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Emerging Trends in Nano-Theranostics: Platinum-based Drug Delivery Systems for Cancer Treatment

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Abstract: *Nanotechnology is the most common and frequently used technology that aims to improve the efficacy of medical procedures, sometimes known as Nanomedicine. With their impressive pharmacological efficacy as nanomedicines and delivery systems, nano materials have been recognized as attractive diagnostic and chemotherapeutic tools to treat diseases. To treat a wide range of solid malignant tumors, Drugs built on platinum complexes are now the foundation for many other therapies. They are often used to treat a variety of solid tumors in the clinic, including head and neck, colorectal, lung and other malignancies. Cell-specific targeting with nano-carriers is possible using both active and passive techniques. This paper provides a thorough overview of platinum-based drug delivery system with the help of nanotechnology. Their mechanisms of action used in the treatment of cancer and potential for further development are all anticipated.*

Key Words: Nanomedicines, Platinum Drugs, Chemotherapeutic, Pharmacological drugs

Introduction

With over 23% of all death reports, cancer is thought to be the second most common cause of death (Hosseini *et al.*, 2016). Since cancer treatment has proved difficult many different therapeutic approaches have been investigated (Shinde *et al.*, 2022). Currently surgery, radiation and chemotherapy are the most effective therapeutic techniques. Cytotoxic chemical or biological substances are used in chemotherapy to kill cancer cells. A recent phrase created from the words therapies and diagnostics is theranostics. A new field of personalized medicine called theranostics combines a therapeutic and diagnostic agent in a single formulation, which is guided by a ligand that targets cells that are malfunctioning (Peng *et al.*, 2015; lyer *et al.*, 2013; jain *et al.*, 2013). For cancer theranostics, numerous strategies, including those that use nanomaterials, metal complexes, and small molecules, have been developed. Additionally, nanoparticles can be directly mixed with medicinal and diagnostic substances. Even though clinical usage of nanomaterials as transport vehicles has been permitted for a long time, the full translation of the nanomaterial-based theranostic system from bench to bedside has faced major hurdles (Zhang

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et al., 2023). Metal, lipid, and polymer nanoparticles (NPs) exhibit a variety of biological characteristics that can be used for theranostic purposes.

Nanotechnology as a Drug Delivery System

Nanotechnology based drug delivery systems (NTDDS) can be seen as a viable means of enhancing patient compliance and increasing treatment results (Sahu *et al.*, 2021). Nano science, which combines with traditional disciplines like applied health, molecular chemistry, molecular science, pharmaceutical science, optics and even engineering is the sole way to learn about the unique features of matter. The most prevalent and financially successful technology of these decades has arisen, and research has proved that it is crucial for maintaining human existence (Galluzzi *et al.*, 2012).

Platinum anticancer drugs have been used for decades to treat a variety of cancers, including the bladder, cervical, colorectal, head, pulmonary, and throat cancers, as well as ovarian and testicular cancer (Wani *et al.*, 2017; Zhang *et al.*, 2023). Chemosynthetic platinum-based antitumor medicines have been successfully researched and used to treat a variety of cancers (Xiao *et al.*, 2018; imran *et al.*, 2018].

With a focus on its usage for drug administration via Platinum complexes, we examine the use of nanotechnology for medicinal purposes in this review. A technique that has promise for the development of intelligent therapeutic systems is the use of smart medication delivery systems. In this study, we first provide an overview of the most widely used platinum medications, including platinum (IV), platinum (II), and non-classical platinum (II) medications that have all received clinical approval. The overview of platinum complex-based nano-carrier based drug delivery systems (NDDSs) is then provided (Anarjan, 2019).

The Benefits of Using Nanoparticles for Drug Delivery

- The ability of nanotechnology to be absorbed into the body without causing any adverse effects or chemical reactions is crucial when using it as a medicine delivery method.
- Drug degradation and regulated delivery aspects can be synchronized fast.
- Due to the improved biological availability of the drug at a specific location for a sustained length of time and the exceptionally minimal drug wastage, it is the optimal method for drug administration.
- Additionally, it can increase a drug's half-life in the bloodstream and the ability of weakly water-soluble medicines to dissolve.
- The effectiveness of nanotechnology is such that it can increase the activity and dispersion of pharmaceuticals in comparison to conventional drugs and also ensure patient consent and satisfaction. Nanotechnology is far more affordable than other types of traditional medications (Wani *et al.*, 2022)

Table 1

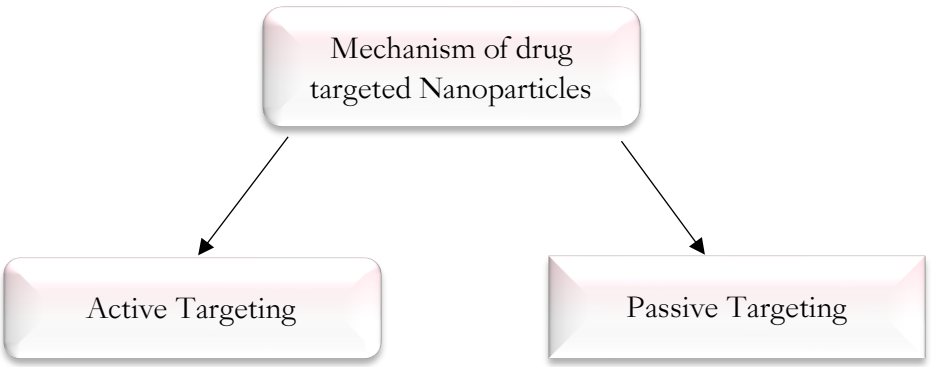
Brief description of Nanosystems, including features and purposes (Koo et al., 2005)

Types of Nano particles	Characteristics	Functions
1. Liposomes	Made up of a hollow main part and a liquid bilayer.	a common method for delivering drugs to treat cancers
2. Polymeric	A polymer that immune cells can absorb, such as PCA or PLGA, is employed.	Effective at delivering drugs because they are hydrophobic.
3. Nanotubes	Insoluble in Water	Used for low-dose targeting of certain cancer cells.

