SASTA OLIPHANT SCIENCE AWARDS

SOUTH AUSTRALIAN SCIENCE TEACHERS ASSOCIATION

Prize Winner

Science Writing

Year 7-8

Amullya Madaan

Glenunga International High School

Amullya Madaan | Glenunga International High School | Year 8 | Science Writing

PLAYING WITH LIGHT: NEAR-INFRARED PHOTOIMMUNOTHERAPY

INTRODUCTION

Light is one of the most familiar physical realities, the most fundamental element of our lives, yet a fascinating subject for physicists and biologists alike. It is a field that has much yet to explore, despite the obvious thought of omniscience. Over the course of humanity, cancer has posed as a pernicious disease, spanning from the Egyptians in 1600 B.C claiming it is incurable (*ACS, 2018*), to current research scientists trying to find solutions to the life-threatening condition. Over recent years, near-infrared photoimmunotherapy has become a fascination, with the possibility of it completely eradicating cancer from the patient's body. Along with curiosities come questions posed - *what is cancer, why are current therapies detrimental to health and how may NIR-PIT be revolutionary to the field of oncology?*

WHAT IS CANCER?

Cancer is a disease in which some of the body's cell processes become dysregulated *(NIH, 2021).* Such abnormal cells multiply uncontrollably and form tumours; growing masses of tissue which are classified as benign and malignant. Benign tumours are not considered cancer as they have not spread and grown locally, thus able to be cured through surgery, whereas malignant tumours have the ability to spread or have already through the process of metastasis, and are considered cancerous. These can form secondary tumours in different parts of the body by invading nearby tissues and travelling to distant places.

Fig. 1.1: Highly mutated breast cancer cells (RACGP, 2020)

According to Dagogo-Jack and Shaw (2017), cancer is a collection of related diseases, a term referred to as heterogeneity. Each type in itself is constituted of a lot of subtypes and further, histology. Within a single tumour in a patient, no two cancer cells are the same, in both respect to time and space, referred to as intra-tumour heterogeneity (ITH). Spatial ITH is the inability of a single biopsy from one view of a tumour to be representative of the whole tumour, due to diversity in all sides of the solid, three-dimensional tumour. Time ITH refers to the evolution of cancer over spans of time, thus being a moving target.

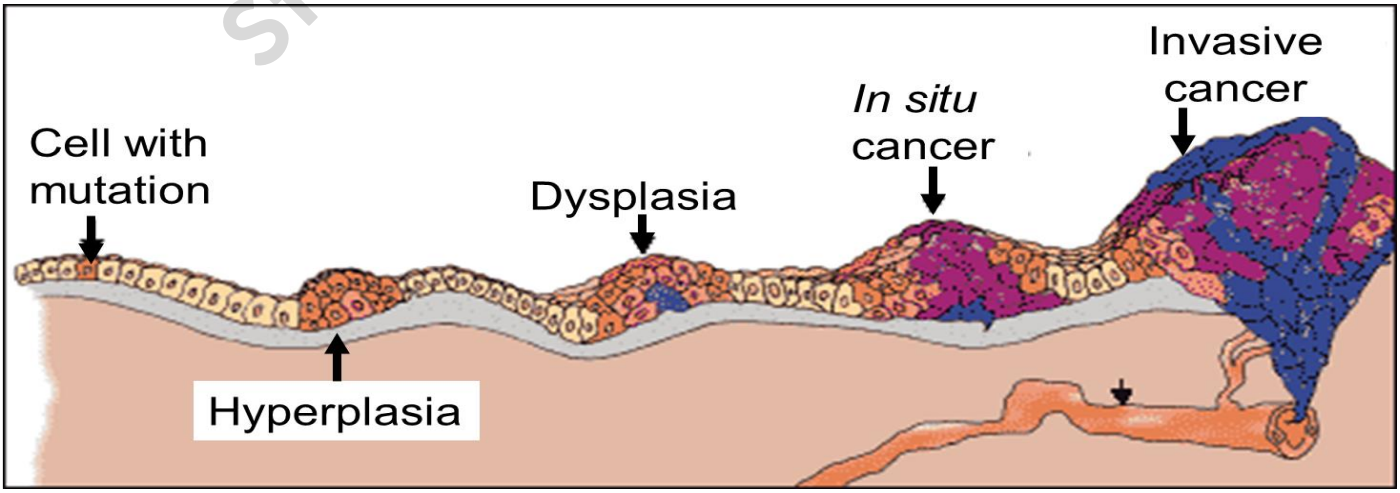

Fig. 1.2: Cancer Evolution stages (ND Health Facts, 2017)

