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A review on the application of marine Bioluminescence organism

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Abstract

Bioluminescence is a natural and fascinating phenomenon in which living organisms produce light by enzymatic activity. Over many years, researchers have been studying the genetic sequence, biochemical, and physiology of bioluminescent organisms. In nature, forty different bioluminescent systems are found in that seven light-emitting reactions are known, and only two chemical pathways have been studied completely. Bioluminescence is used for many purposes but in the last decade, it has been used tremendously in several advanced fields. The ability to isolate and transfer the *lux* genes in both prokaryotic and eukaryotic organisms has potentially made the use of bioluminescent bacteria. It is applied to detect protein-protein interaction, to check the efficiency of drugs, and biosensors to validate environmental pollution, immunology, oncology, neuroscience, the food industry, and so on. This paper will review the discoveries and current applications of marine bioluminescence organisms in the field of biosensors tagged with bioluminescent gene and their applications in various purposes, bioluminescent assay in food industries, and molecular methods, bioluminescent tagged gene and their potential in anti-cancer immunotherapy, bioluminescent imaging to detect the infected cells in animal model, and immunoassay applications of RLux gene extracted from *Renilla reniformis.*

Keywords: Bioluminescence; Luciferase; *Lux* gene; Bio-sensor; Bioluminescence imaging.

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1. Introduction

Bioluminescence is light emission by living organisms as the result of enzyme-catalyzed oxidation. Enzyme- luciferase, and the light-emitting molecule- luciferin are involved in the emission of light (Brodl *et al.*, 2018). The emission of light also requires oxygen and Adenosine triphosphate (ATP) (Ramesh and Mohanraju, 2021). *Lux* operon is responsible for light emission which is found in luciferase enzyme. This gene contains the gene *luxICDABEG. LuxA* and *LuxB* genes code for α and β subunits, *LuxCDE* codes for polypeptides in which fatty acids are reduced to long chain aldehyde (Dybas, 2019). The active site is the α-subunit and it produces less light intensity when β-subunit is absent (Scott *et al.*, 2011). The oxidation between Reduced flavin mononucleotides ($FMNH_2$) and long-chain aldehyde releases excess energy which is liberated as light (Noorian *et al.*, 2015). The light is emitted by the interaction of the luciferase enzyme and luciferin (Dybas, 2019). Luminescent fungi use oxygen, Luciferin, Luciferase, 3-hydroxyhispidin, and NAD(P)H-dependent hydroxylase for the emission of light (Kotlobay *et al.*, 2018). In the fungi pathway, caffeic acid is converted into luciferin (Khakhar *et al.*, 2020). The luminescence may be bright in favorable conditions and slightly blacked out but will be visible to the naked eye. The emission of light may be greenish-blue (490nm) or yellow light (545nm) (Scott *et al.*, 2011). The entire Bioluminescence cyclic process is explained in Figure 1.

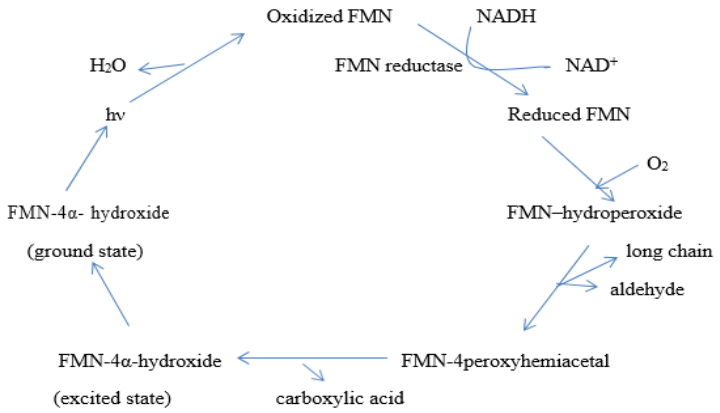

Figure 1. Bacterial bioluminescence mechanism (Brodl *et al.*, 2018).

$FMNH_2 + RCHO + O_2 \rightarrow FMN + H_2O + RCOOH +$ light (490nm) (Noorian *et al.*, 2015).