Types of Nano particles	Characteristics	Functions
4. Nanocrystals	Establish very stable nano-suspensions.	Mainly used for HIV based drug delivery.
5. Dendrimers	On the outside, there are working end groups, layers of branched, repetitive units, and a core. multivalency levels.	It is effective for both phyllic and hydrophobic medicines. used as a coating agent for medications to protect them
6. Solid Lipid Nano-particles	composed of layers that are solid, like tripalmite	effective drug administration methods, including pulmonary, rectal, oral, and ophthalmic.
7. Polymeric micelles	Composed of amphiphillic surfactants.	Drug delivery to tumour cells that is efficient and has fewer negative effects
8. Nano-capsule	Spherical structures with a dielectric core.	Cancer treatment. Biomedical imaging.
9. Ceramic Nanoparticles	Constructed from inorganic materials having porous properties, such as alumina.	Hazardous, non-biodegradable shabby drug loads.
10. Gold Particle	composed of vesicles i.e hydrophobic and hydrophilic molecules that are plated in gold.	being biocompatible. sustainable and reliable.

Mechanism of Targeted Nanoparticles

There are two ways that nanoparticles connect to the drug surfaces and deliver the medication to the body's sick tissue (Sahu *et al.*, 2021).



Passive Targeting:

Enhanced Permeability and Retention Effect.

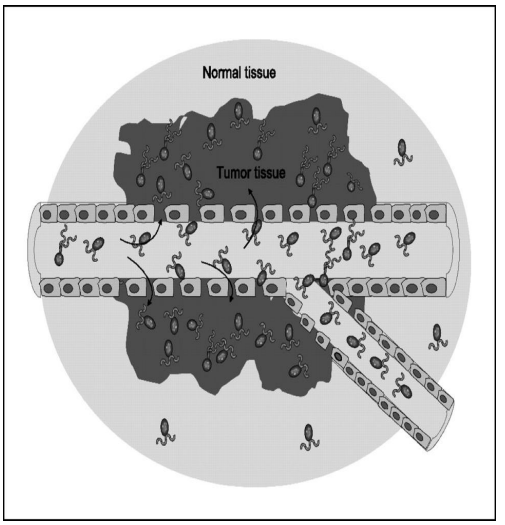
While the enhanced permeability and retention (EPR) effect, which favors the accumulation of therapeutic drugs in the interstitial space of tumors as a result of the deterioration of the vascular and lymphatic system effect, is a result of passive targeting (Pelicano *et al.*, 2006)

Nanoparticles need to be able to circulate in the bloodstream for longer periods of time and have a better chance of getting to the targeted tumor areas. Nanoparticles can gather in tumor tissues due to the special traits of tumor cells. Cancer cells

that are dividing quickly require new blood arteries to feed them with nutrition and oxygen. Due to this, the tumor arteries become dilated and have a large number of pores that display gap junctions between lymphatic and endothelial tissues (Lata *et al.*, 2017;Cho *et al.*, 2008).

Figure. 1:

Passive Targeting by Nanoparticles



Micro-environment of Tumor vessels

Another component of passive targeting is the specific environment that surrounds tumor cells, which is distinct from that of healthy cells. The vascular bed and stroma, functional lymphatic and interstitial pressure, and their capacity to maintain homeostasis are a few of the fundamental elements impacting the tumor microenvironment under mechanical stress (Allen & Lim, 2022). Because of a deficiency in oxygen and nutrients, rapid-growing tumor cells have a high metabolic rate that they are typically unable to maintain. In order to gain additional energy, tumor cells use glycolysis, which creates an acidic environment (Li & Burgess, 2020;Shinde *et al.*, 2022).

Active Targeting by Nanoparticles

The specificity of passive targeting techniques has inherent limitations. The incorporation of a targeted ligand in polymer-drug conjugates can get beyond these restrictions (Lata *et al.*, 2017). The recent development of a wide array of liposomes, polymers, nanotubes, and metals as drug delivery carriers has boosted the number of drugs that can be coupled to targeted nanoparticles without compromising their targeting affinity. By using both passive and active targeting strategies, nanoparticles can boost the intracellular concentration of drugs in cancer cells while limiting harm to normal cells (Cho *et al.*, 2008).

Expression of an Antigen or Receptor

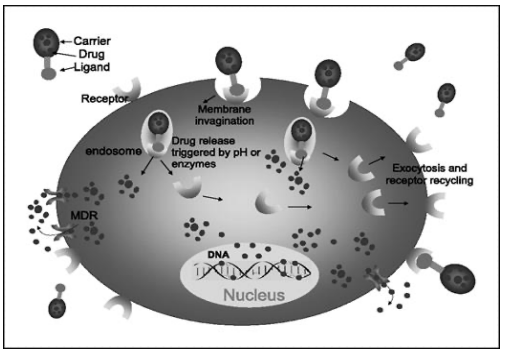
Numerous characteristics of cell-surface antigens and receptors would make them particularly attractive tumor-specific targets (Allen, 2002). Prior to that only tumor cells should display them, not healthy cells. Secondly, they must be expressed consistently across the targeted tumor cells. Finally, it's critical to prevent the circulation from becoming contaminated with cell surface antigens and receptors.

Internalization of Targeted Conjugates

Receptor-mediated endocytosis typically causes internalization. Fig. 2. Using the folate receptor as an example, the encircling plasma membrane creates an endosome by encroaching over the combination of the receptor and ligand when a chemical that targets folate interacts to the cell's surface folate receptor. Target organelles get newly produced endosomes. When the pH level inside the endosome rises to an acidic level and the medication is liberated from the conjugate and enters the cytoplasm once the lysozymes are activated, if it possesses the physicochemical properties needed to penetrate the endosomal membrane. Depending on the medication, the target organelle then traffics the released medicines. The cell membrane receives the folate receptor that was released during conjugation and interacts with new conjugates that are folate-targeted while waiting for the second cycle of transport to start (Leamon & Reddy, 2004).

