The 3rd International Conference on Materials Chemistry and Environmental Engineering
DOI: 10.54254/2755-2721/3/20230341

Co-delivery of Paclitaxel and Adriamycin on Nanoparticle

Chuanming Jiang[1,*], Qiong Wu[2]

[1]Chemical and Biomolecular School, USYD, Sydney, 2006, Australia
[2]School of Beijing New Talent Academy, Beijing,100000, China

*chuanmingjiang83@gmail.com
All the authors contributed equally to this work and should be considered co-first authors.

Abstract. Based on the threat of cancer to human life and the surge in breast cancer prevalence and mortality in recent years, existing drugs and treatments remain harmful and have side effects. A nano-drug delivery platform is proposed to achieve precise drug delivery in time and space aspects. Two anti-cancer drugs were encapsulated in a nanoplatform and the synergistic effect of these two drugs was utilized to reduce the toxicity of a single drug in conventional chemotherapy and to improve the accuracy of drug delivery. Also, in-vitro and in-vivo experiments of this nanoplatform were designed, and data were collected and analysed to demonstrate the feasibility and future development prospects.

Keywords: PLGA, Paclitaxel, Adriamycin.

1. Introduction

1.1. Cancer

The World Health Organization's International Agency for Research on Cancer (IARC) released the latest global cancer burden data for 2020. They estimated the latest incidence and mortality rates of 36 cancer types in 185 countries worldwide and obtained the following data, as shown in figure 1. Ten of the worst cancers with today's worldwide incidence rates are: breast cancer 2.26 million, lung cancer 2.2 million, colorectal cancer 1.93 million, prostate cancer 1.41 million, stomach cancer 1.09 million, liver cancer 0.91 million, cervical cancer 0.6 million, esophageal cancer 0.6 million, thyroid cancer 0.59 million, and bladder cancer 0.57 million, and these ten cancers account for 63% of all new cancers [1]. In 2020, there will be more than 2.26 million new cases of breast cancer and nearly 685,000 deaths from breast cancer worldwide [2]. Breast cancer has replaced lung cancer as the world's number one cancer. The problem of cancer cannot be underestimated, and it becomes a serious threat to human life. It is estimated that the global cancer burden will rise to 10 million deaths in 2020 [3].

However, with the advancement of technology, the treatment methods of cancer have also advanced. Currently, cancer treatment methods mainly use a combination of surgery, chemotherapy, and radiation therapy. It can also be combined with targeted therapy and biological therapy. Based on the impact of cancer on human beings, this article focuses on breast cancer, which has the most affected population, and its pharmacological treatment.

DOI: 10.54254/2755-2721/3/20230341

The prevalence of breast cancer in women has surpassed lung cancer as the most commonly diagnosed cancer worldwide. An estimated 2.3 million new cases suggest that one in eight cancers diagnosed in 2020 will be breast cancer. The disease is and will be the fifth leading cause of cancer deaths worldwide, with 685,000 deaths in 2020. Among women, one in four cancer cases and one in six cancer deaths is breast cancer, and the disease ranks first in most countries worldwide in terms of incidence and mortality [3].

Breast cancer is a malignant disease caused by mutations in cellular genes and is characterized mainly by unlimited cell proliferation and spread. These tumour cells not only have an immune escape function to evade the body's immune system, but also induce angiogenesis to supply them with nutrients and enrich the distribution of blood vessels in the tumour tissue part. These characteristics fundamentally make breast cancer treatment difficult and prolonged. Most of the symptoms of early-stage breast cancer are not obvious, while the advanced stage may be life-threatening due to cancer metastasis and multi-organ lesions.