Luminescence property was observed in some species of bacteria, fungi, and insects to hunt prey, attract mates, or prevent attack from predators (Mostafa *et al.*, 2023; Syed and Anderson 2021). Furthermore, some fishers show this property because of the symbiotic relationship between bacteria and fish (Brodl *et al.*, 2018). While selecting the luciferin and luciferase pair several criteria like PH, protein size, wavelength of emission intensity, and ATP thermo-stability must be taken into account (Fleiss and Sarkisyan, 2019). After discovery of bioluminescence property in fungi, it made to transfer genes into eukaryotic animals and plants (Khakhar *et al.*, 2020). *Lux* genes were cloned and transferred into

biological organism that had made a number of applications in various diversity and detection of substances (Meighen, 1993). Fusion of wild-type *lux* will work on gram-positive bacteria while the fuse *lux* gene works on gram-negative bacteria (Nunes-Halldorson and Duran, 2003). Analysis using bioluminescence is a promising method because it is sensitive as it gives accurate result even for the micro quantity of substances (Scott *et al.,* 2011). In the last decade, bioluminescence has been used because of its effectiveness and fast validation. It has become multidisciplinary and utilized in medicine, physics, biology, and engineering fields (Badr and Tannous, 2011). Immunoassay, drug screening, bio-imaging of live organisms, cancer therapy, gene expression, biosensors, investigation of disease, imaging stem cells, ATP sensing, control of hygiene, food industry, pollutant mapping, protein-protein interaction, and photodynamic therapy are applications of bioluminescence (Dybas, 2019; Syed and Anderson, 2021).

2. Bioluminescent in the food industry

ATP Bioluminescence is a bioluminescent-based assay used to find the biomass. All living cells contain ATP as storage for metabolic energy, so the level of ATP is proportional to the number of living cells (Colaruotolo *et al.,* 2021). Luciferase is also used in this assay process as it is a co-factor for bioluminescence. This method can be used for both prokaryotic and eukaryotic cells (Syed and Anderson, 2021).

ATP bioluminescence was used to check the contamination level of the surface by simple swabbing method (Dostálek and Brányik, 2005). The same procedure was used in milk and milk products, meat and meat products, carbonated beverages, and fruit juices to check the contamination (Kennedy and Oblinger, 1985). This can also be used to detect specific bacterial pathogens and indicator organisms, and even to check the effectiveness of spore destruction (Kricka, 1998).

Bioluminescent genes were inserted into gram-positive *Bacillus sp.* These recombinant bacteria produce spores with bioluminescent genes. The presence of viable spores was detected by light emission during germination. Injured and dead spores do not glow. Thus, it was used to check the presence of spores in food products. Sometimes spores after sub-lethal effect recover themselves and survive, those spores with recombination with bioluminescent genes were shown luminescence and detected.

The presence of bacteriophage and antibiotics may fail cheese and yogurt production. So, Bioluminescent genes inserted into Lactic Acid *Streptococci* were used as indicators. The intensity of bioluminescence is used to detect the presence and absence of bacteriophage.

Biocides were used as preservatives; thus, biocide level is important in food processing. Bioluminescent Microorganism can be used to detect the level, this method was rapid and can detect in 10 – 15 minutes. It was tested on *Listeria monocytogenes.* Virucides have also been tested by inserting the *LuxA* and *LuxB* in λ phage (Kricka, 1998).

Lux gene was tagged with *Salmonella enteritidis* and *Campylobacter jejuni* used to determine eggshell penetration and colonization. In fish processing plants, *Lux* has been used to check the contamination level by using ATP sensing (Syed and Anderson, 2021). This Lux gene assay was used in the dairy industry to detect milk contamination and determine the duration that milk should be preserved. It was also used to detect the number of lactic acid bacteria in starter culture and can indicate antibiotic residues or phage (Griffiths, 1993).