Figure 2

Active Targeting by Nanoparticles



Platinum Drugs

Carboplatin, cisplatin, and oxaliplatin are the three primary platinum anticancer medications with clinical applications. Platinum-based medications should, ideally, solely kill tumor cells while sparing healthy cells any harm. However, platinum medicines have very low selectivity, in addition to killing malignant cells, they also harm normal cells. Platinum medicines have suffered from severe side effects, systemic toxicity, and acquired and intrinsic resistance, which have reduced their therapeutic efficacy. Because of cisplatin's high level of effectiveness, the research and development of platinum medications has rapidly increased, and thousands of them have undergone clinical testing. It is feasible to distinguish between synthetic platinum medicines of the Pt (II) and Pt (IV) kinds based on the valence of platinum atoms at either +2 or +4 (Zhang *et al.*, 2022)

Classical Pt (II) Drugs

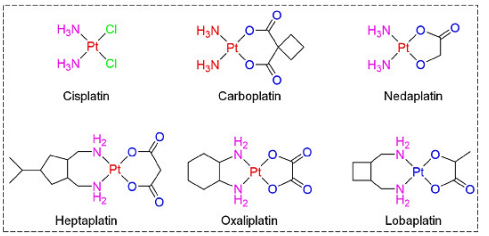
The first Pt (II) medication found was cisplatin (Gosh *et al.*, 2019). Since Rosenberg and colleagues unintentionally made the finding in 1965 while looking into how electric fields effect E. coli differentiation, cisplatin has been shown to have anti-cancer activity (Arnesano & Natile, 2009). Cisplatin, a medication with a broad-spectrum anti-cancer activity, has been used to treat a variety of cancers, including ovarian cancer, testicular cancer, lung cancer, cancer of the bladder, cancer of the cervix, tumors of the head and neck, etc. Its usage in clinical settings was severely constrained due to its significant systemic adverse responses and unfavorable consequences, which included renal toxicity, gastrointestinal reaction, neurotoxicity, ototoxicity (Graham *et al.*, 2004).

The second-generation platinum drug carboplatin gained widespread acceptance in 1989 and was afterwards used mostly to treat head and neck cancer, ovarian cancer, and non-small cell lung cancer (NSCLC).

The second-generation platinum medication nedaplatin, which was first marketed under the trade name 254-S, was only permitted to be sold in Japan. This platinum medication has non-leaving cis ammine ligands, just like cisplatin and carboplatin. Nedaplatin is primarily used to treat breast cancer, NSCLC, SCLC, esophageal cancer, and head and neck cancer in clinical settings. Nedaplatin usage is rising as a result of clinical trials (Wheate *et a*l., 2010).

Figure 3

Structures of Platinum (II) Complexes



Nedaplatin, a second-generation platinum drug that was initially marketed as 254-S, received authorization in 1995, but only in Japan. This platinum drug, like cisplatin and carboplatin, possesses non-leaving cis ammine ligands. Nedaplatin is mostly used in clinical settings to treat breast cancer, NSCLC, small-cell lung cancer (SCLC), esophageal cancer, and head and neck cancer (Misset *et al.*, 2000). Clinical trials are using nedaplatin more frequently (Peng *et al.*, 2013;Choi *et al.*, 2004).

Despite the many advantages that cisplatin has over carboplatin, oxaliplatin, and other popular Pt (II) medications, resistance and unpleasant side effects are still a possibility (Garbutcheon *et al.*, 2013; Xu *et al.*, 2022).

Table 2

Clinically approved Pt(II) drugs (Wheate et al., 2010)

Generic name	Research name	Trade name	Cancer type	Side Effects	Area of Acceptance
Cisplatin	CDDP	Platinol	Testicular, Cervical Lymphoma	Nephrotoxicity, Neurotoxicity, Ototoxicity, Nausea	Global
Carboplatin	JM8	Paraplatin	Ovarian, Lung	Myeloablation	Global
Nedaplatin	254-S	Aqupla	Esophageal cancer Breast, SCLC	Peripheral Neuropathy, Ototoxicity	Japan
Heptaplatin	SKI 2053R	SunPla	Gastric Cancer	Nephrotoxicity, Severe nausea and Vomiting, Neurotoxicity	Korea
Oxaliplatin	1-OHP	Eloxatin	*Head and neck squamous cell cancers* (HNSCC)	Liver Toxicity Peripheral Neuropathy (Anemia)	Worldwide

Non-classical Pt (II) Drugs

Cisplatin offers many advantages over carboplatin, oxaliplatin, and other popular Pt(II) medications, although resistance and unfavourable side effects are still a possibility. Additionally, the low doses of these medications can be administered to the tumour without reaching deadly concentrations due to their limited aqueous stability and high reactivity to bioactive chemicals. To address these problems, numerous structurally distinct non-classical Pt(II) medicines have been developed (Eckardt *et al.*, 2009)

Figure 4

Non classical Platinum (II) drugs

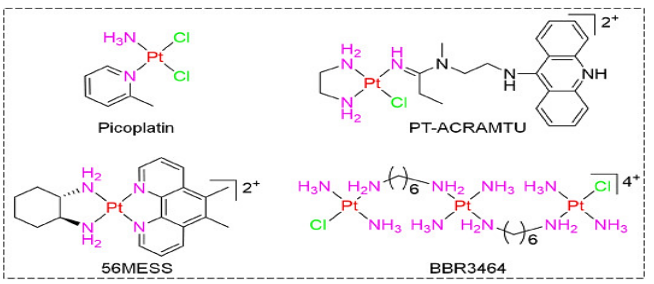


Table 4

Clinical trials for Pt(II) medications (Eckardt et al., 2009)

Generic Name	Stage	Type of Cancer
Picoplatin	Phase I	Prostate cancer, small cell lung cancer, non-small cell lung cancer, prostate cancer, colon cancer, and lymphoma
BBR 3464	Phase II	SCLC, gastric cancer, and ovarian cancer
56MESS	Phase II	Chemotherapeutic drug superior to cisplatin, anticancer agent.

Platinum (IV)

The first orally administered platinum analogue, satraplatin, has a number of potential advantages over other platinum medications, such cisplatin. Its oral bioavailability makes it particularly practical for both patients and healthcare professionals.

Prostate cancer, non-small cell lung cancer, and head and neck cancer are now being treated with satraplatin (JM-216), a Pt (IV) prodrug that does not exhibit cisplatin cross-resistance and can be administered orally (Zhang *et al.*, 2021). Satraplatin has a comparable toxicity profile to that of carboplatin, with no evidence of nephrotoxicity, neurotoxicity, or ototoxicity (Choy *et al.*, 2008).