CURRENT METHODS OF TREATMENT

The three major cancer therapies currently available are surgery, radiotherapy and chemotherapy.

Surgery for treating cancer targets the removal of cancer cells along a clear margin of tumour and normal cells. This treatment is suitable for patients with primary, defined tumours that are more locally spread and also for post-therapy cancer prevention to remove tissues and organs before remaining cancerous tissues relapse. Skandarajah, 2014, states that cancer surgery has evolved significantly to play a role as personalised medicine and one that is patient, cancer type and tumour specific.

Radiotherapy utilises the quantitative differences of normal tissues and tumours through different times of cell division as well as susceptibility to ionising radiation. Barton, 2014, points out that when exposed to radiation at high doses, chemicals within cancerous cells are modified, leading to slower growth and damaged DNA. Thus, cancer cells stop dividing or die as their DNA is damaged beyond repair. Radiation targets specific areas of the body, leading to less side effects. Scheduling and repeated cycles of radiation, sometimes days or weeks, allow for tumours to shrink.

Chemotherapy targets the frequency and phase differences between cell division cycles. Cancer cells, as mentioned previously, divide and form new cells quicker than healthy cells. However, some types of normal tissue naturally divide rapidly, thus leading to their damage when using chemo drugs, which can be delivered through veins, medication ports or taken orally. Although it leads to side-effects, such as fatigue, hair loss or infection, normal cells are able to recover from the effects over time. But, as cancer cells are dysregulated, they usually do not recover and are killed. While radiotherapy cures high volume local cancer, chemotherapy addresses micro metastases as well, which are secondary cancer cells that have been shed from the original tumour to spread locally and in distant parts of the body.

NEAR-INFRARED PHOTOIMMUNOTHERAPY

As the therapies discussed above affect cancer cells as well as healthy cells, they can naturally trigger side effects. These implications can be sidestepped when introducing photoimmunotherapy, a new form of cancer therapy involving near-infrared light that is highly specific to cancer cells with no damage to nearby normal tissue. It is currently in the stage of clinical trials in patients with incurable tumours (Kobayashi, 2020) and is considered a development from the monoclonal antibody (mAb) treatment.

NCI researchers and staff (2016) explained that NIR-PIT uses an antibody to which a photo-absorbing chemical is attached. The antibody-photoabsorber conjugate is injected into the cancer patient to travel through the bloodstream, reach the site of the tumour and leak out of permeable vessels. As the antibody recognises the proteins on the exterior of cancer cells, it binds to the special receptors on their surface.

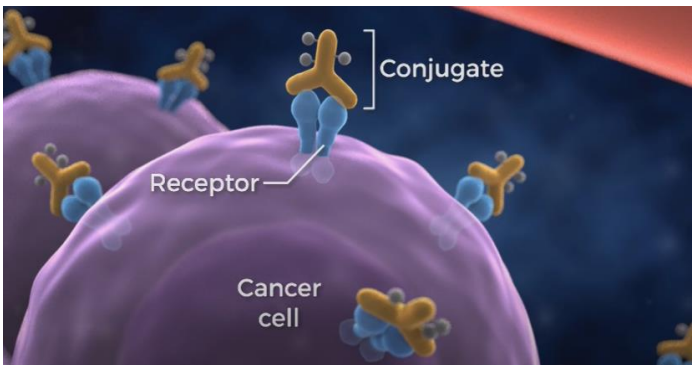

Fig. 2.1: Visual Representation of NIR-PIT (NIH, 2016)

Once the conjugate is bound to cancer cells, the photo receptive chemical is specifically activated by near-infrared light. Upon absorption of this light, a photo-induced reaction occurs and the chemical is activated, causing immediate damage to the cell membrane. Water that is outside of the cancer cell rushes in, causing it to swell. Nearby cells without the special receptors, i.e. normal cells, are not affected. Increased pressure within the swollen cell causes membrane micro-perforations, quickly leading to the cell rupture and releasing intracellular contents. The cell becomes smaller in shape, a process known as necrosis. After treatment, the cell necrosis causes the tumour to shrink and die, creating spaces between the cells, which are replaced with normal cells.