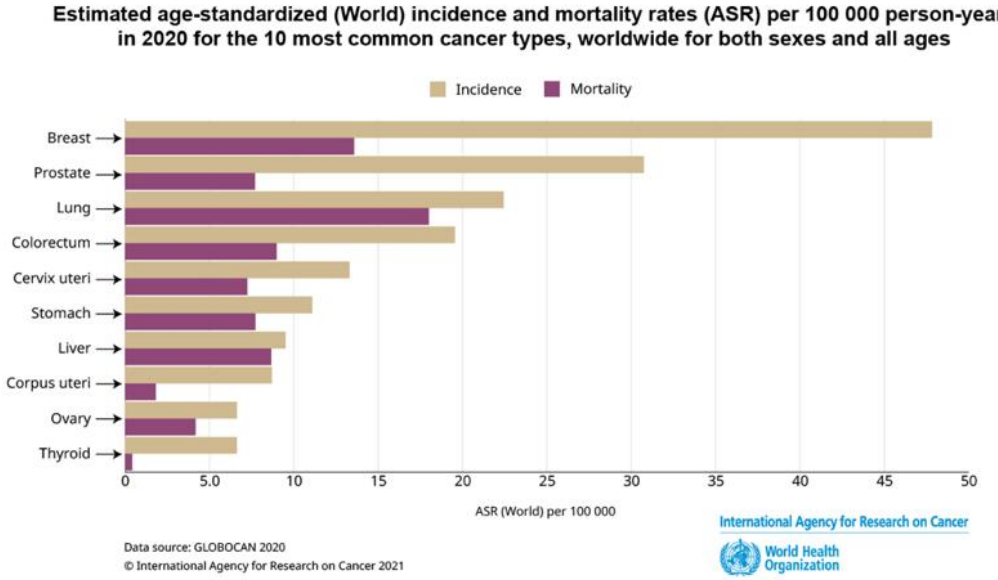

Figure 1. Estimated age-standardized (World)incidence and mortality rates (ASR) per 100 000 person-years in 2020 for the 10 most common cancer types, worldwide for both sexes and all ages [2, 4].

1.2. Limitation of traditional chemotherapy

There are two main treatments for breast cancer: endocrine therapy and chemotherapy. Endocrine therapy works by removing or blocking the action of hormones to stop the growth of cancer cells. Chemotherapy generally uses chemical drugs to alter or inhibit the growth of cancer cells as well as the metabolic process to fundamentally interfere with and inhibit the reproduction of cancer cells.

Since conventional chemotherapy uses chemicals to kill cells that are constantly dividing, it is possible to destroy cancer cells while accidentally injuring normal cell proliferation, such as hair, bone marrow, and immune cells. This leads to side effects such as hair loss, loss of appetite, diarrhea, and decreased immunity. It may also lead to multiple organ damage and allergic reactions.

1.3. Aims

Research on methods and drugs for cancer treatment is urgently needed. It is desired to improve the dose of commonly used chemotherapeutic drugs (e.g., paclitaxel, Adriamycin) using nano-delivery platforms to improve the pharmacokinetics of drug delivery. This achieves controlled drug delivery in a specific time and space, aiming to achieve drug release in the focal area, control the release rate of

DOI: 10.54254/2755-2721/3/20230341

chemotherapeutic drugs, increase, and stabilize blood concentrations, and reduce their side effects on normal tissues. It is hoped that the combination of multiple drugs will help to improve the effectiveness of cancer treatment and achieve synergistic drug therapy.

1.4. Nanoparticle and chemotherapy mechanism

For the design of the nanoparticles, 3 main materials were used, PLGA shell, encapsulated anti-cancer drug: paclitaxel and Adriamycin. The drug (paclitaxel and Adriamycin) is wrapped in a PLGA shell, and folic acid is added to the outer shell to help the drug bind to cancer cells. The ratio of lactic acid and hydroxy-acetic acid in PLGA is then used to control the decomposition time to achieve precise drug delivery.

Polyester PLGA is a copolymer of poly lactic acid (PLA) and polyglycolic acid (PGA). It is a biodegradable functional polymeric organic compound with good biocompatibility, film-forming and low toxicity properties, so it is widely used in medicine, medical engineering materials and modern industry [5]. The degradation products of PLGA are lactic acid and hydroxy-acetic acid, which are by-products of human metabolic pathway and have little toxic side effects. Therefore, it is widely used in pharmaceutical and biological materials [6].

