



**Review article**

**Mitochondria Targeting using Lipophilic Cations for Effective Cancer Therapy**

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**Abstract**

Mitochondria play a pivotal role in maintaining redox balance, facilitating the initiation and propagation of cell death signalling pathways and aiding in the biosynthesis of biological macromolecules. Mitochondria modify metabolic pathways, support malignant growth and contribute to therapeutic resistance. The most effective way to deliver drugs specifically to mitochondria is by covalently linking them or the nanovehicles that carry them, to lipophilic cations such as alkyltriphenylphosphonium moiety. Some other delocalized lipophilic cations, such as rhodamine 123, Dequalinium chloride (DQA) mitochondrial penetrating peptide (MPPs), natural and synthetic mitochondria-targeting peptides, have also been used for mitochondrial delivery of small molecules. Mitochondrial targeting has been utilized to study mitochondrial physiology, dysfunction and its interaction with other subcellular organelles. Mitochondrial targeting has already emerged as a powerful strategy in cancer therapy which exploits the metabolic vulnerabilities and altered dynamics of cancer cells, with a distinct behavior in mitochondrial functions to survive and grow. The therapeutic delivery directly to mitochondria, has been aimed at disrupting the energy production, increasing the oxidative stress, and triggering apoptosis while sparing healthy tissues for effective treatment of a cancer. In this review, we summarize the utility of different mitochondrial targeting conjugates towards cancer treatment.

## Introduction

Cancer remains the second leading cause of death worldwide, and the global cancer burden is projected to rise substantially over the next two decades (Wu, Z., *et al*, 2024). Established methods for treating cancer include surgery, chemotherapy, and radiotherapy; however, these methods often lack the ability to target the diseased cells specifically and can cause severe harmful effects on healthy tissues (Leng, G., *et al*, 2024). Furthermore, the development of resistance to anti-cancer therapy by tumor cells remains a significant challenge to be addressed alongside the occurrence of metastasis, present a formidable obstacle to achieving successful treatment outcomes (Emran, T. B., *et al*, 2022). Therefore, there is an urgent need to develop therapeutic strategies that distinctly target tumor cells while minimizing off-target effects and damage to healthy tissues (Huang, L., *et al*, 2026). In this context, the development of nanoparticles has been a remarkable outcome to address long standing issues in cancer therapy. The nanoparticles are ultra-small engineered particles designed to bypass the limitations of traditional treatments. They act as drug delivery systems, zeroing in on tumor cells while sparing healthy tissues. This approach vastly reduces systemic toxicity and circumvents multi-drug resistance. Furthermore, the nanoparticle-mediated mitochondrial targeting has emerged as an innovative

strategy, as mitochondria represent highly promising therapeutic targets for precise and effective cancer treatment (Pandya, S. R., *et al*, 2024). Mitochondria are central to cellular energy metabolism, generating most of cellular ATP through oxidative phosphorylation (OXPHOS). These organelles play a crucial role in regulating reactive oxygen species (ROS), apoptosis, calcium regulation, and different biosynthetic pathways. This regulatory function underscores their essential role in maintaining cellular homeostasis (Figure1). In cancer, mitochondrial function is often profoundly altered, and it is reflected in the metabolic reprogramming which supports

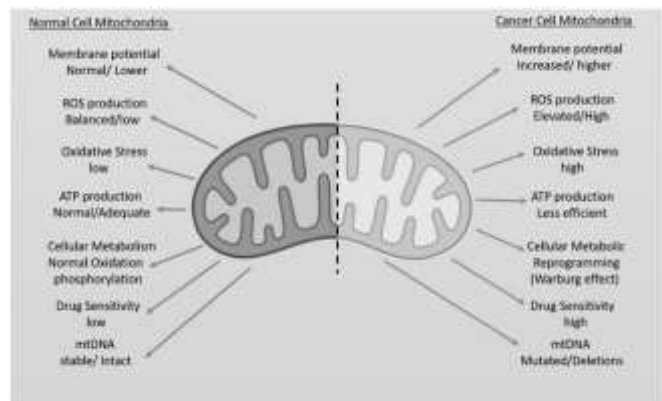


**Figure 1.** Differences between normal cell mitochondria and cancer cell mitochondria.

This is also concerned with the acquired resistance to therapy. These alterations play a crucial role in tumour progression and reduced responsiveness to standard therapies (Awad, A. M. A. M., & Abdul Karim, N., 2025). The procedures of chemotherapy began in the 1940s with the first uses of nitrogen mustards and antifolate drugs.