As stated by Kobayashi and her team (2020), the antibody, called IR700, is water-soluble with no phototoxic or cytotoxic properties, thus being safe for excretion through urine and responds to near-infrared light, which is harmless to the body. In addition, as light would not be able to reach deeply-seated organs, it would only be a potential application for treating tumours that lie in or just beneath the skin. Instead, surgically implanting devices that can illuminate the tumours could provide access to localised cancers.

CLINICAL TRIALS/EXPERIMENTS

Through clinical trials and experiments performed by researchers at the National Cancer Institute (2011), the chosen antibody was settled upon due to its photosensitive quality as well as its fluorescent property to allow the scientists to view progress.

They worked with mice that had been implanted with tumours, where the results were as expected, as shown in figure 2.2, with even a single dose of IR light making a significant difference on rapidity of cancer cell death. In addition, infrared light has the extra benefit of being able to penetrate through more tissue layers than visible light or other wavelengths.

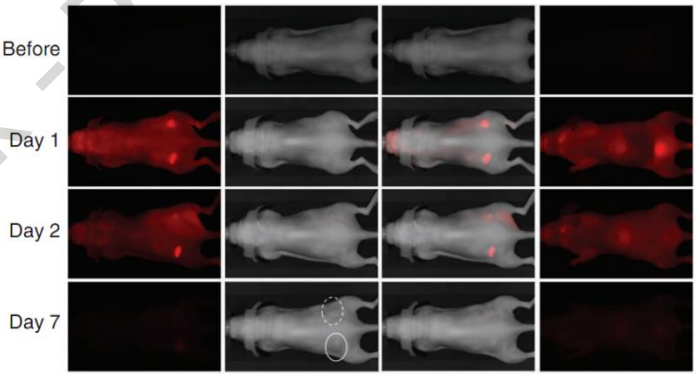

Fig. 2.2: Effects of NIR-PIT on tumour implanted in mice (NCI, 2011)

NIR-PIT has demonstrated its expansive application across a wide range of cancer types:

> *"It has been shown efficacious against bladder, prostate, gastric, primary lung and breast cancers, as well as epidermoid, hepatocellular and head and neck cancers, glioblastoma, melanoma, mesothelioma and B-cell Lymphoma. Far from treating only primary tumours, NIR-PIT has also shown efficacy against metastatic lung cancers, peritoneally disseminated gastric and ovarian cancers and pleural disseminated non-small cell and small cell lung cancer."* (Hisataka Kobayashi, 2020)

HOST IMMUNITY ACTIVATION

NIR-PIT activates the immune system, increasing anti-cancer host immunity. Cancer cells treated with the approach release death signals, which can further activate and enhance the development of nearby immature dendritic cells. K.Wculek and J.Cueto (2019), identified that DCs are crucial in the formation of anti-tumour responses because they overtake cancer-specific antigens produced by ruptured tumour cells. T cells, which are a type of leucocyte, are then stimulated to become cancer-specific CD8+T cells that attack more cancer cells, resulting in the ultimate anti-immune reaction.

The response begins in the treated tumour site but gradually spreads to additional cancer sites when cancer-specific immune cells migrate. Thus, the immunological effects of the treatment, as well as its ability to systematically kill distant metastatic areas by manipulation of DC activity, are seen as another key advantage of the treatment over others.

New research by Verma and E.Foster (2016) suggests that the effects of chemotherapy compromise its abilities and leave patients vulnerable to infections. Therefore, NIR-PIT is considerably better in preventing reduced immunity resulting from chemotherapy.

