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ARTIFICIAL BIOLUMINESCENCE: BRIGHT ASPECT OF BIOLUMINESCENCE TECHNOLOGY IN THE PROCESS OF MAKING: A REVIEW

Koustav Bhattacharjee*

RKM Vidyapith, Deoghar, Jharkhand - 814112, India

Abstract : Bioluminescence is generally called a natural phenomenon that is to emit cold lights from the organisms like firefly, several arthropods, fishes and other living organisms. But now a days this is not constricted only in the natural area rather due to the development of science and technology proceeds and our needs also increasing day by day it is becoming a future technology and a boon for mankind using bioluminescence method in laboratory also by using several energy transfer techniques like LRET, BRET etc. The uses like electricity consumption, testing water turbidity or even in cell and molecular biology researches for new drug discoveries and disease detections like cancer are some ongoing research advancements in various countries.

Key words: Bioluminescence, LRET, BRET, electricity consumption, water turbidity, new drug discovery, disease detection.

Introduction

From fireflies to deep sea creatures bioluminescence has intrigued, confused and delighted us. Bioluminescence is the natural ability of certain plants and animals to create light via chemical interaction. Many have felt that bioluminescent technology is nothing but fad technology with no real point or purpose, but recent innovations have (begun to challenge that idea) (https://sensing.konicaminolta.us/us/). New designs and ideas are beginning to surface that may transform how we light our world. Now, scientists have for the first time identified the biochemical pathway that allows bioluminescent fungi to light up. But they went even further by putting the three genes necessary to generate luminescence into a non-glowing yeast, they created an artificially luminescent eukaryote. The scientists found the key genes responsible for the bioluminescence of *Neonothopanus nambi* (Kanokmedhakul *et al* 2012). Using libraryscreening and genome analysis, the team identified the enzymes that contribute to the synthesis of luciferin. They showed that fungal luciferin, the substrate for the bioluminescence reaction, is only two enzymatic steps away from a well-known metabolite, called caffeic acid, which the fungus generates (Strack, Rita. 2019). 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. Scientists have found a way to simultaneously monitor the switching on and off of circadian "clock" genes and their effects on mouse behaviour in real-time. However, anaesthesia is believed to affect the expression of clock genes. Other techniques not requiring anaesthetization have their own limitations. A team of scientists from Hokkaido University in Japan developed a new imaging technique that allowed them to monitor the expression of clock genes, including the per1 gene, in multiple tissues in moving fully conscious mice. In vivo bioluminescent imaging (BLI) has been used as a non-invasive means of tracking pathogens or tumour cells in animal subjects early in the disease process (Francis *et al* 2001, Rocchetta *et al*.2001,Contag *et al* 1995, Rehemtulla *et al* 2000, Wu *et al* 2001,2002), Rehemtulla *et al* 2002), and to develop new animal models that incorporate reporter genes into the rodent genome as markers of transcription that reveal developmental changes or response to various stimuli (Contag *et al* 1997,Zhang *et al* 2001,Voojis *et al* 2002). A

**For Correspondence.*
(email: koustavbhatti559@gmail.com)

common reporter gene setup will involve inserting a reporter gene downstream of a promoter/response element within a mammalian expression vector, which is then transfected into cultured cells. In the same way researchers are also developing methods to create bioluminescent trees to line city and suburban streets. Bioluminescent plants big enough to be able to generate street light would effectively eliminate the need for more expensive electrical lamps as these would tend to be completely self-sufficient and energy free. The biggest challenge for researchers in this field is increasing bioluminescent brightness to provide sufficient light. This makes the final development of "tree-light" streetlights a more long term goal. Another more immediate application for bioluminescent technology is using it as a tester for water purity. By genetically modifying bioluminescent microorganisms so that their glow brightens under duress researchers have been able to effectively identify certain toxins in polluted water.

Bioluminescence gene switch

Bioluminescence is a technique that often involves modifying certain genes. When the target gene is switched on, it also expresses an inserted gene, leading to the emission of a light signal. Every time the target gene turns on, light is emitted. This technique has been successfully used to monitor gene expression in fully anaesthetized mice. A team of scientists from Hokkaido University in Japan developed a new imaging technique that allowed them to monitor the expression of clock genes, including the per1 gene, in multiple tissues in moving fully conscious mice. Per1 expression was at its peak in all six areas at the onset of mouse daily activity. When the Hokkaido team artificially shifted the hours of night and day for the mice, such as might happen when shifting time zones, per1's rhythmic expression became desynchronized for one day in the different areas and then synchronized again (Izumi et *al* 2017).

