SASTA OLIPHANT SCIENCE AWARDS

Highly Commended

Science Writing

Year 9-10

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BIOLUMINESCENCE: APPLICATIONS IN MEDICINE

INTRODUCTION TO BIOLUMINESCENCE

Bioluminescence is a result of the chemical reaction between luciferin, found in the body, and oxygen in the presence of luciferase enzyme, which causes the emission of light from within the living organism (*National Geographic, 2022*). Bioluminescent creatures are present throughout the world, with common examples including fireflies and fungi on land and plankton, jellyfish and certain species of fish, such as the midshipman fish, found in marine habitats spanning all ocean depths.

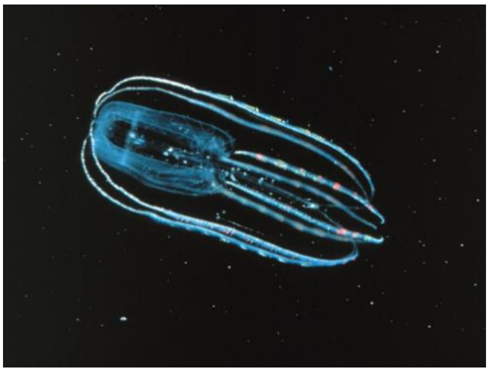

Fig 1: Bioluminescent comb jelly (National Geographic, 2022)

With the discovery of such a breathtaking phenomenon come curiosities about the potential use of bioluminescence in biomedical applications such as in the treatment of diabetes and cancer. However, bioluminescence is not restricted to these topics and has potential in medical imaging and in-vivo and in-vitro assays, which are utilised for observation of organisms in lab procedures *(Sharifian, 2018).*

WHAT IS DIABETES?

Diabetes is a disease in which blood glucose reaches extreme levels due to lack of or inadequacy of the insulin hormone that is the regulator of blood sugar levels *(NIDDK, 2018)*. Insulin, produced by the pancreas, allows for the broken-down glucose obtained from food to reach the body's cells via the bloodstream and assist in their growth and repair. There are two types of diabetes: type 1 and type 2. Type 1 diabetes, a rare condition, is considered an autoimmune response where the immune system attacks the body's own cells, destroying the islets of Langerhans within the pancreas that secrete insulin. This leads to no production of insulin and thus, in order to maintain the glucose levels, people with type 1 diabetes are required to take insulin via injections or pumps daily. On the other hand, type 2 diabetes, the most common type, occurs when the body does not create or utilise insulin well. Type 2 diabetes is affected by one's lifestyle and family history (*Mayo Clinic, 2020).*

Diabetes increases the risk associated with cardiovascular diseases and causes weight loss and fatigue.

Thus, by maintaining a healthy lifestyle, meeting dietary requirements and regularly administering insulin, the negative effects of diabetes can be reduced. Checking blood glucose levels each day is a necessity to ensure glucose levels are within target range.

CURRENT METHODS OF MONITORING GLUCOSE LEVELS

The traditional method for monitoring blood sugar levels is through a home-use blood glucose meter, also known as a finger-prick device. The process involves pricking the side of the fingertip with a sharp lancet to draw out blood, which is then applied to the test strip that indicates the blood glucose levels. For those on multiple insulin injections or pumps, the process has to be repeated several times each day and can be quite painful and invasive. Another device used to monitor glucose is continuous glucose monitoring (CGM). Despite being able to detect glucose levels in real time, it still has implications such as painful sensor insertions, skin irritation and information problems, as shown by a quantitative analysis conducted in the USA *(Miller et al. 2015).*

Fig 2: Finger-prick device (Healthline, 2018)

BIOLUMINESCENCE FOR DETECTION OF GLUCOSE

Bioluminescence can be used for the detection of biomolecules through a process called 'Bioluminescence Resonance Energy Transfer' (BRET). *Pfleger (n.d.),* a professor of biomedical innovation at the University of Western Australia, explains that BRET involves the transfer of energy from luciferase, a bioluminescent molecule, to a fluorescent protein (also known as fluorophore) when the distance between them is minimum. The energy is transferred in a non-radiative manner, as resonance energy, and causes emission of light in the fluorophore. The intensity of light emitted is relatively less in the acceptor as compared to the donor.