Paclitaxel is a natural anticancer drug extracted from the precious plant Sequoia. It can make micro-tubulin and the micro-tubulin dimer that constitutes microtubules lose dynamic balance, induce and promote the polymerization and assembly of micro-tubulin, prevent depolymerization, and thus stabilize microtubules. Paclitaxel inhibits the distribution of cytogenetic material and chromosomes cannot migrate to both sides of the cell and complete mitosis, triggering apoptosis of cancer cells, thus effectively stopping the proliferation of cancer cells, and playing an anti-cancer role [7].

Adriamycin, an antitumor antibiotic, is a cycle non-specific drug that kills tumour cells in all growth cycles. Its planar structure is inserted into the DNA strand, disrupting DNA replication and synthesis, and affecting the transcription and translation functions of DNA, thus achieving the effect of inhibiting cell division. Adriamycin acts as a broad-spectrum antitumor drug against a wide range of tumours and is mostly used in combination with other anticancer drugs. However, it exerts a wide range of biochemical effects on the organism and is highly cytotoxic.

Paclitaxel and Adriamycin are now widely used in clinical treatment after chemotherapy. Both drugs are injected into the patient by intravenous drip for consolidation of chemotherapy and to achieve a direct adjuvant effect of tumour suppression.

1.5. Advantages and future uses

This nano drug delivery platform not only inherits the advantages of traditional chemotherapy by reasonably increasing the drug loading to maintain the blood concentration of the drug in the body to achieve a good effect of killing tumour or cancer cells, but also breaks through the limitations of traditional chemotherapy by using drug targeting to reduce the greater adverse side effects associated with traditional chemotherapy. The emergence of such nanoparticles suggests that polymeric nanomaterials can also be used to achieve drug delivery, giving a new path to explore for future cancer tumour treatment.

2. Methods and results

2.1. In vitro cellular

As mentioned above, PLGA is a synthetic copolymer composed of glycolic acid and lactic acid monomers. From previous work, it appears that the greater the proportion of lactic acid in PLGA copolymers, the less hydrophilic, less water absorption, and slower degradation. This shows that the different composition ratios of polymeric PLGAs have a degree of influence on the in vitro drug release rate due to biodegradation. The graph below shows the variation of drug release rate with time for different composition ratios of PLGA [7].

DOI: 10.54254/2755-2721/3/20230341

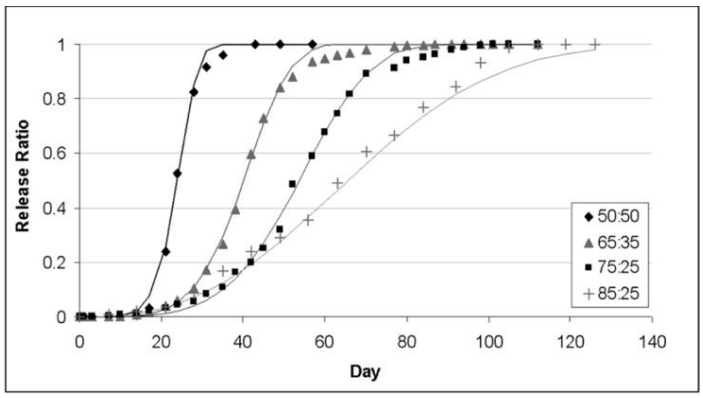

Figure 2. Release profiles for 50:50, 65:35, 75:25 and 85:15 PLGA-Glycolic acid. The 65:35 PLGA implies that 65% of the copolymer is lactic acid and 35% is glycolic acid.

In Figure 2, based on the images a biphasic release profile can be observed which shows the period for PLGA polymers with different lactic to glycolic acid ratios to undergo complete drug release. During the first 15 days, there is zero release period for any percentage of PLGA. In the following period, PLGA copolymers with higher lactic acid content have lower hydrophilicity and a slower degradation rate [8]. In summary, PLGA copolymers with a molar ratio of 50:50 can not only maintain a relatively stable drug release rate but also achieve a sustained drug release in a short time cycle.

Stability and In vitro drug release profiles of Adriamycin and hydrophobic paclitaxel [9].