3. Bioluminescent sensors

Microorganisms were immobilized on the transducer to detect the analyte (Nwankwo *et al.,* 2019). The genetically modified whole cells or active luciferase were immobilized on a solid surface. The solid support is made up of agarose, collagen, and epoxy methacrylate. The gel entrapment method was predominantly used (Girotti *et al.,* 2008). It is based on the bioluminescent principle, in the presence of contaminants and toxicants it illuminates (Nwankwo *et al.,* 2019). Bioluminescent-based biosensors can able to analyze and detect pH, metals (mercury, lead, cadmium), ions, Reactive Oxygen species, polycyclic aromatic hydrocarbons, contaminants in the environment, and toxicants (Nwankwo *et al.,* 2019; Nunes-Halldorson and Duran, 2003). It can even detect contaminants like *Escherichia coli, Bacillus subtilis, Pseudomonas sp.* Samples from air water, and soil can be used. *Pseudomonas fluorescens* HK44 carry *nah-lux* reporter plasmid used in the degradation of salicylate and naphthalene. *Mer-lux* biosensor was used to detect the inorganic Hg in water. The *lux* genes were fused with *Escherichia coli* and used to detect linear alkanes (Mancini *et al.,* 1988). These biosensors are fast, give accurate results, are cost-effective, and reliable. Thus, bioluminescent-based biosensors can be used in various fields like medicine, hygiene control, food industry.

3.1. Biosensor in the medical field

There are thirteen bioluminescence sensors designed to check the effectiveness of the drug. These sensors were based on G- Protein-Coupled receptors (GPCRs) which is involved in communication between cells. Many medicines present in the market were aimed at these receptors. In vitro tests showed whether the drug compound activates or blocks the cell's response. The test is like a lamp that could switch on or off. The researchers added the bioluminescent enzyme luciferase to GPCR. The drug activates the receptors and the protein interacts with the receptors. The enzyme luciferase transferred the lighting property to protein. This has brought a new impact on drug development (Dybas, 2019). The antibodies in blood plasma, *Escherichia coli* level in urine sample can also be detected by bioluminescent biosensors (Syed and Anderson, 2021).

3.2. Environmental control

Bioluminescence-based biosensor was used to detect pollutants like heavy metals, gases, toxicity, organic compounds, and biological contaminants. Bioluminescent bacteria were

genetically modified to use for the remediation process. A bacterial bioluminescence assay was used to check the quality of seawater, field water, and drinking water to determine toxicity levels and can determine bacteria fungal, and protozoa contamination levels (Syed and Anderson, 2021; Girotti *et al.,* 2008). It is also applied to check the air for the presence of gaseous chemicals. The biosensor was connected to the Luminometer and the of benzene was detected in air. In addition, it was used to detect organic compounds like toluene, naphthalene, and metals like zinc, and uranium (Girotti *et al.*, 2008).

Plant diseases and infections were monitored in plant seedlings by tagging the Lux gene. They were also used to detect the biofilms and efficacy of hand sanitizers and disinfectants. In antique work, bioluminescence-based ATP sensing was used to detect bacteria, fungi, yeast, algae, and lichen contamination levels. This method was used to find hot spots of contamination and help in preservation. These ATP bioluminescence-based assays are commercially available and fast detection systems (Syed and Anderson, 2021).

3.3. Hygiene control

ATP bioluminescence is widely used to detect hygiene in hospitals, industries, and additive manufacturing materials (Veiga-Malta, 2016; Messina *et al.*, 2014; Hansen *et al.*, 2008). ATP bioluminescence is based on the principle that ATP is present as cellular constituents in all living organisms except for viruses which do not have ATP. The intensity of light produced gives the amount of organic contamination and is measured using a luminometer (Hansen *et al.*, 2008).

The hospital environment contributes to nosocomial pathogens like MRSA (Methicillin-resistant *Staphylococcus aureus*), and VRE (Vancomycin-resistant *Enterococcus, Clostridium difficile*). To prevent these infections hospitals should be maintained and sterility must be checked continuously. ATP bioluminescence is used to detect the sterility level (Messina *et al.*, 2014; Moore *et al.*, 2010)

ATP bioluminescence is also used in additive manufacturing material to check sterility and are used in various medical applications (O'Malley *et al.*, 2016). The commercially available ATP bioluminescence can be used to determine the sterility of surgical instruments and other medical devices. ATP assessment of the surgical instrument; ≤15 RLU- pass range, 16 to 30 RLU- caution range, >30 RLU- fail range. It is an easy swab method and rapid but the disadvantage is that it is difficult to check the cleanliness of hands because it also measures the quantity of ATP in the skin (Doyle *et al*., 2004).

4. Cancer immunotherapy

Cancer is a complex disease, as it interacts with surrounding normal cells and spread throughout the body. Bioluminescence was used in cancer treatment to differentiate cancer

cells from normal cells and to kill them. For understanding the tumor growth in host cell to analyze anti-tumor treatments, bioluminescence had been used (Badr and Tannous, 2011).