Figure 5

(a) Representative Pt (IV) drug structures (b)The JM-216 structure (Zhang et al., 2020)

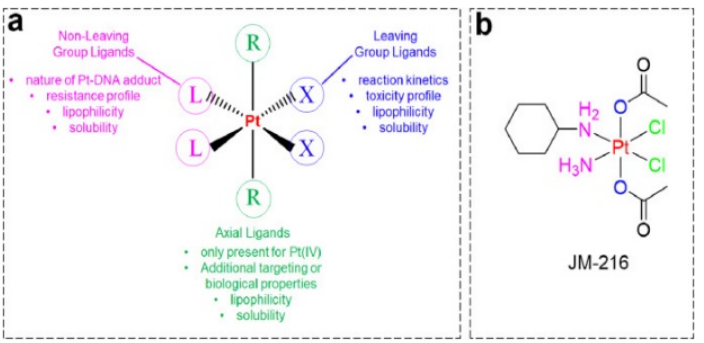
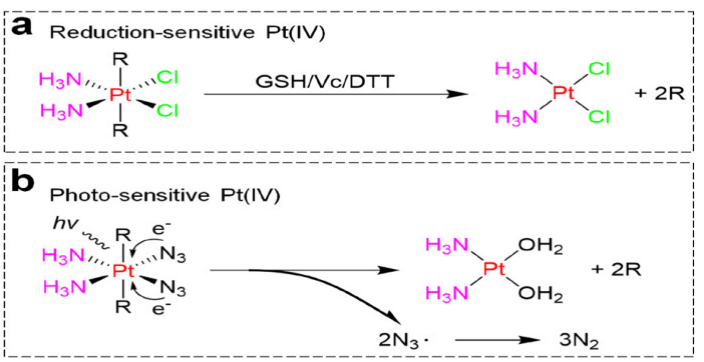


Figure 6

Mechanics of (a) reduction-sensitive and (b) photo-sensitive Pt (IV) prodrugs (Zhang et al., 2022; Kuang et al., 2020; Li et al., 2022).



Specific Side Effects of Platinum Drugs

9.6 million people worldwide died from cancer in 2018, and there were 18.1 million new cases (Wheate *et al.*, 2010). Numerous advancements have been achieved in conventional cancer therapies like radiotherapy and chemotherapy, which don't seem to be working very well. As some drawbacks, including chemoresistance, prevent it (Um *et al.*, 2019).

Nephrotoxicity, a generic term that covers more than 12 distinct adverse consequences linked to the kidneys' vital filtration, reabsorption, and excretion activities, refers to damage to the kidneys (Bai *et al.*, 2017; Ahn *et al.*, 2002). A patient's hearing and balance are impacted by ototoxicity, or injury to the inner ear. The side effects of drugs containing platinum ear discomfort, tinnitus (echo problem) and vestibular abnormalities. However, the most typical ototoxicity is bilateral irreversible hearing loss (affects balance) (Wheate *et al.*, 2010).

Conclusion and Future Perspective

Nanomedicine is advancing quickly and significantly, which points to its bright future and tremendous potential for creating innovative and effective diagnostic and therapeutic approaches, particularly for cancer. To address the difficulties in cancer therapy, nanomedicine provided a variety of medication delivery alternatives (Oroojalian *et al.*, 2020). There has been a huge increase in the usage of platinum drugs in chemotherapy. One of the most dynamic subspecialties of oncology is the use of drugs with a platinum base. Different cancer types are now being treated using a variety of platinum compounds. The discipline of theranostic NP has seen expanding advancements in disease management. Despite the significant progress that has been made in the field of theranostic NPs, such as active tumor site targeting, many obstacles still stand in the way of its successful application in clinical settings, such as the creation of stimuli-responsive NPs and the viability of therapeutic combinations, the possibility for adopting the controlled-release method and enhancing the therapeutic effects using magnetic fields or photothermal therapy (Biswas *et al.*, 2022). The polymer-based platinum drug delivery technology will undoubtedly drive the medication delivery sector to a better future (Kandasamy & Maity, 2021). The size of the global nanomedicine market is anticipated to increase from an estimated $53 billion in 2009 to more than $100 billion in 2014 at a compound annual growth rate (CAGR) of 13.5%. The potential for creating a system that produces nanoproducts more successfully is limited. Understanding how nanomaterials are dispersed within the body is crucial. In connection with a second restriction, imaging methods are required to monitor the biodistribution of nanomedicine over time (Hosseini *et al.*, 2023).

References

Advanced nanomedicine and cancer: Challenges and opportunities in clinical translation. (2021). International Journal of Pharmaceutics, 599, 120438. https://doi.org/10.1016/j.ijpharm.2021.120438

Ahn, J. S., Kang, Y.-K., Kim, T. Y., Bahng, H., Chang, H.-M., Kang, W., Kim, W. H., Lee, J. P., & Park, J. T. (2002). Nephrotoxicity of heptaplatin: a randomized comparison with cisplatin in advanced gastric cancer. Cancer Chemotherapy and Pharmacology, 50(2), 104–110. https://doi.org/10.1007/s00280-002-0483-x

Allen, G. M., & Lim, W. A. (2022). Rethinking cancer targeting strategies in the era of smart cell therapeutics. Nature Reviews Cancer, 22(12), 693–702. https://doi.org/10.1038/s41568-022-00505-x

Anarjan, F. S. (2019). Active targeting drug delivery nanocarriers: Ligands. Nano-Structures & Nano-Objects, 19, 100370. https://doi.org/10.1016/j.nanoso.2019.100370

Anselmo, A. C., & Mitragotri, S. (2019). Nanoparticles in the clinic: An update. Bioengineering & Translational Medicine, 4(3). https://doi.org/10.1002/btm2.10143

Bai, L., Gao, C., Liu, Q., Yu, C., Zhang, Z., Cai, L., & Liao, X. (2017). Research progress in modern structure of platinum complexes. European Journal of Medicinal Chemistry, 140, 349-382. https://doi.org/10.1016/j.ejmech.2017.09.034

Barnes, K. R., & Lippard, S. J. (2004). Cisplatin and related anticancer drugs: recent advances and insights. Metal Ions in Biological Systems, 42, 143-178.