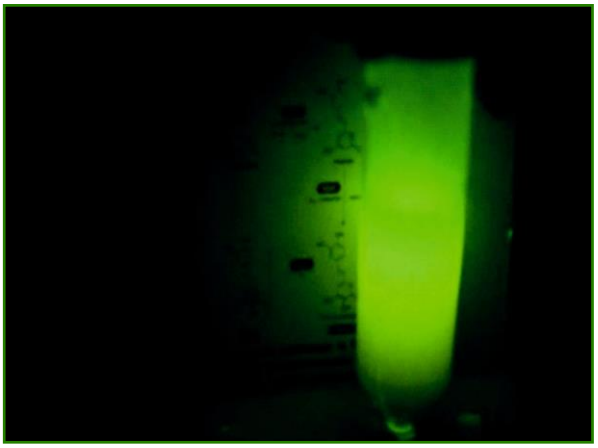

Fig 1: Artificially glowing yeast cells in a test tube

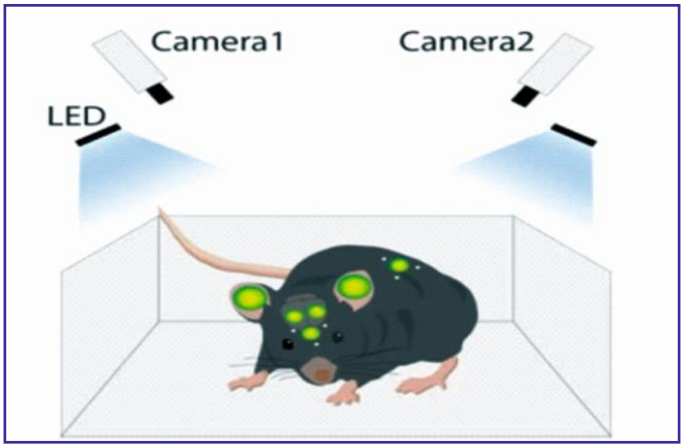

Fig 2: Arc expression in laboratory mouse

It is also shown in case of laboratory mouse in to check their movements by tagging some fluorescence emitter on different parts of the body. The team also developed a set of algorithms that allowed them to identify the intensity of the bioluminescent signals from target tissues (olfactory bulb, right and left ears and cortex, skin) despite the movement of the mice.

The activity-regulated cytoskeleton-associated protein gene (Arc) is rapidly transcribed in response to neuronal inputs. The transcripts of Arc, in a form of being ready for translation (Na et *al* 2016), are distributed to neuronal dendrites in activated neurons and surrounding cells (Pastuzyn *et al*. 2018). Arc is classified as a pyrethroid [deltamethrin considered to be one of the key proteins in neurobiology because of its roles in the regulation of spine morphology through α-amino-3-hydroxy-5-

methyl-4-isoxazolepropionic acid (AMPA) receptor endocytosis neuronal development and maintenance of neuronal networks (Mikuni *et al* 2013), and cognitive function through neuronal-activity-dependent synaptic development (Evert and Greenberg 2013; West and Greenberg 2011). Furthermore, recent studies also suggest that Arc is a possible therapeutic target for neural plasticity and disease (Jenks *et al* 2017; Mandel- Brehm et *al* 2015; Zhang *et al* 2015). They developed reporter transgenic (Tg) mouse strains expressing the firefly luciferase (Luc) gene under regulation of the Arc gene promoter (Izumi et *al* 2011, 2017). These Arc-Luc Tg mice enable the non-invasive detection and quantification of changes in neuronal activity in the mouse brain throughout lifespan. Based on this background, they decided to examine the usefulness of our Tg mouse strains for monitoring the effect of pesticides on the CNS and selected four different representative pesticides (DM)], an organophosphate [glufosinateammonium (GLA)], a carbamate [methylcarbaryl (NAC)],and a neo nicoteinoid [imidacloprid (IMI)] as subjects of our investigation (Casida and Durkin2013). By tracking spatio temporal changes in the bioluminescence signal of Arc-Luc Tg mice, detected the acute induction of Arc-Luc by DM and GLA treatments in the adult and juvenile stages.

In addition, they also characterized the specific behavioural changes associated with each pesticide in the mice. They found that reporter mice are useful for monitoring long-term effectsupon chronic treatment with low-dose DM or GLA. This study shows that the Arc-Luc Tg mice will be valuable for the evaluation of the cumulative effects of pesticides on neuronal activity-dependent processes in the CNS.