The change in the size of nanoparticles was measured by redissolving them at three different pH values (pH 4.4, 5.3, and 7.4) for 3 days, which tested the stability of nanoparticles for long-term storage, transport, and processing.

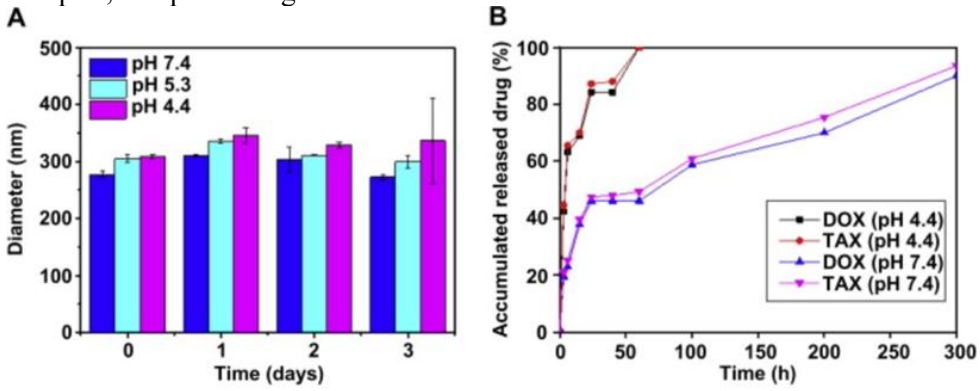

Figure 3. A: Release profiles for 50:50, 65:35, 75:25 and 85:15 PLGA-Glycolic acid.
B: The 65:35 PLGA implies that 65% of the copolymer is lactic acid and 35% is glycolic acid.

As known from figure 3A [9], the average diameter of nanoparticles did not change significantly in different pH environments. Compared to the neutral environment in the dark blue region (pH = 7.4) in figure A, the purple region (pH=4.4, acidic environment) has a larger diameter of nanoparticles. It can be concluded that the nanoparticles are more stable in a neutral environment for long-term storage, transport, and processing.

Figure 3B [9] shows the in vitro release profiles of Adriamycin/doxorubicin (DOX) and paclitaxel (TAX) at pH 7.4 and 4.4. It is clear from the images that the pH of the environment has a large effect on the in vitro release rate of these two anticancer drugs. In the acidic environment (PH=4.4), the release rate of both drugs was larger, with nearly all total drug content released within the first 50 hours. In contrast, the release rate of Adriamycin and paclitaxel was slow and sustained in a neutral environment (PH=7.4), with approximately 90% of the drug released cumulatively within 300 hours.

DOI: 10.54254/2755-2721/3/20230341

2.2. Cytotoxicity test

PLGA copolymers are hydrolysable, where the polymer backbone with ester bonds is randomly hydrolysed. Shearing of the long polymer chains leads to a decrease in molecular weight resulting in an increase in hydrophilic properties, additional reduction in molecular weight leads to the formation of water-soluble polymer fragments. These fragments are further degraded to produce ethanoic and lactic acids, and through the body via common metabolic pathways it can be eliminated [8].

Polymeric nanodrugs have the advantages of proper structural design and synthetic versatility, as well as more fitting size distribution, higher stability, good biocompatibility, more controllable drug liberation profile, amendable pharmacokinetics and bodily biodistribution, which provide greater advantages compared to traditional therapeutic agents. The use of conventional anticancer drugs is limited because of rapid degradation, adverse reactions in normal organs after administration, and severe systemic toxicity.

These two articles were cited to show that the synergistic effect was confirmed by two chemotherapeutic agents in the same vector. Like the one shown in Figure 4, the coadministration of doxorubicin as well as Taxol has a good effect in reducing cell viability. NPs of free and simplex - loaded drugs induced similar cytotoxicity, indicating the validity of the trigger mechanism that releases the drug from the endosome/lysosome into the cytoplasm.