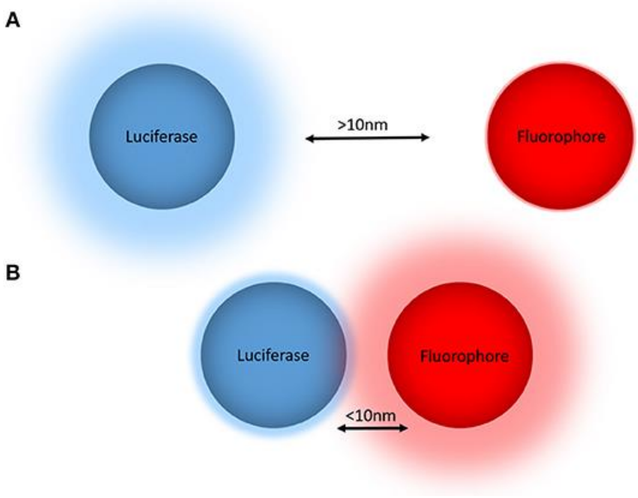

Fig 3: BRET - Interaction between luciferase and fluorophore molecule (Dale et al, 2019)

The above mechanism can be slightly altered to specifically test for glucose molecules in sweat. Glucose molecules compete with the fluorophore and act as inhibitors to the transfer of energy. Thus, the bioluminescence is restored in the luciferase and has a higher intensity, which can be studied quantitatively. *Chen et al. (2017)* found that bioluminescence intensity increases in equal proportion to increasing glucose concentration since the binding of the fluorophore to luciferase and subsequent transfer of energy is restricted, which would have otherwise led to lower intensity in the fluorescent protein.

The biosensor for detection of glucose has not yet been completed and is in the prototyping stage after research has confirmed that bioluminescence can be utilised for detection of glucose.

As discussed by *Zhen et al (2017)*, advantages of the technique, when it comes in use as a device, could include non-invasiveness since it would not require an instrument to be inserted inside the body. In addition, according to *Chen et al. (2017),* researchers from the University of Ontario, Canada, the technique is going to be non-toxic due to the inability for the luciferase enzyme to harm the human body and also cost-effective since it does not require an external energy source.

WHAT IS CANCER?

Cancer is a disease in which the cell cycle of the body becomes dysregulated (*NCI, 2021*). Malfunction and loss of control over cell division results in the formation of an abnormal cell mass called a neoplasm or tumour. However, not all neoplasms are cancerous. They are classified as benign or malignant. Benign tumours are not cancerous since they are localised and are often removable through surgery. However, malignant tumours are cancerous cell masses that invade surroundings and often travel to distant parts of the body to form new masses via metastasis.

CURRENT TREATMENTS OF CANCER

The treatment for either type of neoplasm is surgical removal. In cases where surgery is not possible, such as when the cancer cells have spread widely, radiotherapy and administration of drugs during chemotherapy are used (*NCI, n.d.).* Such therapies target all fast-dividing cells; however, some types of normal tissue naturally divide rapidly so damage to these healthy cells can induce side effects including nausea, vomiting and hair loss. Thus, current cancer treatments seem effective, yet painful, with promising new methods focusing on sidestepping the implications of previous treatments and efficiently killing cancer.

PHOTODYNAMIC THERAPY FOR CANCER

According to the *NCI (2021)*, photodynamic therapy is a recent development in cancer treatment which utilises light of appropriate wavelength in activating an anticancer drug, also known as photosensitizer agent, that makes a cell vulnerable to light. The drug is absorbed by cancer cells and, when exposed to light, induces the formation of active oxygen species that are extremely cytotoxic and destroy the tumour.