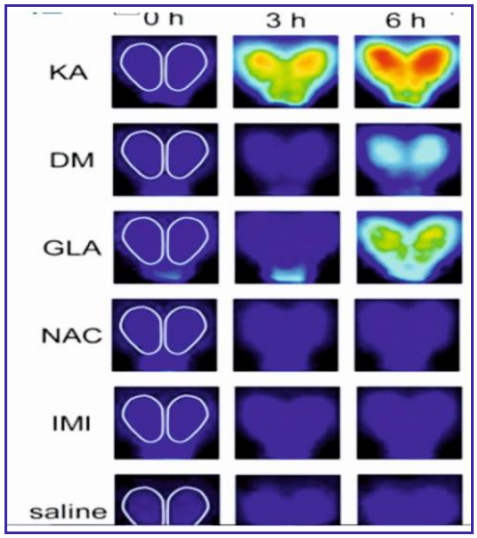

Fig 3: Expression of several chemicals and showing of bioluminescence in various parts of mouse brain (after Casida and Durkin, 2013).

Use of bioluminiscence technology in cancer treatment

In a new study, researchers from London inserted the firefly gene that activates bioluminescent light into modified cancer cells, hoping to set off a chain of events that has a proven track record at fighting the disease. This light source, known as Luciferin, caused the modified cancer cells to glow much like it does with the firefly. When a photosensitizing agent was added, the combination proved lethal. This firefly technique Bioluminescence Activated Destruction of cancer, or BLADe) may add a further layer of depth to photodynamic therapy, an effective treatment that uses bursts of light to attack tumour that sit near the skin's surface or on the lining of internal organs. As part of the therapy, cancer cells are treated with a photosensitizer

and then exposed to lasers or another external beam. The light triggers the production of active oxygen species that can destroy cancer cells.

Application of bioluminiscence reporters

The broader aspect of gene expression entails much more than transcription alone, and reporter genes can be used to study these other cellular events (Wood K 1995,Allard STM, Kopish K 2008) illustrates many of the applications to which our simple add-mix-measure genetic reporter assays can be applied including:-

- Understanding promoter structure.
- Activating / binding of surface receptors(e.g., GPCRs).
- Monitoring stem cell differentiation.

Analyzing transcription factor structure.

Observing viral infection & activating nuclear receptors.

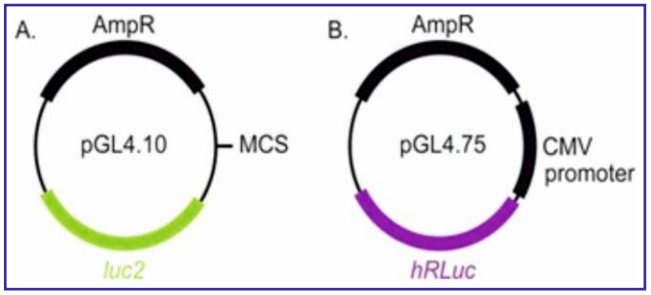

Fig 4: Structure of bioluminescence Vector (pGL4).

In fact, the pGL4 Luciferase Reporter Vectors incorporate several advances in genetic reporter technology including codon optimization of the reporter gene to enhance expression in mammalian cells, inclusion of reporter genes that respond rapidly to transcriptional dynamics and incorporation of mammalian selection markers that facilitate stable cell line generation. By selecting the right pGL4 Vector for your system and using any of our Luciferase Assay Systems, you can create an ultrasensitive assay that enables the accurate probing of the regulation and activity of a protein or a pathway inside the cell or in a cell lysate (Davis et *al*.2016).

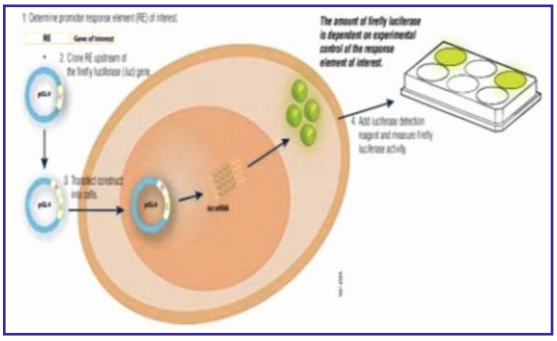

Fig 5: pGL4 Luciferase Reporter Vector (after Allard, 2008)

In vivo bioluminiscence imaging

In vivo bioluminescent imaging (BLI) has been used as a non-invasive means of tracking pathogens or tumour cells in animal subjects early in the disease process (Francis *et al* 2001,Rocchetta *et al*.2001,Contag *et al*.1995, Rehemtulla *et al* 2000,Wu *et al* 2001,2002), Rehemtulla *et al* 2002), and to develop new animal models that incorporate reporter genes into the rodent genome as markers of transcription that reveal developmental changes or response to various stimuli (

Contag *et al* 1997,Zhang *et al* 2001,Voojis *et al*. 2002). BLI is an opticalimaging modality that is based on the ability of light to penetrate tissues, although limited by absorbance and scattering, and incorporates the use of genes encoding luciferases as internal biological sources of light. BLI is an ideal imaging modality for understanding the parameters that govern gene delivery and effective expression, or inhibition of expression in model systems, and can be used to accelerate the development of therapies that are based on the delivery of biomolecules to target tissues.