4.1. Luciferase enzyme

Renilla Luciferase (RLuc) is an enzyme extracted from a soft coral, *Renilla reniformis* (Sea pansy). RLuc enzyme catalyzes the oxidative decarboxylation of *Renilla* luciferin in the presence of oxygen and result in the emission of blue and green light. These enzymes were used in the bioluminescence-activated Activated Destruction of Cancer or BLADe to kill cancer cells. Scientists inserted an RLuc laminating gene into cancer cells, thus luciferase made cancer cells glow. The light emitted was enough to trigger their death. Then, Photosensitizing agent was added that made cancer cells produce toxic substances, which also caused self-destruction. This method can be used to treat various cancers as they are very specific and targeted (Dostálek and Brányik, 2005).

The DLuc (*Gaussia* Luciferase) was extracted from the marine copepod *Gaussia princeps,* a monomeric protein, the smallest known natural luciferase enzyme, emits light at the peak of 480nm range. It has several advantages as it is 2000 times more sensitive than RLuc gene expression. GLuc has been used in mammalian cell *in vivo* signalling giving the strongest bioluminescent light emission peak and has also been used in the detection of cell expression in cell-based assays (Badr, 2013).

4.2. Assay method

Scientists have tried bioluminescent tests in cancer immunotherapies. Radioactive Chromium release assay was the gold standard method for working on immunotherapy, but it is an expensive and complicated method. To overcome this very accurate method was developed based on Luciferase. Matador assay was developed by introducing the Luciferase enzyme into cancer cells. If the cancer cells die after treatment, the luciferase enzyme leaks out and glows. The visible glow was detected. Very accurate method even single cell glow can be detected and time-saving method, within 30 minutes it can be detected (Dybas, 2019). MiRNA mutation correlates with human cancer, so it was taken for diagnosis of cancer. Scientists developed an assay for microRNA for the detection of miRNA. Using *Renilla* luciferase the presence of miRNA in breast cells was detected (Fleiss and Sarkisyan, 2019).

4.3. Photodynamic therapy (PDT)

It is a non-invasive medical technique used for the treatment of bacterial, and fungal, skin diseases and cancer. The rapid attenuation of external light through tissue might occur in PDT, which causes limitations in the treatment process. So, to overcome this Near-infrared light (NIR) and X-rays were used but they also showed some limitations. So, Scientists used intracellular bioluminescence as a light source for PDT. *In vitro* Bioluminescence PDT showed significant deaths of cancer cells due to toxicity, and *in*

vivo treatment inhibited the subcutaneous tumor. In future the Bioluminescence PDT can be developed by using nanocarrier technology to deliver internal light to the tumor tissues (Coleman and McGregor, 2015).

4.4. Bioluminescent reporter imaging

This type of imaging was used for imaging bone marrow metastases. This method was used to monitor the continuously effective localization of growth. For this study, CMV promoter-driven mammalian expression vector for luciferase (CMV-Luc) was used. These cancer cells were injected into the mice and observed. For detection, the mice were dosed with sedative, and luciferase expression cells were recorded. The photon emission was integrated and recorded as pseudo-color (Wetterwald *et al.,* 2002).

5. Bioluminescence imaging (BLI)

BLI is a powerful tool designed for imaging *in vivo* ongoing molecular biological processes of small laboratory animals. BLI is used to track the injection and monitor the efficacy of antimicrobial therapy (Sadikot, 2005). Fungi, bacteria, and viruses are engineered with the illuminating gene thus making it very much used to study tumor biology, and signals from deep inside the body can be detected. The illuminating gene-tagged cells were engineered in culture and transferred to an animal model to study (Doyle *et al*., 2004). This type of optical imaging technique is cost-effective, non-invasive, and enables to analysis of disease of living organism in the molecular level.

