

Bioluminescent, Biofluorescent Species Light the Way to New Biomedical Discoveries

By Cheryl Lyn Dybas



The bioluminescent crystal jellyfish *Aequorea victoria*. Image Credit: Sierra Blakely, Wikimedia Commons

Throughout history, humans have been fascinated with the “living light” produced by luminescent organisms. Today, the glimmering power of bioluminescence has been harnessed for lifesaving uses in medicine, from lighting up structures inside the brain to illuminating the progression of cancer cells.

One of the first accounts of bioluminescence and health was written in 77 CE. In *Historia Naturalis*, Roman physician and naturalist Pliny the Elder described medicinal substances derived from aquatic animals, including *pulmo marinus*. A jellyfish now known as *Pelagia noctiluca*, Latin for “night light of the sea,” the species emits a glowing substance from the outer edge of its bell. When boiled in water or taken in wine, Pliny believed, *pulmo marinus* treated “the gravell and the stone.”

Also in the first century, Greek physician and botanist Pedanius Dioscorides posited in *De Materia Medica*, an herbal medicine encyclopedia he penned, that “*pulmo marinus* being beaten small whilst it is new and so applied, doth help such as are troubled with chillblanes and such as ye have goute.”

Some two thousand years have passed since the time of Pliny and Dioscorides. Only recently, however, have researchers discovered exactly how bioluminescence is created, let alone how to employ it in cures for disease.

The sparkle of marine bioluminescence occurs in species from fish in the deep ocean to jellyfish and dinoflagellates in the shallows, among others. They create light through the interaction of the enzymes luciferase and luciferin (the terms are derived from the Latin word *lucifer*—light-bringer), or by hosting light-emitting bacteria. Biofluorescence, sometimes confused with bioluminescence, is released when

an animal such as a jellyfish or eel absorbs light and re-emits it in a different color.

Now, “a vast range of analytical techniques has been developed based on bioluminescence,” write Zinaida Kaskova, Aleksandra Tsarkova, and Ilia Yampolsky of the Russian Academy of Sciences and the Pirogov Russian National Research Medical University in a 2016 paper in *Chemical Society Reviews*.

“Immunoassays, gene expression assays, drug screening, bioimaging of live organisms, cancer studies, and the investigation of infectious diseases,” the scientists state, are just the beginning of a tale of 1,001 lights, as the researchers refer to the growing number of bioluminescence discoveries with applications in medicine.

A REVOLUTION IN SCIENCE

An early chapter in the tale of 1,001 lights, according to neurobiologist Vincent Pieribone, director of the John B. Pierce Laboratory at the Yale University School of Medicine, is green fluorescent protein (GFP). GFP is found in the crystal jellyfish *Aequorea victoria*. This and other fluorescent proteins have revolutionized research in fields from immunology to neuroscience.

Many organisms are now known to manufacture fluorescent proteins. “These proteins are extending the boundaries of science, including allowing researchers to understand, manipulate, and interact with the living brain,” says Pieribone.

When scientists develop methods that allow them to see things that were once invisible, research takes a giant

leap forward. For example, in the seventeenth century, Anton van Leeuwenhoek invented the microscope. A new world opened. Scientists could suddenly observe previously unknown bacteria and blood cells. So it is with fluorescent proteins, Pieribone says.

BRIGHT GREEN EEL PATENT

Based on a bright green fluorescent protein found in two fish—the false moray eels *Kaupichthys hyoproroides* and *Kaupichthys n. sp.*—Pieribone’s team was awarded a patent for a new method of detecting bilirubin in blood or urine. Bilirubin is produced in bone marrow cells and in the liver as the end product of red blood cell (hemoglobin) breakdown.

High levels of bilirubin may indicate liver damage or other disease. Molecular Tools LLC, a biotech company in Frederick, Maryland, is working with the scientists to develop new ways of testing for bilirubin based on these proteins.



Image of the bioluminescence of *Chaetopterus*, the parchment tubeworm. Image credit: David Liittschwager, Scripps Institution of Oceanography

The eels' biofluorescence could be related to their unusual management of bilirubin, says Pieribone. Unlike other vertebrates, he says, the blood plasma of some eels, such as *Anguilla japonica*, is blue-green due to a high concentration of biliverdin, the precursor of bilirubin and the pigment responsible for the greenish color sometimes seen in bruises.

