, Chalfie successfully inserted a copy of it into the DNA of simple roundworms.

Chalfie’s accomplishment was important because it solved a longstanding problem. Biologists already had a variety of molecular tags and chemical stains with which to mark cellular proteins, but they often poisoned the cells and altered their activities in the process. With GFP, biologists can precisely study the formation and dynamics of proteins in healthy organisms. “You don’t have to do anything but shine light on them,” Chalfie says.

“Basically, you’re hanging a light bulb at the end of a protein,” Zimmer says. “You can see when it’s made, where it’s made, and where it goes to.”

Who's a glowing kitty? Courtesy Mayo Clinic

What made the GFP labeling technique far more useful, however, was the further contribution of Tsien at the University of California, San Diego. By tweaking the DNA sequence in the original GFP gene—and later, ones for similar proteins found in coral—Tsien created fluorescent markers that glow in a wide range of colors.

With a spectrum of fluorescent markers to choose from, researchers can find one best suited to their needs or “do multiple labeling and keep track of more than one thing at a time,” Chalfie says. For example, Jeffrey W. Lichtman, Joshua R. Sanes and their colleagues at Harvard Medical School genetically engineered mice whose individual brain cells fluoresce with varying amounts of red, green, and blue pigments. In close-up, the illuminated tissues appear as a “brainbow” in which the interconnections of more than 100 individual neurons can easily be mapped at once.

Fluorescent proteins can do more than just mark the presence of a protein, however: they can also monitor its

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activities. Chalfie explains that with carefully chosen pairs of GFP variants, experimenters can take advantage of a phenomenon called Förster resonance energy transfer (FRET). In FRET, the energy from one fluorescing molecule stimulates a second one to glow—but only if they are close together. FRET can therefore monitor how enzymes and other proteins alter their shape, position and activity inside living cells.

GFP labeling is still primarily a research technique, not a clinical one, because inserting genes into human beings is currently unsafe and unethical. For example, Mayo Clinic virologist Eric Poeschla and his colleagues created their fluorescent felines in the course of their studies of HIV and similar viruses that cause an AIDS-like condition in cats. The glow proved that the researchers had succeeded in adding a protective gene to the cats' DNA—a result that the researchers hope will eventually help to yield new therapies.

Moreover, GFP is already saving lives. Biotechnologists have spliced GFP genes into bacteria to make them light up in the presence of target compounds and act as low-cost chemical sensors. They have been immensely useful in regions such as Bangladesh and Vietnam, where well water is often highly contaminated by arsenic, and in former battle zones that must be cleared of land mines or unseen explosives.

Courtesy Mayo Clinic

Improvements and extensions of the GFP technique are also constantly emerging—many of them from Tsien's lab. In 2009, for example, Tsien and Xiaokun Shu adapted molecules found in certain bacteria to create a new fluorescent pigment that glows in the infrared. Its light passes through mammalian tissues more easily than other colors can, which means that it may be better for monitoring deep tissues in the body.

Tsien and Quyen T. Nguyen are developing a clinical technique for linking GFP to tiny particles that tumor cells will preferentially absorb. The glow from those particles could help surgeons removing tumors to be sure that they are not leaving any invaded tissues behind. It could also help to illuminate nerves that surgeons would not want to cut accidentally.

Various labs are also trying to modify GFP so that instead of fluorescing it would turn on the activity of a linked protein. Researchers could then control biochemical processes simply by shining the right color of light on a cell.

Notwithstanding all that GFP is illuminating about biology, the protein itself in many ways remains a mystery. For the jellyfish that make GFP, the advantage of lighting up is unclear, and the corals and other organisms that make GFP don't even fluoresce under natural conditions. "We don't know what the function is in nature," Zimmer says. "You'd think that's something fundamental we would have solved by now.

Top image: A glowing cat with a control (ie. nonglowing) cat. Courtesy Mayo Clinic.

John Rennie is an editor at large for Txchnologist. He served as editor in chief of Scientific American between 1994 and 2009 and is an adjunct instructor in New York University's Science, Health and Environmental Reporting Program. His last story for Txchnologist was about the death of his dog, Newman, from cancer. John blogs at The Gleaming Retort can be found on Twitter as @tvjrennie.

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