PDT has demonstrated the therapy's application across a range of cancer types:

> *"The FDA has approved photodynamic therapy to treat actinic keratosis, advanced cutaneous T-cell lymphoma, Barrett oesophagus, basal cell skin cancer, esophageal (throat) cancer, non-small cell lung cancer and squamous cell skin cancer. It is also used to relieve symptoms of some cancers including esophageal cancer when it blocks the throat and non-small cell lung cancer when it blocks the airways." (NCI, 2021)*

However, despite being minimally invasive and reducing side effects, the technique poses limitations since it is only able to attack tumours seated near the skin's surface or on the lining of internal organs. Its prominent restriction arises from the inability for visible light, which activates the photosensitizer, to be able to reach deep-seated neoplasms since the wavelength restricts the light's penetration depth into human tissues.

BIOLUMINESCENCE ACTIVATED DESTRUCTION OF CANCER (BLADe)

An extension of PDT, one that is able to resolve its issues by targeting far-reaching malignancies, utilises bioluminescence to activate the destruction of cancer and is appropriately named BLADe. *UCL* researchers *(2003)*, studied that after modifying cancer cells to express the firefly luciferase gene that activates bioluminescent light, luciferin causes the cells, situated both deeply and superficially, to glow uncontrollably. After the addition of a photosensitizer, the cells release the same toxic substances that 'force them to commit suicide'. However, *Fan et al. (2021)* state that the technique can require a high concentration of the luciferase, posing a considerable challenge to the existing system of enzyme loading, delivery, activity and retention of drugs. Thus, it may not prove to be cost-effective and can dramatically increase the price of the treatment. Despite future obstacles, London researchers from *UCL (2003)* discuss that a separate team has proven the feasibility of delivering the luciferase gene to prostate cancer cells and as a mobile light source, the applications can be extended to incorporate further types of cancers. The luciferase enzyme also has the potential of being transferred to primary tumours and being able to migrate to cancer cells that spread. Such a powerful technique may well change scientists' perceptions on cancer treatment and encourage further exploration since it has the potential to eradicate cancer from the body.

IMPACT ON SOCIETY

In general, the experiments performed and research added to the expanse of knowledge concerning monitoring of diabetes and treatment of cancer have only been possible through the collaboration and sharing of results by biotechnologists and nanoparticle researchers. Technological advances have enabled scientists to utilise and introduce vast applications of bioluminescence in biomedicine. Ultimately, the purpose for the applications is to influence and benefit society in local, national and global contexts. An example of the economic value of implementation of improved self-monitoring glucose devices is evident in the research conducted by *McQueen et al., 2018*. The researchers state that, specifically in England, investment in accurate yet cost-effective devices is an efficient strategy, both for the patients' wellbeing and quality of life but also the economy and healthcare sector. The development and introduction of further treatments of cancer, such as BLADe, can alleviate the immense stress associated with being diagnosed with cancer and can offer a new light of hope for those suffering by enhancing their quality of life.