Although there has been a recent revolution of cancer drug generation for targeted therapy, the chemotherapy is still a major therapeutic approach for cancer treatment in the clinic (Chabner, B. A., & Roberts Jr, T. G., 2005). Several mechanisms have been proposed to explain how mitochondria contribute to chemoresistance wherein well-established mechanisms include alterations in mitochondrial metabolism, activation of anti-apoptotic pathways, changes in mitochondrial DNA, interplay with autophagy, inflammation etc. All these mechanisms are still being studied, and the field of cancer research is constantly providing, more research needed to understand how these mechanisms interact with each other, and how they can be targeted to overcome chemoresistance in cancer (Mukherjee, S., *et al*, 2023). Recent mitochondrial targeting methods have opened up new avenues for improving cancer detection and treatment. There are interesting research endeavours which mention that the developing conjugates using mitochondrial targeting agents like TPP (methyltriphenylphosphonium), dequaliniumchloride (DQA), mitochondrial targeting signal peptides (MTS) have been advantageous for the treatment of different cancer cell types (Figure 2). This review surveys mitochondria-targeting ligand modified agents for drug delivery application, the potential of this approach

and challenges for advancing cancer treatments.

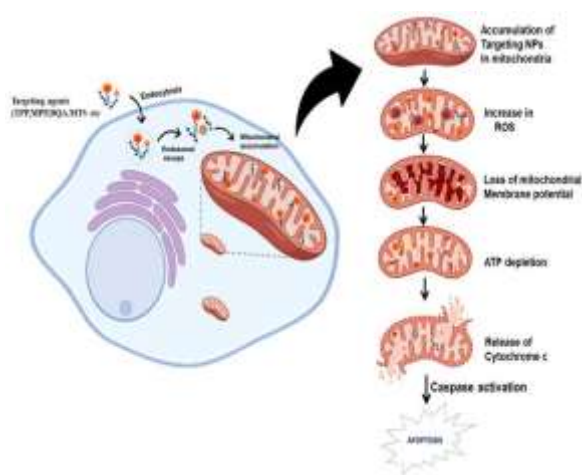


**Figure 2.** Mitochondrial targeting strategy for cancer therapy using targeted nanoparticles.

## 2. The mitochondria targeting strategy based on the lipophilic cations

The delocalized lipophilic cations (DLCs) are positively charged, membrane-permeable molecules that selectively accumulate within mitochondria driven by the organelle's natural negative-inside transmembrane potential. DLCs are heavily utilized in drug delivery and cancer therapy because they can be conjugated to therapeutics, peptides, or polymers. Delocalized lipophilic cations (DLCs), due to large hydrophobic surface areas and a delocalized positive charge, are readily absorbed through mitochondrial membranes. The lipophilic nature of DLCs allows for rapid passage through membrane bilayers, while the permanent cationic charge, leads to their accumulation inside the mitochondrial matrix driven by the negative membrane

potential (Chen, L. B., 1988). The mitochondrial membrane potential of tumor cells is more than that of normal cells. Based on the analysis of more than 200 cell lines/types of adenocarcinomas, melanoma, transitional cell carcinoma, squamous cell carcinoma, and normal epithelial cells, it was demonstrated in 1988 that cancer cells possess an elevated mitochondrial membrane potential in comparison to mitochondria in non-malignant cells (Johnson, L. V., *et al*, 1981). The most common DLCs are methyltriphenylphosphonium (TPP), dequaliniumchloride (DQA), Rhodamin123 (Rh123), and F16 (Figure 3).

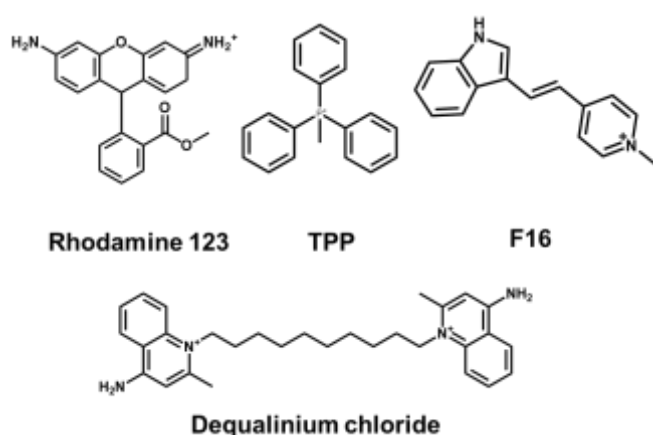


**Figure 3.** Structure of delocalised lipophilic cations (DLCs) (Chen, Z.P., *et al*, 2016).

### 2.1 Methyltriphenylphosphonium (TPP)

It is one of the most widely used delocalized lipophilic cations for mitochondrial targeting (Murphy, M. P., 1997). TPP features a positively charged phosphorus center connected by three hydrophobic phenyl