The experimental cell survival data revealed that the doxorubicin / Taxol concentration ratio of 2:1 particle had better cell survival and doxorubicin / Taxol 2:1 concentration alone had a better performance. Among them, when treating three different types of tumour cells, NP with a doxorubicin / Taxol concentration ratio of 2:1 resulted in the strongest anti-arsenoma activity on the cells. Based on the above data the treatment of cancer cells using doxorubicin and Taxol and a 2:1 ratio is likely to produce the best synergistic effect and accelerate tumour cell death [9].

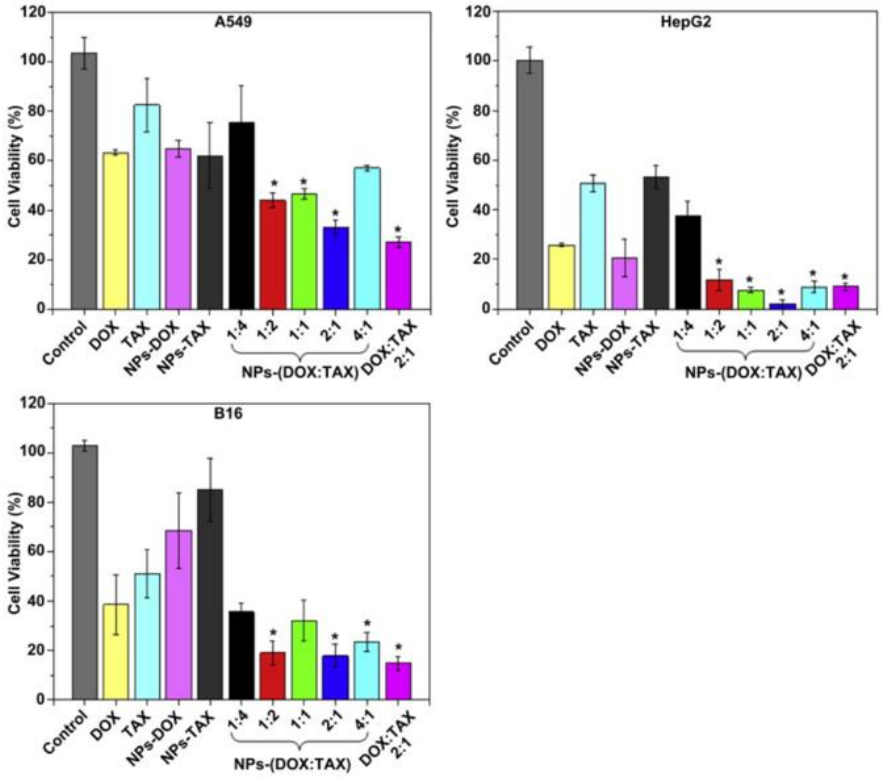

Figure 4. Cell viability measurements. Cell viability of A549, HIepG2 and B16 cells after exposure to free DOX (doxorubicin), TAX (paclitaxel), DOX, DOX & TAX, NPS-DOX, NPS-TAX and NPS-DOX-TAX at different ratios at 37°C. The total drug content was maintained at 0.25 μmol/ml for all tests. Know < 0.05 compared to DOX group [9].

DOI: 10.54254/2755-2721/3/20230341

2.3. In vivo test

In order to conduct the experiment, A549 human lung tumour nude mice were injected with tumours to examine the in vivo antitumor activity and systemic toxicity of dual drug-loaded nanoparticles. Every four days, mice were given intravenous injections of PBS and various medication formulations, as well as every two days, tumour volume and body weight measurements were made. In contrast to the quick tumour growth in the PBS-treated group, all medication formulations displayed various degrees of tumour growth suppression, as shown in Figure.5A [10].

