SASTA OLIPHANT

SCIENCE AWARDS

SOUTH AUSTRALIAN SCIENCE TEACHERS ASSOCIATION

Prize Winner

Science Writing

Year 11-12

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Polymeric nanoparticle drug delivery systems - the future of cancer treatment?

Introduction

Polymeric nanoparticles (PNPs) are a relatively new, but rapidly developing technology that can provide an innovative and non-invasive approach for drug delivery applications in cancer. The development of PNPs has been greatly influenced by the disadvantages of conventional treatments such as chemotherapy and radiotherapy, which has resulted in a surge of interest and funding for PNP research. The applications of PNP drug delivery systems in cancer treatment are predicted to have many positive future impacts on society, as they provide a more efficient and targeted approach. However, PNP drug delivery systems are not free of limitations, as more clinical trialling and long-term research is required to address safety concerns (Sur, 2019).

Chemical Background Overview

PNPs are a class of nanoparticles, which are defined as materials with sizes ranging from 1 to 100 nm. The large surface area to volume ratio of PNPs is a very valuable feature for drug delivery, as it enables them to bind to many other compounds such as drugs, probes and proteins (Jong, 2008). Many polymers can be used to synthesise PNPs, but the most popular options are polyethylene glycol (PEG), polylactic acid (PLA), and poly lactic-*co*-glycolic acid (PLGA) (Calzoni, 2018). The popularity of these polymers can be accredited to their biocompatibility and biodegradability, meaning they can be broken down into simple monomers which are naturally present in the body.

PNP Structure

PNPs are usually synthesised in a nanosphere or nanocapsule structure (as illustrated in Fig. 1) (Bhasarkar, 2021). Nanospheres are colloidal particles where the drug molecules are attached to their particle surface or confined within their particle matrix through chemical bonding or other physical mechanisms. On the other hand, nanocapsules are vesicular systems where the drug molecules are dissolved in an oily or aqueous core and encapsulated in a polymer shell (Sur, 2019).

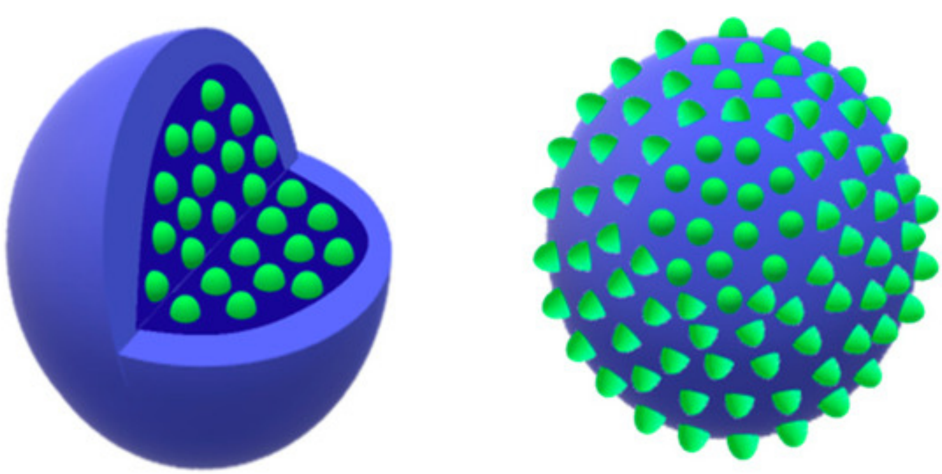

Fig. 1: A pictorial representation illustrating the difference between nanocapsules (left) and nanospheres (right) (Calzoni, 2018)

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Active Targeting for Intracellular Drug Delivery for Cancer Treatment

The chemical structure of PNPs allows them to actively target tumour cells and directly deliver drug molecules (Lee, 2012). To increase selectivity for tumour cells, targeting ligands – such as monoclonal antibodies, peptides, aptamers, and small molecules like folic acid – can be attached to the shell of the PNPs. Targeting ligands act as binding sites for specific receptors that are overexpressed on tumour cells, enabling selective intracellular drug delivery (Avramović, N., et al., 2020). This ensures that the drug isn't delivered to healthy cells, reducing drug toxicity and various side effects. By choosing ligands based on their binding affinities to specific receptors, scientists can design a range of PNPs and create custom delivery mechanisms to match different cancer types (Calzoni, 2018). Once the ligand has attached to the receptor, the PNP is endocytosed into the tumour cell and the drugs are released into the intracellular environment (as seen in Fig. 2) (Subjakova, 2021).