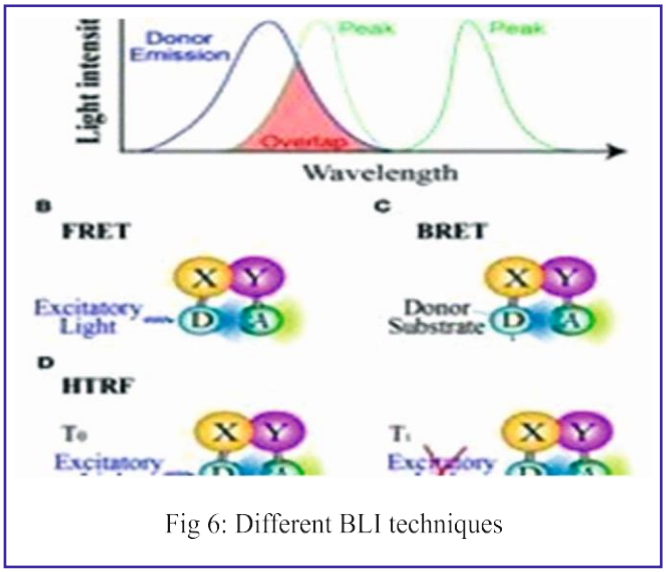

Fig 6: Different BLI techniques

Emerging reporter gene strategies for BLI

BLI has largely been used as a marker of transcription a regulation or, when expressed constitutively, as a marker of tumour burden or cell migration. Recently, there have been several developments, in the use of luciferase as a reporter protein, that may increase the number of functional assays that can be performed in vivo using BLI. These include use of dual-function reporters that are fluorescent and bioluminescent, modifications to the luciferase gene that lead to the expression of sensor proteins, and modification that lead spectral changes that can be used for improved detection or added function. Nonetheless, review of these modifications is warranted given their potential for improving in vivo assays.

Towards in vivo assayes for protein protein interaction

Bioluminescence resonance energy transfer (BRET), also known as chemiluminescent resonance energy transfer (CRET) and luminescent resonance energy transfer (LRET), is the process of transferring energy from a light-emitting enzyme to a fluorophore with the net result of a color shift to a longer wavelength (Wang *et al* . 2001, ,Xu *et al* 1999, 2002, 2003). Energytransfer from Renilla luciferase to GFP has been used to study protein–protein interactions in cultured cells using the known association of two proteins (Wang *et al*. 2001). Here, the association between the two fusion proteins was assessed spectrophotometrically. When the proteins were not associated the blue emission from Renilla luciferase was detected and when the binding regions of the fusion partners brought the reporter genes into close proximity, the green light was emitted. The wavelengths of emission in this assay (in the blue-green region of the spectrum) are in the range that is attenuated in vivo due to absorption by the primary absorbing pigment in the body, haemoglobin. Although, this demonstration of BRET (Brasier AR, Ron D. (1992) suggests that it may be possible to monitor protein–protein interaction in vivo, at the present wavelengths it will have limited in vivo utility due to attenuation of signal. The luciferase activity in the reconstituted protein was a small fraction.

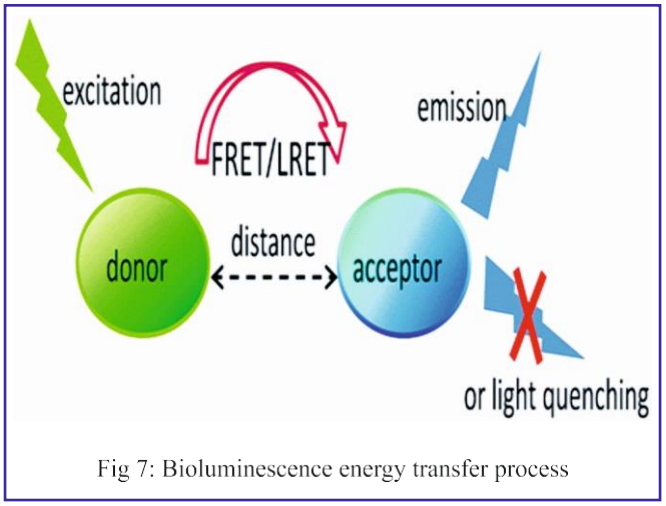

Fig 7: Bioluminescence energy transfer process

It is observed in the wild-type luciferase, likely a consequence of the amino acid residues left in the hinge region by the splicing event. The flexible polypeptide comprising the hinge region and holding the two globular regions of the enzyme together forms the critical substrate-binding region (Baldwin TO 1996, Conti *et al* 1996, Sandalove TP, Ugarova NN 1999).