5.1. BLI in viruses

Viruses cause life-threatening diseases in immunocompromised patients. Initially, an Adeno-associated viral vector was used to transfer the gene to the host cell (O'Malley *et al.,* 2016). RLuc (*Renilla* Luciferase) gene was inserted in HSV-1 and studied. The mice were infected with this recombinant virus to check the antiviral drug efficacy. The result can be determined by ex-vivo imaging and real-time PCR was used to get absolute viral load. A recombinant virus was prepared by inserting a bioluminescence gene, in order to study its replication, genes, area of infection, and for vaccine production. Both DNA and RNA viruses were tagged with luciferase genes and studied (Coleman and McGregor, 2015). Moreover, some viruses were used for gene therapy to deliver the gene or drug in a specific site. For such therapy virus was modified, tagged with luciferase, and delivered in the targeted site, so the gene expression was easily detected in the targeted cell using the BLI system. This study was very much useful for analyzing specific route for effective drug delivery by vectors (Girotti *et al.,* 2008).

Varicella-Zoster virus was tagged with the RLuc gene and studied for the spread of viral infection in xenografts. Likewise, the Pox virus was inserted with the RLuc gene and injected into mice to study its replication over the interferon effect. BLI was also used to find areas of virus infection in animal models. Luciferase-tagged Ebola virus was

developed, and injected into animals and the antiviral assay was studied. This study provided highly informative data on viral disease at the time of spread of the disease. Even RNA viruses like Dengue virus and influenza virus were studied using Bioluminescence (Coleman and McGregor, 2015).

5.2. BLI in bacteria

For the successful Luciferase operon expression in gram-positive bacteria, the introduction of the gene in gram-positive ribosome binding site before each of the five genes. This expression was used in *Streptococcus pneumonia*, *Listeria monocytogenes*, *Streptococcus pyogenes* and introduced in the host. The route, target organ, course of injection, and efficacy of the antimicrobial drug can be determined by viewing the host organism (O'Malley *et al.,* 2016).

5.3. BLI fungal injection

RLuc genes was used to form recombinant fungi. The studies were made in *Saccharomyces cerevisiae, Neurospora crassa, Candida albicans, Aspergillus oryzae, Aspergillus niger,* and *Aspergillus fumigatus.* A charged Coupled Device (CCD) camera was used to detect the emission of light that collects even a single photon. *Candida albicans* cause vaginal infection, so FLuc tagged *C.albicans* was used to visualize infection in the vaginal lumen. After treatment with an antifungal drug, a decrease in infection and a reduction in cell number were also recorded. Here the light emission was correlated with the presence of the number of live cells. *A.fumigatus* was tagged with the RLuc gene and used to monitor deep tissue infection. It showed an even minute amount of hyphae growth in infected tissues. It can also able to track deep infections far above 600nm with the help of light emission (Brock, 2012).

6. Gene assay

The number of genes was determined by bioluminescent-based readout for various analyses (Syed and Anderson, 2021). Normal immunoassay uses radiolabels which are unstable and cause radio waste to overcome this immunoassay uses the RLuc gene for specific identification of antigens (Figure 2) (Fleiss and Sarkisyan, 2019), The antigen was coated on a polystyrene plate and made to react with a suitable antibody. Enzyme DNA bound to biotin-streptavidin tagged with RLuc gene. Then, finally D-Luciferin was added to get light output. Thus, the light output was directly proportional to number of antigens present. The most important application of this reporter gene is that it can be used to study gene expression in both prokaryotes and eukaryotes (Syed and Anderson, 2021).

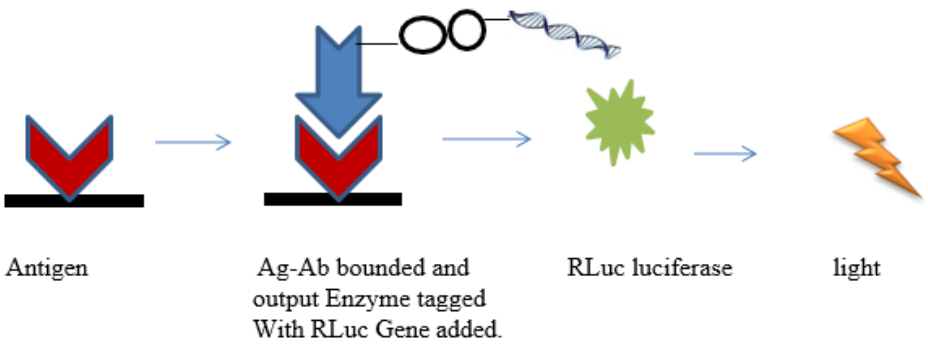

Figure 2. Immunoassay using RLuc gene (Syed and Anderson, 2021).