The following summaries were obtained. (1) Utilizing doxorubicin and PTX together was more successful than using either medicine alone. (2) For the same medications, loaded drugs outperformed free drugs in terms of anticancer effects, and comparable outcomes were seen with drug combinations. Almost all tumour development was inhibited during the course of treatment, which was among the strongest anti-tumour activity ever seen, and there was no discernible tumour recurrence. The best group's tumour volume was only 9.0 percentage points of the control group at the end of the experiment, which was 3,2, 6.3, and 2.4 times less than the tumour volumes treated with free doxorubicin, free PTX, and free doxorubicin + PTX, respectively. This superior antitumour effect could be attributed to the improvement of nanoparticle stability during blood circulation, the proper simultaneous administration of both drugs at the tumour site, effective cellular uptake in tumour tissue, and the synergistic effect of joint application of Adriamycin and paclitaxel PEG-peptide for non-small cell lung cancer and PTX for tumour suppression. Posttreatment resected A549 tumours were dissected and photographed. The results were consistent (Figure 6A) [10].

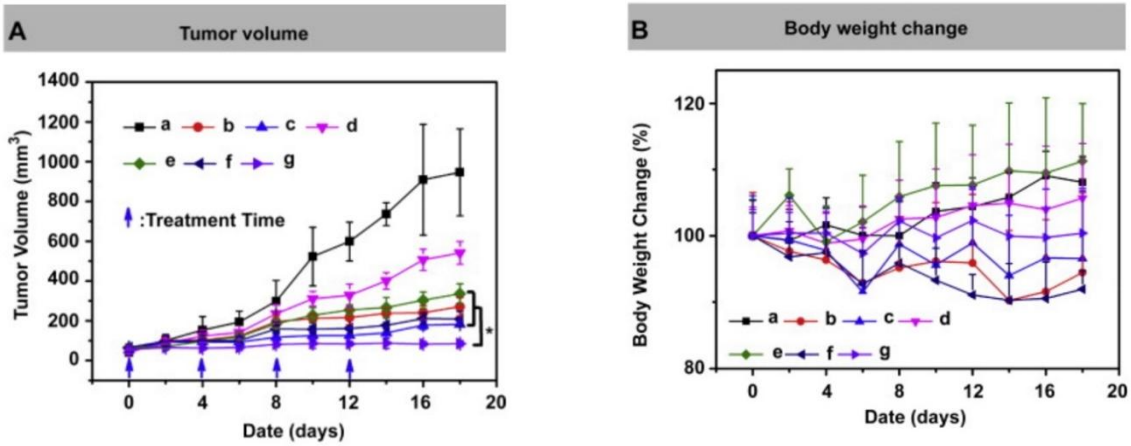

Figure 5. Changes in tumour volume and body weight following cancer therapy with different drug formulations in naked mice with human lung cancer xenograft A549. Note: PBS (a), DOX (b), DOX-NPs (c), PTX (d), PTX-NP (e), DOX + PTX (f) and Co-NPS (g). Data are shown as mean Shi SD (n=6), large < 0.01 [10].

DOI: 10.54254/2755-2721/3/20230341

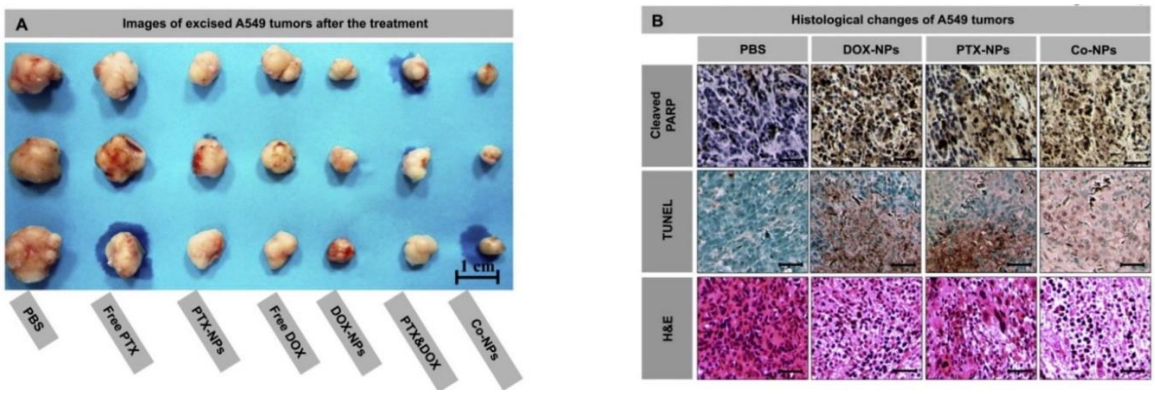

Figure 6. Images of excised A549 tumours and histological changes in different drug delivery strategies in the treatment of human lung cancer A549 implanted in a ringless mouse model. Changes in tumour volume and body weight after anticancer treatment with different drug formulations in nude mice with A549 human lung cancer xenografts [10].