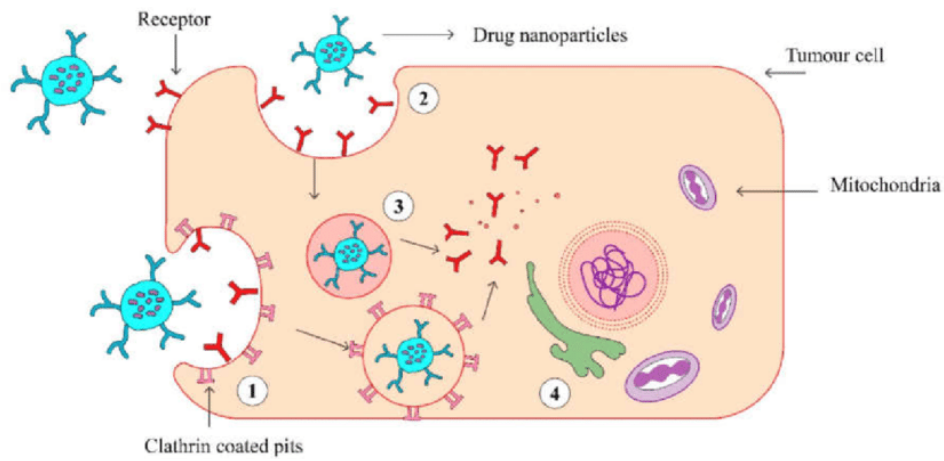

Fig. 2: A schematic illustration of the process of intracellular drug delivery through active targeting. In this case, the ligands on the PNP recognise the clathrin-coated pits in the tumour cell and bind to it. The PNP is then phagocytosed, facilitating the transport of the drug into the cell (Subjakova, 2021).

What has influenced the development of PNP drug delivery systems in cancer treatment?

As the second leading cause of death, cancer is a massive issue that requires close collaboration between researchers around the world (Bray, F., et al., 2018). In 2020, there was an estimated 150,000 new cases of cancer diagnosed in Australia and approximately 50,000 deaths from cancer (Cancer Council, 2022). Cancer is an extremely common disease (as seen in Fig. 3), and Cancer Council estimates that one in two Australians will be diagnosed with cancer before the age of 85. Furthermore, as the average lifespan of the global population increases, the prevalence of cancer is expected to rise by 70% within the next 20 years (Gagliardi, A., et al., 2021). Therefore, cancer has been recognised as a significant threat to global health, leading to an urgent societal need for a solution that can successfully address this growing issue.