GROUND-TRUTHING CANCER IMMUNOTHERAPIES

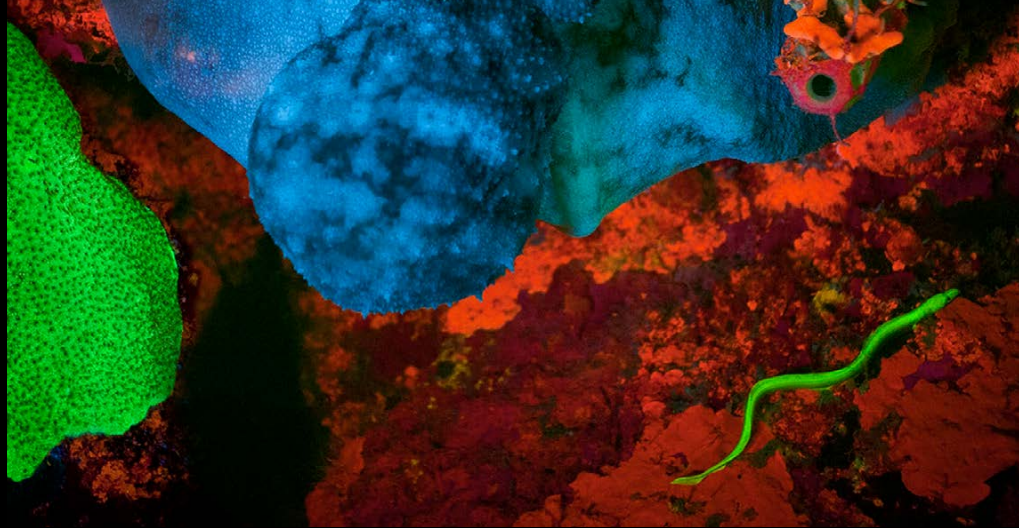
Bioluminescence is also leading to better ways of developing cancer immunotherapies. Researchers at the University of Southern California (USC)'s Keck School of Medicine created a bioluminescence test to find out whether an immunotherapy is in fact killing the cancer cells that are its targets. The results of the study were published on January 9, 2018, in *Scientific Reports*.

"One of the most promising areas in cancer research is immunotherapy, including CAR-T [chimeric antigen receptor-T] cells," says senior author Preet Chaudhary, a hematologist at USC. The gold standard for finding out whether immunotherapy is working, he says, has been an expensive and complicated radioactive chromium release assay. Now Chaudhary and colleagues have developed an assay based on luciferase.

The researchers used bioluminescent Pacific Ocean crustaceans for the test, named the Matador assay after the El Matador State Beach in Malibu, California. Luciferase from the creatures is introduced into cancer cells, then leaks out as the cells die, leaving a visible glow that can be measured.

The scientists tested the Matador assay's effectiveness in several cancers, including chronic myelogenous leukemia, acute myelogenous leukemia, and Burkitt's lymphoma. The assay could accurately recognize the death of a single cancer cell. "The Matador assay can detect cell death in 30 minutes," says Chaudhary. "That will lead to faster treatments for patients receiving immunotherapies such as CAR-T cells."

Chaudhary's team recently developed a related assay based on bioluminescence, called the Topanga assay after Topanga Beach in Malibu. The researchers published their results in the February 13, 2019, issue of *Scientific Reports*. "The work is inspired by and celebrates the beauty and endless possibilities the ocean rep-



An eel whose unique green fluorescence led to a patent. It was photographed near Little Cayman Island. Image credit: Jim Hellemm

resents," says Chaudhary. "That's why the inventions are named after local beaches."

Like the Matador assay, the Topanga assay uses luciferase to measure the expression of chimeric antigen receptors on the surfaces of patients' disease-fighting T cells.

"Academic labs and biotech companies are developing CAR-T cells directed against different cancers," says Chaudhary, "but a major challenge is the lack of a fast, economical, sensitive assay for the detection of cancer-fighting CARs on the surfaces of immune T cells."

The Topanga assay, he says, like the Matador assay, can be employed in as little as half an hour. "It has major uses not only in research on next-generation CAR-T cell therapies, but also on CAR-T cells that are in current clinical use."

Chaudhary is planning studies to determine whether the Topanga assay can monitor the expansion and persistence of CAR-T cells after they've been given to patients. That would allow doctors to identify people at risk of a toxic reaction if the CAR-T cells expand too quickly, and to find patients who might relapse if the CAR-T cells die out too soon.

THE SUPERPOWERS OF BIOLUMINESCENCE

Chaetopterus sp. It sounds like an alien being. In its own way, it is. Also known as the parchment tubeworm, its souped-up ferritin may be as linked with bioluminescence as spinach is with Popeye.

Ferritin is an important protein; it manages iron metabolism in cells by storing and releasing it in a controlled way.

In this tubeworm, known for its bioluminescence, ferritin has the fastest performance discovered, almost eight times

faster than ferritin in humans. The secret may be in the worm's light show, scientists have discovered. The study was funded by the Air Force Office of Scientific Research. Biologists there are interested in learning more about the bioluminescent properties of this unusual worm and the speed of its ferritin.

Tubeworms are common in muddy nearshore habitats in temperate coastal waters around the world. This tubeworm has another unique ability: it can keep its bioluminescent blue light glowing for hours—and sometimes days. That's much longer than most bioluminescent organisms, which usually "light up" for seconds or even milliseconds.

The worm's bioluminescence may rely on the iron dissolved in seawater. But it's more likely, researchers think, that the worm's mucus contains iron that regulates its light production. *Chaetopterus* kept in seawater with no iron can still produce mucus with strong luminescence. More research, marine scientists say, will lead to new answers.

In *One Thousand and One Nights*, storyteller Scheherazade spun a never-ending tale. So, too, in the saga of 1,001 living lights, the sequel awaits.

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