3. Conclusion

In summary, although the use of PLGA drug delivery systems in clinical practice is still hampered by safety concerns, this combined nano-delivery platform of paclitaxel and Adriamycin provides a direction for the development of new anticancer drugs. By promoting the development of drug delivery systems, nanotechnology has been used in medicine to break through the limitations of traditional diagnosis and treatment. Enabling drug delivery to specific disease organs through nano-delivery platforms not only achieve that the safety and efficacy of therapeutic drugs are improved and guaranteed, but also enables controlled and sustained drug release at the target site to reduce the negative impact on the patient's normal cells.

Acknowledgement

All the authors contributed equally to this work and should be considered co-first authors.

References

[1] Ferlay, J., Colombet, M., Soerjomataram, I., Parkin, D.M., Piñeros, M., Znaor, A. and Bray, F. (2021). Cancer statistics for the year 2020: an overview. *International Journal of Cancer*, 149(4). doi:10.1002/ijc.33588.

[2] www.iarc.who.int. (n.d.). *Breast Cancer Awareness Month 2021 – IARC*. [online] Available at: https://www.iarc.who.int/featured-news/breast-cancer-awareness-month-2021/.

[3] PRESS RELEASE N° 292. (2020). [online] Available at: https://www.iarc.who.int/wp-content/uploads/2020/12/pr292_E.pdf.

[4] www.iarc.who.int. (n.d.). *IARC – INTERNATIONAL AGENCY FOR RESEARCH ON CANCER*. [online] Available at: https://www.iarc.who.int/.

[5] Huang, H., Lou, Z., Zheng, S., Wu, J., Yao, Q., Chen, R., Kou, L. and Chen, D. (2022). Intra-articular drug delivery systems for osteoarthritis therapy: shifting from sustained release to enhancing penetration into cartilage. *Drug Delivery*, 29(1), pp.767–791. doi:10.1080/10717544.2022.2048130.

[6] Brigger, I., Dubernet, C. and Couvreur, P. (2012). Nanoparticles in cancer therapy and diagnosis. *Advanced Drug Delivery Reviews*, 64, pp.24–36. doi:10.1016/j.addr.2012.09.006.

[7] Makadia, H.K. and Siegel, S.J. (2011). Poly Lactic-co-Glycolic Acid (PLGA) as Biodegradable Controlled Drug Delivery Carrier. *Polymers*, [online] 3(3), pp.1377–1397. doi:10.3390/polym3031377.

DOI: 10.54254/2755-2721/3/20230341

[8] Mir, M., Ahmed, N. and Rehman, A. ur (2017). Recent applications of PLGA based nanostructures in drug delivery. *Colloids and Surfaces B: Biointerfaces*, 159, pp.217–231. doi:10.1016/j.colsurfb.2017.07.038.

[9] Wang, H., Zhao, Y., Wu, Y., Hu, Y., Nan, K., Nie, G. and Chen, H. (2011). Enhanced anti-tumor efficacy by co-delivery of doxorubicin and paclitaxel with amphiphilic methoxy PEG-PLGA copolymer nanoparticles. *Biomaterials*, 32(32), pp.8281–8290. doi:10.1016/j.biomaterials.2011.07.032.

[10] Lv, S., Tang, Z., Li, M., Lin, J., Song, W., Liu, H., Huang, Y., Zhang, Y. and Chen, X. (2014). Co-delivery of doxorubicin and paclitaxel by PEG-polypeptide nanovehicle for the treatment of non-small cell lung cancer. *Biomaterials*, 35(23), pp.6118–6129. doi:10.1016/j.biomaterials.2014.04.034.