WORD COUNT: 1571

BIBLIOGRAPHY

- Chen, L., Chen, L., Dotzert, M., Melling, C.W.J. and Zhang, J. (2017). Nanostructured biosensor using bioluminescence quenching technique for glucose detection. Journal of Nanobiotechnology, 15(1). doi:10.1186/s12951-017-0294-1. [Accessed 13 Jun. 2022]
- Dale, N. et al. (2019) "NanoBRET: The Bright Future of Proximity-Based Assays", Frontiers in Bioengineering and Biotechnology, 7. doi: 10.3389/fbioe.2019.00056. [Accessed 13 Jun. 2022]
- education.nationalgeographic.org. (2022). bioluminescence | National Geographic Society. [online] Available at: https://education.nationalgeographic.org/resource/bioluminescence. [Accessed 13 Jun. 2022]
- Fan, D., Wang, T., Hu, J., Zhou, L., Zhou, J. and Wei, S. (2021). Plasmid DNA-Based Bioluminescence-Activated System for Photodynamic Therapy in Cancer Treatment. ChemMedChem, 16(12), pp.1967–1974. doi:10.1002/cmdc.202000979. [Accessed 13 Jun. 2022]
- Healthline. (2018). Blood Glucose Monitoring: How It Works. [online] Available at: https://www.healthline.com/health/blood-glucose-monitoring#risks. [Accessed 13 Jun. 2022]
- Mayo Clinic. (2020). Diabetes - Symptoms and causes. [online] Available at: https://www.mayoclinic.org/diseases-conditions/diabetes/symptoms-causes/syc-20371444#:~:text=Diabetes%20dramatically%20increases%20the%20risk. [Accessed 13 Jun. 2022]
- McQueen, R.B., Breton, M.D., Craig, J., Holmes, H., Whittington, M.D., Ott, M.A. and Campbell, J.D. (2018). Economic Value of Improved Accuracy for Self-Monitoring of Blood Glucose Devices for Type 1 and Type 2 Diabetes in England. Journal of Diabetes Science and Technology, 12(5), pp.992–1001. doi:10.1177/1932296818769098. [Accessed 13 Jun. 2022]
- Miller, K.M., Foster, N.C., Beck, R.W., Bergenstal, R.M., DuBose, S.N., DiMeglio, L.A., Maahs, D.M. and Tamborlane, W.V. (2015). Current State of Type 1 Diabetes Treatment in the U.S.: Updated Data From the T1D Exchange Clinic Registry. Diabetes Care, [online] 38(6), pp.971–978. doi:10.2337/dc15-0078. [Accessed 13 Jun. 2022]
- National Cancer Institute (2021). Photodynamic Therapy for Cancer - National Cancer Institute. [online] Available at: https://www.cancer.gov/about-cancer/treatment/types/photodynamic-therapy. [Accessed 13 Jun. 2022]
- National Cancer Institute (2021). What Is Cancer? [online] National Cancer Institute. Available at: https://www.cancer.gov/about-cancer/understanding/what-is-cancer. [Accessed 13 Jun. 2022]
- National Cancer Institute (n.d.). Types of Cancer Treatment. [online] National Cancer Institute. Available at: https://www.cancer.gov/about-cancer/treatment/types. [Accessed 13 Jun. 2022]
- National Institute of Diabetes and Digestive and Kidney Diseases (2018). What is Diabetes? [online] National Institute of Diabetes and Digestive and Kidney Diseases. Available at: https://www.niddk.nih.gov/health-information/diabetes/overview/what-is-diabetes. [Accessed 13 Jun. 2022]
- ocean.si.edu. (2018). Bioluminescence | Smithsonian Ocean. [online] Available at: https://ocean.si.edu/ocean-life/fish/bioluminescence#:~:text=Protection [Accessed 13 Jun. 2022].
- Pfleger. (n.d.). Keynote Presentation: Profiling of Receptor Complexes using BRET. [online] Available at: https://www.labroots.com/ms/webinar/keynote-presentation-profiling-receptor-complexes-using-bret [Accessed 13 Jun. 2022].

- Sharifian, S., Homaei, A., Hemmati, R., B. Luwor, R. and Khajeh, K. (2018). The emerging use of bioluminescence in medical research. Biomedicine & Pharmacotherapy, [online] 101, pp.74–86. doi:10.1016/j.biopha.2018.02.065. [Accessed 13 Jun. 2022]
- UCL (2003). Firefly light helps destroy cancer cells. [online] UCL News. Available at: https://www.ucl.ac.uk/news/2003/apr/firefly-light-helps-destroy-cancer-cells#:~:text=In%20a%20new%20study%2C%20UCL [Accessed 13 Jun. 2022].
- Zhan, D., Chen, L., Tse, W.H., Chen, L. and Zhang, J. (2017). Bioluminescence Resonance Energy Transfer (BRET) Based Nanostructured Biosensor for Tear Glucose Detection. International Conference of Theoretical and Applied Nanoscience and Nanotechnology. [online] doi:10.11159/tann17.122. [Accessed 13 Jun. 2022]