Use of bioluminiscence in electricity consumption

Although biological lighting is in its infancy, it is a particularly promising solution for public authorities and future sustainable urban planning projects as it has host of advantages:

It is an *inexhaustible resource*. The bacteria used can be cultivated infinitely! Of course, they have to be changed regularly, but the resulting biomass can be recycled as renewable energy.The *light emitted is not harsh*. Also called "cold" light, bioluminescence can fight visual pollution which affects 80% of the population.

It *cuts costs*. The use of these bacteria, which only consume sugar, would make it possible to reduce energy-related costs and do away with electrical distribution networks which are expensive to produce, maintain and recycle. New lighting technologies would save 140 billion dollars worldwide .(Girotti *et al* 2008, Ren S, Frymier PD. 2003).

It *reduces mankind's ecological footprint*. As a result of the foregoing, bioluminescence would make it possible to use fewer resources, emit less CO_2 into the atmosphere and protect animal and vegetable ecosystems weakened by traditional street lights.

A simple method has been developed to support human tumour stem cell colony growth in soft agar. The technique appears suitable for culture of a variety of neoplasms of differing histopathology. Tumour stem cell colonies arising from different types of cancer have differing growth characteristics and colony morphology. This bio assay should be suitable for clinical studies of effects of anti-cancer drugs or irradiation on human tumour stem cells (Hamburger AW, Salmon SE. 1977). In a new study, researchers from London inserted the firefly gene that activatesbioluminescent light into modified cancer cells, hoping to set off a chain of events that has a proven track record at fighting the disease (De Meulenaere E et al. 2017). Application of bioluminescent bacteria in toxicity testing of chromium. The bacterial bioluminescence test (BBT) is metabolic inhibition test that uses a standardized suspension of luminescent bacteria as test organisms under standardized conditions. This test method provides a rapid, reliable and convenient means of determining the toxicity of waste material. They have performed this test for checking out the chromium (heavy metal) toxicity on one of their bioluminescent tec-hnology.

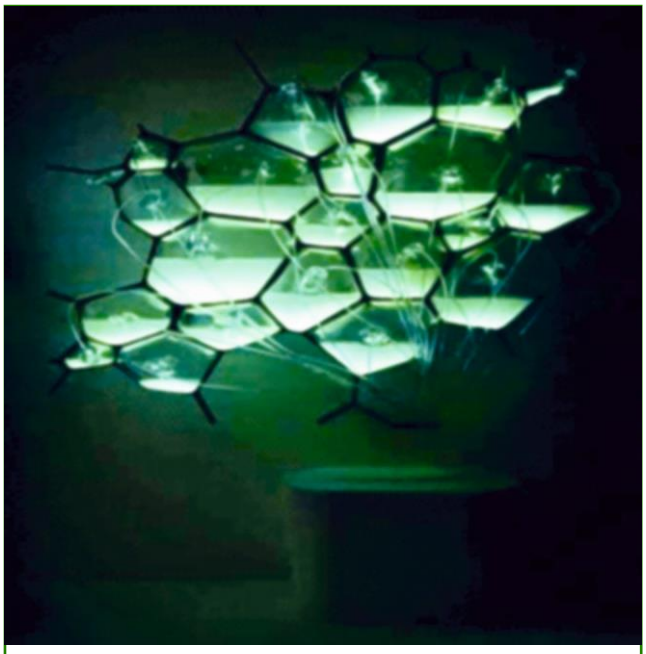

Fig 8: Philip's bioluminescent bulb

Dipteran in the Neotropics paves the way for researchers to investigate other bio-chemical functions of the molecule in these organ-ism. Ferritin with the fastest catalytic performance ever described. (De Meulen-aere E *et al* 2017).

Parchment tubeworm, found to have belonging to diptera, smell messages that they exchange, but now their secret is out, were able to tap into a new study scientists communications Among freely interacting flies using Bioluminescent technology to monitor their brain activity. They discovered that males signal their presence by placing droppings that act as a calling card for flies to find each other and even lure females to designated locations. (Hensley *et al* 2019).

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