Biswas, R., Alam, M., Sarkar, A., Haque, M. I., Hasan, Md. M., & Hoque, M. (2022). Application of nanotechnology in food: processing, preservation, packaging and safety assessment. Heliyon, 8(11), e11795. https://doi.org/10.1016/j.heliyon.2022.e11795

Boca, S. C., Potara, M., Gabudean, A.-M., Juhem, A., Baldeck, P. L., & Astilean, S. (2011). Chitosan-coated triangular silver nanoparticles as a novel class of biocompatible, highly effective photothermal transducers for in vitro cancer cell therapy. Cancer Letters, 311(2), 131–140. https://doi.org/10.1016/j.canlet.2011.06.022

Chen, M., Xie, Y., Luo, Q., Xu, J., Ren, Y.-X., Liu, R., Zhao, H., Chen, Y., Feng, H., Du, Y.-F., Li, J.-W., Wang, G., & Lu, W.-L. (2022). Switchable nanoparticles complexing cisplatin for circumventing glutathione depletion in breast cancer chemotherapy. Chinese Chemical Letters, 34(5), 107744–107744. https://doi.org/10.1016/j.cclet.2022.107744

Cheng, L., Gong, H., Zhu, W., Liu, J., Wang, X., Liu, G., & Liu, Z. (2014). PEGylated Prussian blue nanocubes as a theranostic agent for simultaneous cancer imaging and photothermal therapy. Biomaterials, 35(37), 9844–9852. https://doi.org/10.1016/j.biomaterials.2014.09.004

Cheng, Z., Dai, Y., Kang, X., Li, C., Huang, S.-S., Lian, H., Hou, Z., Ma, P., & Lin, J. (2014). Gelatin-encapsulated iron oxide nanoparticles for platinum (IV) prodrug delivery, enzyme-stimulated release and MRI. Biomaterials, 35(24), 6359–6368. https://doi.org/10.1016/j.biomaterials.2014.04.029

Cho, K., Wang, X., Nie, S., Chen, Z., & Shin, D. M. (2008). Therapeutic Nanoparticles for Drug Delivery in Cancer. Clinical Cancer Research, 14(5), 1310–1316. https://doi.org/10.1158/1078-0432.ccr-07-1441

Choi, C. H., Cha, Y. J., An, C. S., Kim, K. J., Kim, K. C., Moon, S. P., Lee, Z. H., & Min, Y. D. (2004). Molecular mechanisms of heptaplatin effective against cisplatin-resistant cancer cell lines: less involvement of metallothionein. Cancer cell international,

4(1), 6. https://doi.org/10.1186/1475-2867-4-6

Choti, M. A. (2009). Chemotherapy-Associated Hepatotoxicity: Do We Need to Be Concerned? Annals of Surgical Oncology, 16(9), 2391–2394. https://doi.org/10.1245/s10434-009-0512-7

Crucho, C. I. C., & Barros, M. T. (2017). Polymeric nanoparticles: A study on the preparation variables and characterization methods. Materials Science and Engineering: C, 80, 771–784. https://doi.org/10.1016/j.msec.2017.06.004

Eckardt, J. R., Bentsion, D. L., Lipatov, O., Polyakov, I. V., MacKintosh, F. R., Karlin, D., Baker, G., & Breitz, H. B. (2009). Phase II Study of Picoplatin As Second-Line Therapy for Patients With Small-Cell Lung Cancer. Journal of Clinical Oncology, 27(12), 2046–2051. https://doi.org/10.1200/jco.2008.19.3235

Elzoghby, A. O., Abd-Elwakil, M. M., Abd-Elsalam, K., Elsayed, M. M., Hashem, Y., & Mohamed, O. A. (2016). Natural Polymeric Nanoparticles for Brain-Targeting: Implications on Drug and Gene Delivery. *Current Pharmaceutical Design*, *22*(22), 3305–3323. https://doi.org/10.2174/1381612822666160204120829

Galluzzi, L., Vitale, I., Abrams, J. M., Alnemri, E. S., Baehrecke, E. H., Blagosklonny, M. V., Dawson, T. M., Dawson, V. L., El-Deiry, W. S., Fulda, S., Gottlieb, E., Green, D. R., Hengartner, M. O., Kepp, O., Knight, R. A., Kumar, S., Lipton, S. A., Lu, X., Madeo, F., & Malorni, W. (2011). Molecular definitions of cell death subroutines: recommendations of the Nomenclature Committee on Cell Death 2012. Cell Death & Differentiation, 19(1), 107–120. https://doi.org/10.1038/cdd.2011.96

Garbutcheon-Singh, K. B., Leverett, P., Myers, S., & Aldrich-Wright, J. R. (2013). Cytotoxic platinum(ii) intercalators that incorporate 1R,2R-diaminocyclopentane. Dalton Trans., 42(4), 918–926. https://doi.org/10.1039/c2dt31323e

Guari, Y., Cahu, M., Félix, G., Sene, S., Long, J., Chopineau, J., Devoisselle, J.-M., & Larionova, J. (2022). Nanoheterostructures based on nanosized Prussian blue and its Analogues: Design, properties and applications. Coordination Chemistry Reviews, 461, 214497–214497. https://doi.org/10.1016/j.ccr.2022.214497

Hamzah, R. N., Alghazali, K. M., Biris, A. S., & Griffin, R. J. (2022). Nanoparticle-Labeled Exosomes as Theranostic Agents: A Review. ACS Applied Nano Materials, 5(9), 12265–12275. https://doi.org/10.1021/acsanm.2c01426

Hani, U., Begum, Y. M., Wahab, S., Siddiqua, A., Osmani, R. A. M., & Rahamathulla, M. (2021). A Comprehensive Review of Current Perspectives on Novel Drug Delivery Systems and Approaches for Lung Cancer Management. Journal of Pharmaceutical Innovation, Journal of Pharmaceutical Innovation(4). https://doi.org/10.1007/s12247-021-09582-1

Hosseini, M., Haji-Fatahaliha, M., Jadidi-Niaragh, F., Majidi, J., & Yousefi, M. (2015). The use of nanoparticles as a promising therapeutic approach in cancer immunotherapy. Artificial Cells, Nanomedicine, and Biotechnology, 44(4), 1–11. https://doi.org/10.3109/21691401.2014.998830