Likewise, this *Renilla* luciferase was fused with *Escherichia coli* which gave 48% more quantum yield, even detecting 0.02pg of protein. To get highly sensitive results luciferase was genetically fused with either antigen or antibody. In nucleic acid hybridization to detect the gene of interest, the probe was tagged with a bioluminescent gene. This bioluminometric assay had a wide range, higher detection, and was simple to use (Fleiss and Sarkisyan, 2019).

6.1. SARS-Cov-2

SARS-Cov-2 coronavirus was found in bats and transmitted its infection to humans. Spike proteins on their surface played an important role in the invasion of the virus into the cells. The interaction and binding of spike protein and Angiotension - Converting enzyme 2 (ACE2) in mammalian cells is the key point of entry of viruses in the human body. Plasmids were prepared in such a way that they contain spike protein genes and luciferase genes. Plasmids were allowed to enter the host cell to produce a pseudo-virus with spike proteins on their surface and genetic code for RLuc. Then, it was made to infect the human cells, if the infection is successful the daughter cells have RLuc genes. To detect the infectivity rate D-Luciferin was added to emit light (Syed and Anderson, 2021). This was a notable relevant example of the use of a luciferase-based assay for virus infectivity in the pandemic period.

7. Plants glowing

Bioluminescence has been limited in plants because chlorophyll absorbs light from 450-650nm, resulting in low light output (Fleiss and Sarkisyan, 2019; Kotlobay *et al.*, 2018). To overcome this difficulty, scientists have delivered D-Luciferin to cells of interest to make auto-luminescent plants. The bacterial *lux* operon was expressed in plant plastids but resulted in low light intensity and the gene expression was toxic to plants. After the failure of the bacterial *lux* operon, Scientists concentrated on the RLuc gene, combined with silica nanoparticle and D-luciferase was combined with poly lacto-co-glycolic acid nanoparticles. These two nanoparticles were delivered into plant cells to take place in bioluminescence activity. This reaction gave a yellow-green glow to the plant (Syed and Anderson, 2021).

After the discovery of the fungal bioluminescent pathway, the genetically modified plants with fungal pathway encoded the plant to auto-illuminate. Some fungi produce luminescence by converting Caffeic acid into luciferin. Caffeic acid also found in plants, so that, by inserting gene from fungi produce light in plants (Mitiouchkina *et al.,* 2020). A Fungal illuminating system was expressed on tobacco lines (*Nicotiana tabaccum)* in which Caffeic acid was converted into luciferin and luminescence was observed in the naked eye (Kotlobay *et al.,* 2018). This opens up new avenues in the plant bioluminescent imaging (BLI) field research, as it moves from laboratory Petri dishes to real-life soil plants grown in soil.

8. Natural light- a future perspective

The beauty of Bioluminescent bacteria systems has been considered as a green alternative to public outdoor street lights. These bioluminescent organisms are being researched by many universities to replace street lights with commercial natural bioluminescent bulbs and plants on the roadsides have been genetically engineered to tag them with bioluminescent genes making them glow during the night time, thus producing sustainable energy (Latz, 2017). Recently a French company "Glowee" attempted to increase the bioluminescent bacteria life span from three days to one month and made a sustainable lamp in public place. Likewise, many companies are now interested in working further on commercial bioluminescent bacterial lamps as they could become a futuristic reality.

Conclusion

Bioluminescence has their applications in various fields in recent years. The light-emitting phenomenon has attracted researchers to work on this further, it has got its application in various fields like physics, chemistry, medical and has become a multidisciplinary topic. Although, it has reached several territories of the field, still has limited usage in a wider range due to its low quantum yield, poor stability, bioactivity, and biocompatibility. As it is an emerging field, initial research has been carried out and still a lot more time and technology are required for great novel inventions.

The research on marine bioluminescence organisms and the Luciferase enzyme led to the designing of Luciferin and Luciferase enzyme developed a lot of great technology work to assist the progress of this field. Research has been carried out on developing new luciferin and luciferase pairs with improved properties with high stability and further advancement in the cloning process and biotechnology area which will led to novel applications. This review briefly explains the mechanism of marine bioluminescence and the Luciferase enzyme's recent application in the medical and biotechnology fields, which stimulates future exciting research in the Bioluminescence field.

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