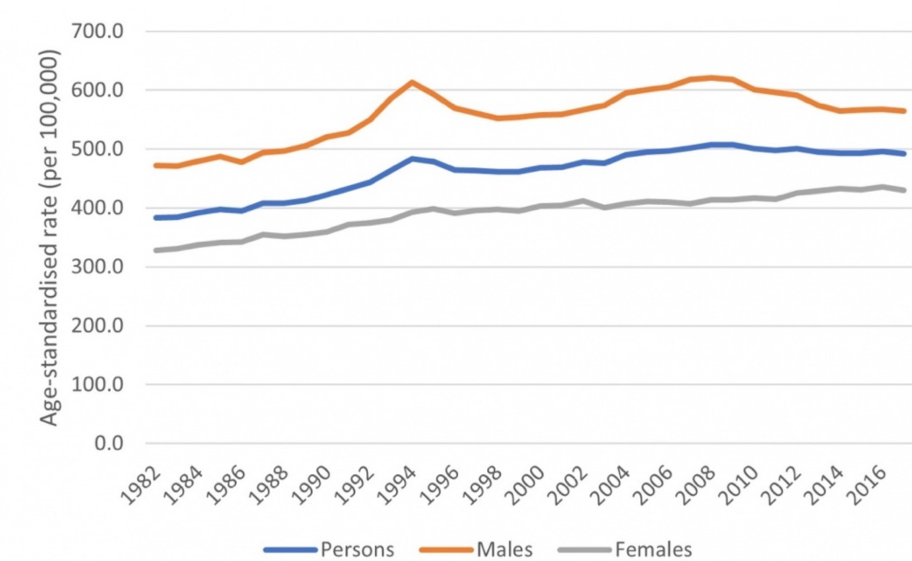

Fig. 3: A graph from a study by Cancer Australia that shows the high incidence rates of cancer from 1982 to 2019. All types of cancer were counted in the study (Cancer Australia, 2022).

However, cancer treatment is considered a massive multidisciplinary challenge, as finding an effective but safe treatment option is extremely difficult. Current conventional treatments (including chemotherapy and radiotherapy) function indiscriminately, meaning they have devastating impacts on normal cells and inflict irreparable damage to healthy tissue.

Chemotherapy is one of the most common treatment methods, but it does not have the ability to target tumour cells without destroying normal cells, leading to severe adverse effects, such as bone marrow suppression, gastrointestinal reactions and substantial hair loss (see Fig. 4). A 2017 study of NSW cancer patients found that 86% of patients experienced serious side-effects, with 85% experiencing fatigue and 75% experiencing significant pain (Pearce, A., et al., 2017). Due to the systematic toxicity of chemotherapy, there is a strict limit on the maximum dosage of anti-cancer drugs, which decreases the therapeutic efficacy of such treatments. In addition, chemotherapy has also been shown to be largely ineffective in treating solid tumours (failure rates of approximately 90%), due to its poor tumour cell selectivity (Maeda, H., Khatami, M., 2018).

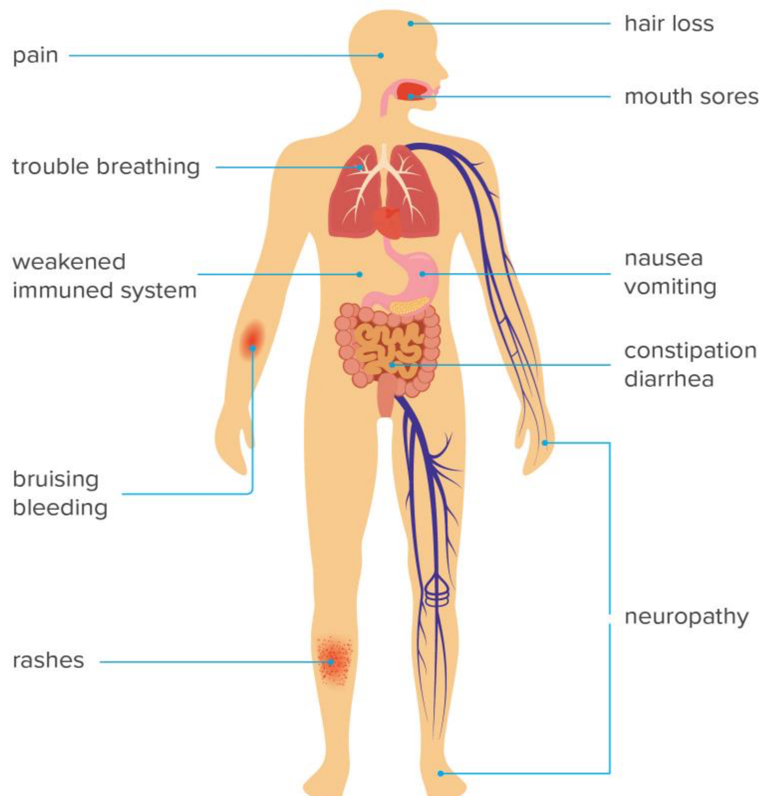

Fig. 4: A medical illustration of the negative effects of chemotherapy on the body (Kelly, 2021).