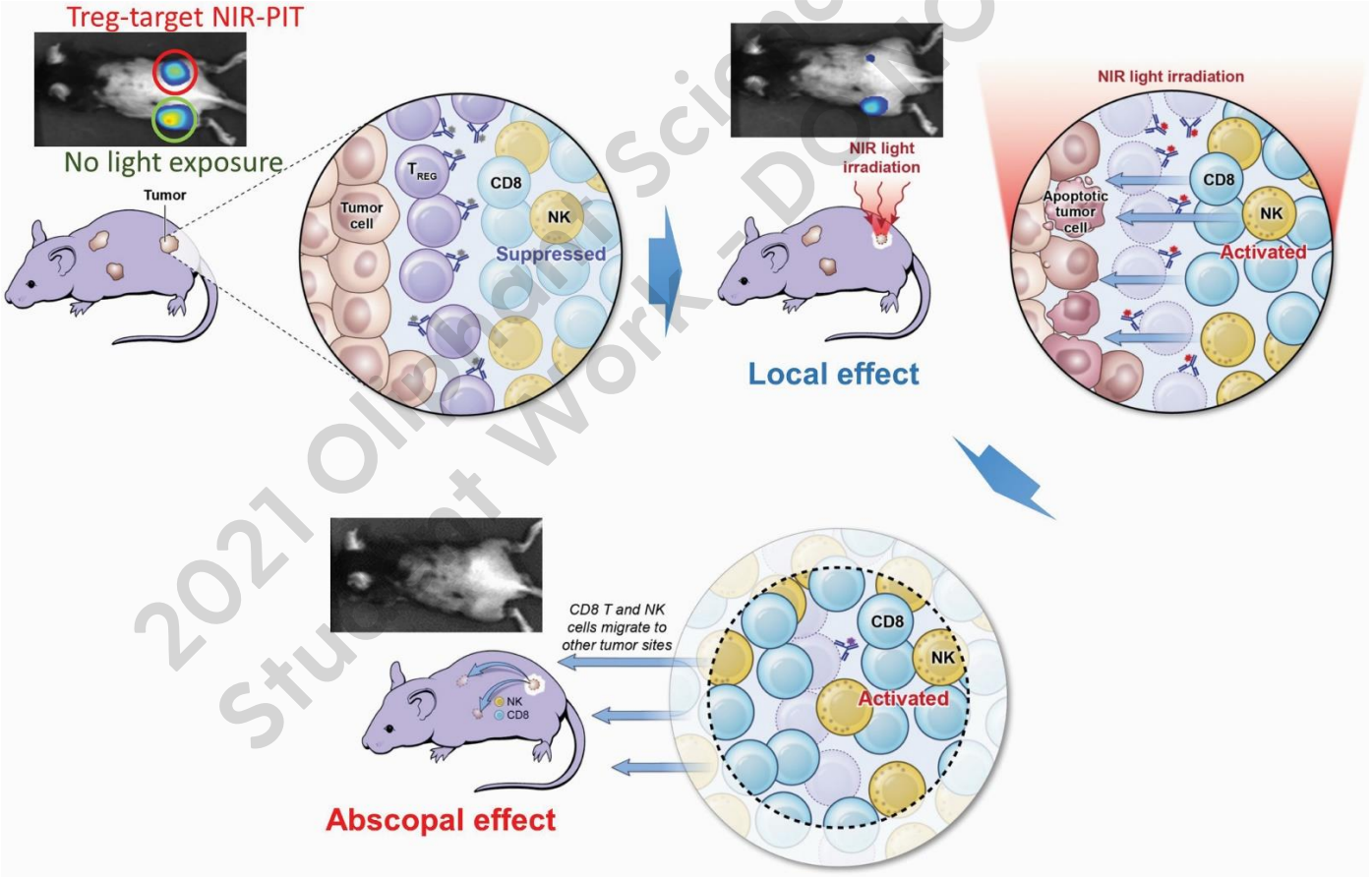

Fig. 2.3: Host Immunity Activation Response by CD8T cells (Kobayashi, 2020)