Hu, Q., Sun, W., Wang, C., & Gu, Z. (2016). Recent advances of cocktail chemotherapy by combination drug delivery systems. Advanced Drug Delivery Reviews, 98, 19–34. https://doi.org/10.1016/j.addr.2015.10.022

Imran, M., Rauf, A., Khan, I. A., Shahbaz, M., Qaisrani, T. B., Fatmawati, S., Abu-Izneid, T., Imran, A., Rahman, K. U., & Gondal, T. A. (2018). Thymoquinone: A novel strategy to combat cancer: A review. Biomedicine & Pharmacotherapy, 106, 390–402. https://doi.org/10.1016/j.biopha.2018.06.159

Iyer, A. K., Duan, Z., & Amiji, M. M. (2014). Nanodelivery Systems for Nucleic Acid Therapeutics in Drug Resistant Tumors. Molecular Pharmaceutics, 11(8), 2511–2526. https://doi.org/10.1021/mp500024p

Iyer, A. K., Singh, A., Ganta, S., & Amiji, M. M. (2013). Role of integrated cancer nanomedicine in overcoming drug resistance. Advanced Drug Delivery Reviews, 65(13-14), 1784–1802. https://doi.org/10.1016/j.addr.2013.07.012

Jain, S., Doshi, A. S., Iyer, A. K., & Amiji, M. M. (2013). Multifunctional nanoparticles for targeting cancer and inflammatory diseases. Journal of Drug Targeting, 21(10), 888–903. https://doi.org/10.3109/1061186x.2013.832769

Jodrell, D. I., Evans, T., Steward, W. P., Cameron, D., Prendiville, J., Aschele, C., Noberasco, C., Lind, M. J., Carmichael, J. C., Dobbs, N., Camboni, G., Gatti, B., & Filippo de Braud. (2004). Phase II studies of BBR3464, a novel tri-nuclear platinum complex, in patients with gastric or gastro-oesophageal adenocarcinoma. European Journal of Cancer, 40(12), 1872–1877. https://doi.org/10.1016/j.ejca.2004.04.032

Johnstone, T. C. (2014). The crystal structure of oxaliplatin: A case of overlooked pseudo symmetry. Polyhedron, 67, 429–435. https://doi.org/10.1016/j.poly.2013.10.003

Kapp, T., Dullin, A., & Gust, R. (2010). Platinum(II) Dendrimer Conjugates: Synthesis and Investigations on Cytotoxicity, Cellular Distribution, Platinum Release, DNA, and Protein Binding. Bioconjugate Chemistry, 21(2), 328–337. https://doi.org/10.1021/bc900406m

Kelland, L. (2007). The resurgence of platinum-based cancer chemotherapy. Nature Reviews Cancer, 7(8), 573–584. https://doi.org/10.1038/nrc2167

Koo, O. M., Rubinstein, I., & Onyuksel, H. (2005). Role of nanotechnology in targeted drug delivery and imaging: a concise review. Nanomedicine: Nanotechnology, Biology and Medicine, 1(3), 193–212. https://doi.org/10.1016/j.nano.2005.06.004

Kuang, G., Zhang, Q., He, S., Wu, Y., & Huang, Y. (2020). Reduction-responsive disulfide linkage core-cross-linked polymeric micelles for site-specific drug delivery. Polymer Chemistry, 11(44), 7078–7086. https://doi.org/10.1039/dopy00987c

Lata, S., Sharma, G., Joshi, M., Kanwar, P., & Mishra, T. (2017). Role of nanotechnology in drug delivery. International Journal of Nanotechnology Nanoscience, 5, 1-29. http://dx.doi.org/10.20530/IJNN363

Li, J., & Burgess, D. J. (2020). Nanomedicine-based drug delivery towards tumor biological and immunological microenvironment. *Acta Pharmaceutica Sinica B*, *10*(11), 2110–2124. https://doi.org/10.1016/j.apsb.2020.05.008

Li, J., & Burgess, D. J. (2020b). Nanomedicine-based drug delivery towards tumor biological and immunological microenvironment. *Acta Pharmaceutica Sinica B*, *10*(11), 2110–2124. https://doi.org/10.1016/j.apsb.2020.05.008

Li, J., Yap, S. M., Chin, C. T., Tian, Q., Yoong, S. L., Pastorin, G., & Ang, W. H. (2012). Platinum(iv) prodrugs entrapped within multiwalled carbon nanotubes: Selective release by chemical reduction and hydrophobicity reversal. *Chemical Science*, *3*(6), 2083. https://doi.org/10.1039/c2sc01086k

Li, J., Yu, F., Chen, Y., & Oupický, D. (2015). Polymeric drugs: Advances in the development of pharmacologically active polymers. Journal of Controlled Release, 219, 369–382. https://doi.org/10.1016/j.jconrel.2015.09.043

Li, Y., & Lin, W. (2023). Platinum-based combination nanomedicines for cancer therapy. *Current Opinion in Chemical Biology*, *74*, 102290. https://doi.org/10.1016/j.cbpa.2023.102290

Lian, H., Hu, M., Liu, C., Yamauchi, Y., & Wu, K. C. (2012). Highly biocompatible, hollow coordination polymer nanoparticles as cisplatin carriers for efficient intracellular drug delivery. *Chemical Communications*,

48(42), 5151. https://doi.org/10.1039/c2cc31708g

Ma, P., Xiao, H., Li, C., Dai, Y., Cheng, Z., Hou, Z., & Lin, J. (2015). Inorganic nanocarriers for platinum drug delivery. *Materials Today*, *18*(10), 554–564. https://doi.org/10.1016/j.mattod.2015.05.017

Makadia, H. K., & Siegel, S. J. (2011). Poly Lactic-co-Glycolic Acid (PLGA) as Biodegradable Controlled Drug Delivery Carrier. *Polymers*, *3*(3), 1377–1397. https://doi.org/10.3390/polym3031377

Masood, F. (2016). Polymeric nanoparticles for targeted drug delivery system for cancer therapy. *Materials Science and Engineering: C*, *60*, 569–578. https://doi.org/10.1016/j.msec.2015.11.067