Radiotherapy, another conventional treatment, also causes undesirable effects, such as headaches, vomiting and memory problems (National Cancer Institute, 2022). Furthermore, there is also a tolerance limit to the amount of radiation that the body can safely receive, meaning radiotherapy must be carefully regulated to ensure safety (National Cancer Institute, 2022).

Therefore, the short-comings of current therapies and alarming prevalence of cancer has produced a pressing demand for an innovative and improved treatment method (Yao, Y., et al., 2020). The needs of society have led to increased funding for research into new methods, directly influencing the development of PNP as a viable treatment option (Bhasarkar, 2021). PNP drug delivery systems have gained a lot of attention, as unlike chemotherapy and radiotherapy, they can actively target the tumour, guiding the chemotherapeutic agents to the cancerous cells and averting toxicity in healthy cells (Adepu, S., Ramakrishna, S., 2021).

Therefore, there has been a surge of interest in in PNPs and other nanoparticle technologies, as illustrated by the BCC Research report "Nanoparticles in Biotechnology, Drug Development and Drug Delivery", which predicted a compound annual growth rate of 22% in the global market (as seen in Fig. 5). As the nanoparticle market becomes increasingly profitable, more companies will choose to invest in nanoparticle research, leading to accelerated development and more opportunities for advancements in cancer treatment. However, it is important to note that the widespread implementation of PNPs will also be influenced by societal factors such as public opinion, as conventional cancer treatments are generally better accepted by patients, who are more familiar with traditional forms of medicine (Dang, Y., Guan, J., 2020).

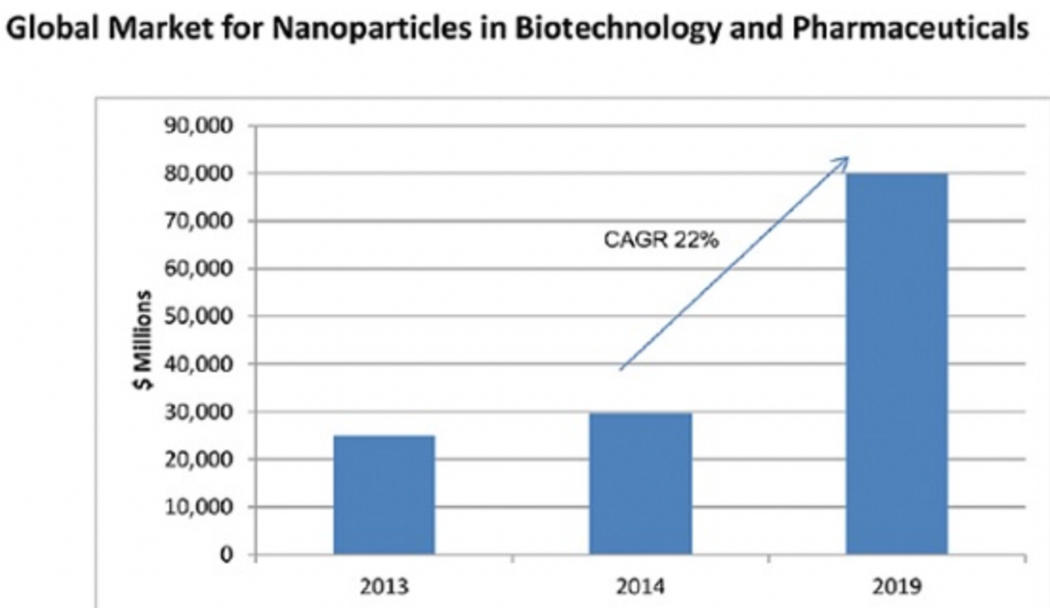

Fig. 5: The global market for nanoparticles in biotechnology, drug development, and drug delivery experienced a period of rapid growth due to the demand for improved therapeutic methods (Pandotra, 2017)

Application of PNP Drug Delivery Systems in Cancer Treatment and Future Impacts on Society
Recent research has shown that PNP drug delivery systems have the potential to replace conventional cancer treatments. A study from the University of Michigan Rogel Cancer Center found that PNPs can provide a new approach in treating metastatic triple negative breast cancer in mice models (See Fig. 6) (Henderson, 2022). PNP drug delivery led to almost 200 days of tumour remission, which was more than double of the remission period produced by chemotherapy (90 days). Dr Sun, who led the study, stated that PNPs allowed them to "achieve long-term tumour remission and eliminate lung metastases, which [they] had never seen before" (Henderson, 2022). By improving therapeutic efficacy, PNPs benefit cancer patients, helping them experience a higher quality of life and giving them significantly higher survival rates.