CONCLUSION

In conclusion, the proposed design strategy for the near-infrared photoimmunotherapy (NIR-PIT) works on the principle of direct cancer killing through immunogenic cell death (ICD) by selectively destroying cancer cells along with activating a robust host immune response. Currently, the technique is in the phase 3 clinical trials and may soon be available to patients. As Kobayashi (2020) states: NIR-PIT will be particularly targeted towards patients with localised cancers and help such patients avoid detrimental side-effects associated with current therapies. He also provides suggestions on enhancing its effects by combining cancer-targeted and immune-suppressor-targeted NIR-PIT. With its extensive range of applications and opportunities for further advancement, NIR-PIT has the potential to become a valuable cancer therapy.

WORD COUNT: 1468

BIBLIOGRAPHY

What Is Cancer? *(2021). Available at: https://www.cancer.gov/about-cancer/understanding/what-is-cancer (Accessed: 30 June 2021).*

Dagogo-Jack, I. and Shaw, A. (2017) "Tumour heterogeneity and resistance to cancer therapies", Nature Reviews Clinical Oncology*, 15(2), pp. 81-94. doi: 10.1038/nrclinonc.2017.166.*

Early History of Cancer | American Cancer Society *(2021). Available at: https://www.cancer.org/cancer/cancer-basics/history-of-cancer/what-is-cancer.html (Accessed: 30 June 2021).*

Kobayashi, H. et al. (2020) "Near-infrared photoimmunotherapy of cancer: a new approach that kills cancer cells and enhances anti-cancer host immunity", International Immunology*, 33(1), pp. 7-15. doi: 10.1093/intimm/dxaa037.*

"Light-Activated Therapy Kills Cancer Cells" (2015), (9), pp. 897.1-897. doi: 10.1158/2159-8290.cd-nb2015-110.

Boyle, R. (2019) Using Light to Target and Kill Cancer Cells, Without Chemotherapy's Side Effects, Popular Science*. Available at: https://www.popsci.com/science/article/2011-11/light-therapy-targets-and-kills-cancer-cells-without-chemotherapys-side-effects/ (Accessed: 28 June 2021).*

Targeted Light Therapy Destroys Cancer Cells *(2015). Available at: https://www.nih.gov/news-events/nih-research-matters/targeted-light-therapy-destroys-cancer-cells (Accessed: 28 June 2021).*

surgery, P. (2021) Principles of cancer surgery - Oncology for Medical Students, Wiki.cancer.org.au*. Available at: https://wiki.cancer.org.au/oncologyformedicalstudents/Principles_of_cancer_surgery (Accessed: 28 June 2021).*

Radiation vs. Chemo: Uses, Benefits, Side Effects, More *(2021). Available at: https://www.healthline.com/health/radiation-vs-chemo (Accessed: 28 June 2021).*

Radiation Therapy for Cancer *(2021). Available at: https://www.cancer.gov/about-cancer/treatment/types/radiation-therapy#:~:text=During%20Radiation%20Therapy-,How%20Radiation%20Therapy%20Works%20Against%20Cancer, and%20removed%20by%20the%20body. (Accessed: 28 June 2021).*

How Radiation Therapy Is Used to Treat Cancer *(2021). Available at: https://www.cancer.org/treatment/treatments-and-side-effects/treatment-types/radiation/basics.html (Accessed: 28 June 2021).*

After chemotherapy, immune system recovery may be slower than believed *(2016). Available at: https://www.fredhutch.org/en/news/center-news/2016/01/chemotherapy-immune-system.html (Accessed: 28 June 2021).*

Wculek, S. et al. (2019) "Dendritic cells in cancer immunology and immunotherapy", Nature Reviews Immunology*, 20(1), pp. 7-24. doi: 10.1038/s41577-019-0210-z.*

T cell | Definition, Function, & Facts *(2021). Available at: https://www.britannica.com/science/T-cell (Accessed: 28 June 2021).*

Oncology (Cancer) - Health Facts *(2021). Available at: http://www.ndhealthfacts.org/wiki/Oncology_%28Cancer%29 (Accessed: 28 June 2021).*