McGoron, A. J. (2020). Perspectives on the Future of Nanomedicine to Impact Patients: An Analysis of US Federal Funding and Interventional Clinical Trials. *Bioconjugate Chemistry*, *31*(3), 436–447. https://doi.org/10.1021/acs.bioconjchem.9b00818

Mitchell, M. E., Billingsley, M. M., Haley, R. M., Wechsler, M. E., Peppas, N. A., & Langer, R. (2021c). Engineering precision nanoparticles for drug delivery. *Nature Reviews Drug Discovery*, *20*(2), 101–124. https://doi.org/10.1038/s41573-020-0090-8

Nevozhay, D., Kanska, U., Budzynska, R., & Boratyński, J. (2007). [Current status of research on conjugates and related drug delivery systems in the treatment of cancer and other diseases]. *PubMed*, *61*, 350–360. https://pubmed.ncbi.nlm.nih.gov/17554238

O. Elzoghby, A., M. Abd-Elwakil, M., Abd-Elsalam, K., T. Elsayed, M., Hashem, Y., & Mohamed, O. (2016). Natural Polymeric Nanoparticles for Brain-Targeting: Implications on Drug and Gene Delivery. Current Pharmaceutical Design, 22(22), 3305–3323. https://doi.org/10.2174/1381612822666160204120829

Peer, D., Karp, J. M., Hong, S., Farokhzad, O. C., Margalit, R., & Langer, R. (2007). Nanocarriers as an emerging platform for cancer therapy. *Nature Nanotechnology*, *2*(12), 751–760. https://doi.org/10.1038/nnano.2007.387

Pelicano, H., Martin, D. S., Xu, R., & Huang, P. (2006). Glycolysis inhibition for anticancer treatment. *Oncogene*, *25*(34), 4633–4646. https://doi.org/10.1038/sj.onc.1209597

Peng, H., Zhang, Y., Wang, G., Li, M., Bratlie, K. M., Cochran, E. W., & Wang, Q. (2015). Polymeric multifunctional nanomaterials for theranostics. *Journal of Materials Chemistry B*, *3*(34), 6856–6870. https://doi.org/10.1039/c5tb00617a

Rani, A., Asgher, M., Qamar, S. A., & Khalid, N. (2019). Nanostructure-mediated Delivery of Therapeutic Drugs -A Comprehensive Review. *ResearchGate*. https://www.researchgate.net/publication/335841976_Nanostructure-mediated_Delivery_of_Therapeutic_Drugs_-A_Comprehensive_Review

Sahu, T., Ratre, Y. K., Chauhan, S., Bhaskar, L. V., Nair, M., & Verma, H. K. (2021). Nanotechnology based drug delivery system: Current strategies and emerging therapeutic potential for medical science. *Journal of Drug Delivery Science and Technology*, *63*, 102487. https://doi.org/10.1016/j.jddst.2021.102487

Sahu, T., Ratre, Y. K., Chauhan, S., Bhaskar, L. V., Nair, M., & Verma, H. K. (2021). Nanotechnology based drug delivery system: Current strategies and emerging therapeutic potential for medical science. *Journal of Drug Delivery Science and Technology*, *63*, 102487. https://doi.org/10.1016/j.jddst.2021.102487

Samet, J. M., Chiu, W. A., Cogliano, V., Jinot, J., Kriebel, D., Lunn, R. M., Beland, F. A., Bero, L., Browne, P., Fritschi, L., Kanno, J., Lachenmeier, D. W., Lan, Q., Lasfargues, G., Curieux, F. L., Peters, S., Shubat, P., Sone, H., White, M. A., . . . Wild, C. P. (2020). The IARC Monographs: Updated Procedures for Modern and Transparent Evidence Synthesis in Cancer Hazard Identification.

Journal of the National Cancer Institute, *112*(1), 30–37. https://doi.org/10.1093/jnci/djz169

Sau, S., Agarwalla, P., Mukherjee, S., Bag, I., Sreedhar, B., Pal-Bhadra, M., Patra, C. R., & Banerjee, R. (2014). Cancer cell-selective promoter recognition accompanies antitumor effect by glucocorticoid receptor-targeted gold nanoparticle. *Nanoscale*, *6*(12), 6745. https://doi.org/10.1039/c4nr00974f

Sau, S., Alsaab, H. O., Kashaw, S. K., Tatiparti, K., & Iyer, A. K. (2017). Advances in antibody–drug conjugates: A new era of targeted cancer therapy. *Drug Discovery Today*, *22*(10), 1547–1556. https://doi.org/10.1016/j.drudis.2017.05.011

Sau, S., Tatiparti, K., Alsaab, H. O., Kashaw, S. K., & Iyer, A. K. (2018). A tumor multicomponent targeting chemoimmune drug delivery system for reprograming the tumor microenvironment and personalized cancer therapy. *Drug Discovery Today*, *23*(7), 1344–1356. https://doi.org/10.1016/j.drudis.2018.03.003

Shinde, S. J., Satpute, D. P., Behera, S. K., & Kumar, D. (2022). Computational Biology of BRCA2 in Male Breast Cancer, through Prediction of Probable nsSNPs, and Hit Identification. *ACS Omega*, *7*(34), 30447–30461. https://doi.org/10.1021/acsomega.2c03851

Sobhana, S., Sarathy, N. P., Karthikeyan, L., Shanthi, K., & Vivek, R. (2023). Ultra-small NIR-Responsive Nanotheranostic Agent for Targeted Photothermal Ablation Induced Damage-Associated Molecular Patterns (DAMPs) from Post-PTT of Tumor Cells Activate Immunogenic Cell Death. *Nanotheranostics*, *7*(1), 41–60. https://doi.org/10.7150/ntno.76720

Su, Y., Jiang, X. Y., Zheng, L. J., Yang, Y. W., Jiang, X. Y., Tian, Y., Weiwei, T., Liu, W. F., Teng, Z. G., Yao, H., Wang, S., & Zhang, L. J. (2022). Hybrid Au-starPrussian blue for high-performance towards bimodal imaging and photothermal treatment. *Journal of Colloid and Interface Science*, *634*, 601–609. https://doi.org/10.1016/j.jcis.2022.12.043

Tran, S., DeGiovanni, P., Piel, B., & Rai, P. (2017). Cancer nanomedicine: a review of recent success in drug delivery. *Clinical and Translational Medicine*, *6*(1). https://doi.org/10.1186/s40169-017-0175-0