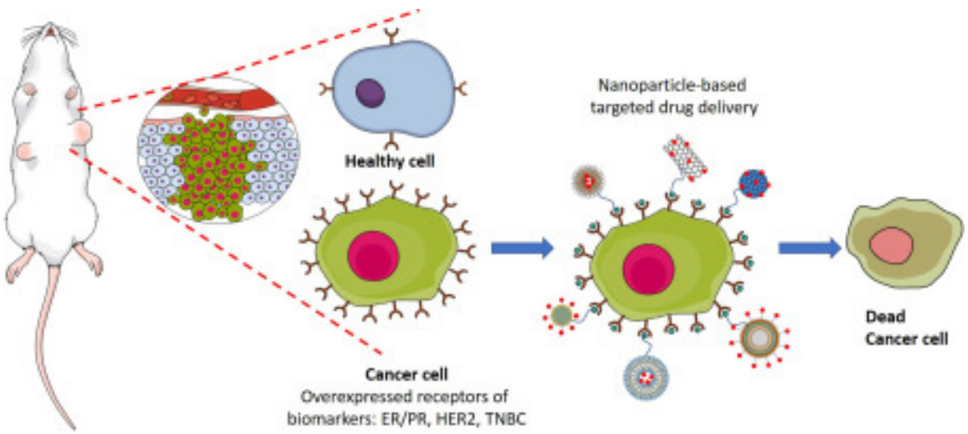

Fig. 6: A diagram showing how tumour cells were targeted using PNPs to treat breast cancer in mice (Liyanage, P., et al., 2019).

Furthermore, the application of PNPs in cancer treatment could have an immensely positive impact on society and the economy. Research from the Cancer Council indicates the staggering future of cost of cancer, revealing that cancer costs the Australian health care system over $6 billion per year (Cancer Council NSW, 2021). In addition, a 2018 study published in BMC Public Health showed that Australia loses a further $1.7 billion of GDP each year due to people with cancer having to leave the workforce, greatly decreasing national productivity levels (Bonnett, 2018). The study also showed that compared with other long-term health conditions - such as diabetes, chronic epilepsy and heart disease - those suffering from cancer were twice as likely to not be in the workforce, which highlights the devastating impact cancer can have on the Australian economy (Bonnett, 2018). Therefore, by providing a more effective and efficient treatment option, PNP drug delivery systems can positively impact the economy, relieving financial pressure on health systems and increasing productivity.

Limitations
However, despite their many advantages, PNP drug delivery systems are still subject to limitations. Current PNP synthesis methods are only lab-scale, limiting their widespread application in society as only small amounts can be produced at once (Dang, Y., Guan, J., 2020). As a consequence, PNP technology is significantly more expensive to manufacture than traditional medicines, leading to higher selling prices and decreased affordability and accessibility for cancer patients (Bosetti, 2019).

Furthermore, PNPs are a relatively new breakthrough, so scientists are yet to develop an extensive understanding of their functionality and long-term behaviour. Although trials have been successful in mouse models, most PNP drug delivery systems have not shown to be effective in humans, meaning there may be unknown side effects such as adverse side-effects and toxicity (Sun, 2022). Therefore, many more studies and clinical trials must be conducted before PNPs can be fully accepted as a standard option in the pharmaceutical market, requiring a large amount of resources, money and time (Gagliardi, A., et al., 2021).

Conclusion

In conclusion, PNPs are a very exciting tool for drug delivery systems and could potentially pave the way towards a new era of cancer treatment. PNPs provide a much improved alternative to conventional therapies, opening the door to safer, target-specific and more effective methods. Although more research must be conducted to solve current limitations, it is undoubtable that the applications of PNPs will positively impact society and revolutionise the field of cancer treatment.

Word Count: 1497

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