Tsang, R. Y., Al-Fayea, T. M., & Au, H. (2009). Cisplatin Overdose. *Drug Safety*, *32*(12), 1109–1122. https://doi.org/10.2165/11316640-000000000-00000

Um, I. S., Armstrong-Gordon, E., Moussa, Y. E., Gnjidic, D., & Wheate, N. J. (2019). Platinum drugs in the Australian cancer chemotherapy healthcare setting: Is it worthwhile for chemists to continue to develop platinums? *Inorganica Chimica Acta*, *492*, 177–181. https://doi.org/10.1016/j.ica.2019.04.023

Verma, H. K. (2019). Exosomes facilitate chemoresistance in gastric cancer: Future challenges and openings. *Precision Radiation Oncology*, *3*(4), 163–164. https://doi.org/10.1002/pro6.1081

Wang, E., & Wang, A. H. (2014). Nanoparticles and their applications in cell and molecular biology. *Integrative Biology*, *6*(1), 9–26. https://doi.org/10.1039/c3ib40165k

Wang, Q., Alshaker, H., Böhler, T., Srivats, S., Chao, Y., Cooper, C., & Pchejetski, D. (2017). Core shell lipid-polymer hybrid nanoparticles with combined docetaxel and molecular targeted therapy for the treatment of metastatic prostate cancer. *Scientific Reports*, *7*(1). https://doi.org/10.1038/s41598-017-06142-x

Wang, X., Wang, X., & Guo, Z. (2015). Functionalization of Platinum Complexes for Biomedical Applications. *Accounts of Chemical Research*, *48*(9), 2622–2631. https://doi.org/10.1021/acs.accounts.5b00203

Wani, S. P., Kaul, D., Mavuduru, R., Kakkar, N., & Bhatia, A. (2017). Urinary-exosomal miR-2909: A novel pathognomonic trait of prostate cancer severity. *Journal of*

Biotechnology, *259*, 135–139. https://doi.org/10.1016/j.jbiotec.2017.07.029

Wheate, N. J., Walker, S., Craig, G. E., & Oun, R. (2010). The status of platinum anticancer drugs in the clinic and in clinical trials. *Dalton Transactions*, *39*(35), 8113. https://doi.org/10.1039/c0dt00292e

Wheate, N. J., Walker, S., Craig, G. E., & Oun, R. (2010b). The status of platinum anticancer drugs in the clinic and in clinical trials. *Dalton Transactions*, *39*(35), 8113. https://doi.org/10.1039/c0dt00292e

Wu, C., Zhou, X. S., & Wei, J. (2015). Localized Surface Plasmon Resonance of Silver Nanotriangles Synthesized by a Versatile Solution Reaction. *Nanoscale Research Letters*, *10*(1). https://doi.org/10.1186/s11671-015-1058-1

Wurm, F. R., & Weiss, C. K. (2014). Nanoparticles from renewable polymers. *Frontiers in Chemistry*, *2*. https://doi.org/10.3389/fchem.2014.00049

Xiao, H., Yan, L., Higbee-Dempsey, E., Song, W., Qi, R., Li, W., Huang, Y., Jing, X., Zhou, D., Ding, J., & Chen, X. (2018). Recent progress in polymer-based platinum drug delivery systems. *Progress in Polymer Science*, *87*, 70–106. https://doi.org/10.1016/j.progpolymsci.2018.07.004

Xiao, H., Yan, L., Higbee-Dempsey, E., Song, W., Qi, R., Li, W., Huang, Y., Jing, X., Zhou, D., Ding, J., & Chen, X. (2018b). Recent progress in polymer-based platinum drug delivery systems. *Progress in Polymer Science*, *87*, 70–106. https://doi.org/10.1016/j.progpolymsci.2018.07.004

Xiao, H., Yan, L., Higbee-Dempsey, E., Song, W., Qi, R., Li, W., Huang, Y., Jing, X., Zhou, D., Ding, J., & Chen, X. (2018c). Recent progress in polymer-based platinum drug delivery systems. *Progress in Polymer Science*, *87*, 70–106. https://doi.org/10.1016/j.progpolymsci.2018.07.004

Xu, Z., Wang, Z., Deng, Z., & Zhu, G. (2021). Recent advances in the synthesis, stability, and activation of platinum(IV) anticancer prodrugs. *Coordination Chemistry Reviews*, *442*, 213991. https://doi.org/10.1016/j.ccr.2021.213991

Zein, R., Sharrouf, W., & Selting, K. A. (2020). Physical Properties of Nanoparticles That Result in Improved Cancer Targeting. *Journal of Oncology*, *2020*, 1–16. https://doi.org/10.1155/2020/5194780

Zhang, C., Xu, C., Gao, X., & Wang, L. (2022b). Platinum-based drugs for cancer therapy and anti-tumor strategies. *Theranostics*, *12*(5), 2115–2132. https://doi.org/10.7150/thno.69424

Zhang, Q., Kuang, G., Zhang, L., & Zhu, Y. (2023). *Nanocarriers for platinum drug delivery*. *2*, 77–89. https://doi.org/10.1016/j.bmt.2022.11.011

Zhang, Q., Kuang, G., Zhou, D., Qi, Y., Wang, M., Li, X., & Huang, Y. (2020). Photoactivated polyprodrug nanoparticles for effective light-controlled Pt(iv) and siRNA codelivery to achieve synergistic cancer therapy. *Journal of Materials Chemistry B*, *8*(27), 5903–5911. https://doi.org/10.1039/d0tb01103g

Zhang, Q., Wang, X., Kuang, G., Yu, Y., & Zhao, Y. (2022). Photopolymerized 3D Printing Scaffolds with Pt(IV) Prodrug Initiator for Postsurgical Tumor Treatment. *Research*, *2022*. https://doi.org/10.34133/2022/9784510

Zhang, R., Hao, L., Chen, P., Zhang, G., & Liu, N. (2023). Multifunctional small-molecule theranostic agents for tumor-specific imaging and targeted chemotherapy. *Bioorganic Chemistry*, *137*, 106576. https://doi.org/10.1016/j.bioorg.2023.106576