groups; which shows its lipophilic properties (Wu, H., *et al*, 2016). TPP has been extensively explored as a mitochondrial-targeting moiety for more than four decades. Its selective accumulation in mitochondria is driven by the highly negative inner mitochondrial membrane potential (approximately  $-180$  mV) (Zielonka, J., *et al*, 2017). TPP undergoes a multistep mitochondrial targeting process involving initial association with the outer mitochondrial membrane (OMM) crossing the inner mitochondrial membrane (IMM) and finally dissociating from IMM. Its cationic nature effectively allows for electrostatic interaction based targeting and preferential accumulation within the matrix which has a highly negative membrane potential relative to the cell membrane potential ( $-25$  mV) (Wang, H., *et al*, 2021). Several bioactive molecules have been conjugated with triphenylphosphonium (TPP<sup>+</sup>) to target mitochondria. A chemical combination of TPP<sup>+</sup> in nano-formulations has also been widely used to target mitochondria. For example, in a report by Biswas *et al.* paclitaxel-loaded liposomes functionalized with TPP<sup>+</sup>-modified polyethylene glycol-phosphatidylethanolamine (PEG-PE) (Figure 4a) have proven effective in targeting mitochondria in cancer cells (Biswas, S., *et al*, 2012). All these TPP<sup>+</sup>-modified nanovehicles demonstrated excellent anti-tumor effect and efficient mitochondrial

targeting in both in vivo and in vitro studies. Furthermore, TPP<sup>+</sup> has been used in the design of fluorogenic probes for the mitochondrial biomarker detection (Wang, B., *et al*, 2014, Fu, G., *et al*, 2021). Z Hu *et al.* derived methyl-functionalized derivatives (T\*PP<sup>+</sup>) of the drug carrier triphenyl phosphonium (TPP<sup>+</sup>) that exhibit significant enhancement of the accumulation of both the cation and its conjugated cargo in cell mitochondria. This represents in a (hexachloro-fluorescein) –TPP<sup>+</sup> conjugate system, where an ~12 times increase in the rate of mitochondrial uptake and 2 times increase in photodynamic therapy (PDT) efficacy against HeLa and FU97 cancer cells are achieved when TPP<sup>+</sup> is replaced with T\*PP<sup>+</sup> (Hu, Z., *et al*, 2017). Boddapati *et al.* conjugated TPP<sup>+</sup> to a non-polar stearyl residue to synthesize stearyl triphenyl phosphonium (Stearyl TPP<sup>+</sup>). This amphiphilic molecule was injected into the liposomal lipid bilayer to produce Stearyl TPP<sup>+</sup>-modified nanocarriers. This conjugation showed the efficient mitochondrial targeted delivery of ceramide to colon cancer cells followed by a robust apoptotic response (Boddapati, S. V., *et al*, 2008). Q. Ding *at el.* boosted the mitochondria-related ferroptosis and ICD for encouraging CBI in bladder cancer, for which a mitochondrial targeted and BQR-loaded liposome (BQR@MLipo) was developed by decorating with hexadecyltriphenylphosphonium bromide

(TPP). BQR@MLipo could also effectively prolong the duration of BQR in blood circulation and facilitate the accumulation of BQR into tumor tissues. On the other hand, after entering into the tumor cells, BQR@MLipo could selectively be accumulated within mitochondria due to the affinity of positive charged TPP with negative mitochondrial membrane, which led to enhancement of the inactivation of DHODH by BQR (Ding, Q., *et al*, 2023). Similarly, W Q Li *et al.* generated nature-inspired dopamine-derived polydopamine (PDA) nanoparticles. Using triphenylphosphonium (TPP) as the mitochondrial penetration molecule to improve the target efficiency, they synthesize poly-(ethylene glycol) (PEG)-modified PDA (PDA-PEG) and TPP functionalized PEG-modified PDA (PDA-PEG-TPP) nanoparticles. Then anticancer drug doxorubicin (DOX) was loaded on PDA-PEG and PDA-PEG-TPP (PDA-PEG-DOX and PDA-PEG-TPP-DOX) nanoparticles, which were apt to deliver DOX to cell nuclei and mitochondria, respectively. To mimic the repeated anticancer drug treatment procedures as in clinical cases, multiple treatments were made to MDAMD-231 cancer cells for a long-time using DOX-loaded nanoparticles and it was found that the mitochondria targeting PDA-PEG-TPP-DOX had higher potential to overcome the drug resistance than the regular delivery nanoparticles, PDA-PEG-DOX.

These results showed the promising potential of applying PDA-PEG-TPP-DOX nanoparticles in mitochondria-targeted drug delivery to overcome the drug resistance in long-time anticancer chemotherapy (Li, W. Q., *et al*, 2017). Jara, J. A. *et al*. synthesized Gallic acid ester derivatives (Figure 4b) which readily induced mitochondrial dysfunction. The compound ( $\text{TPP}^+\text{C}_{10}$ ) possessed 10 carbon atoms within the linker chain and demonstrated highest efficacy with  $\text{IC}_{50}$  value from 0.4-1.6  $\mu\text{M}$  for tumor cells and approximately 17-fold higher selectivity for tumor compared to normal cells. The compound stimulated oxygen consumption and NAD(P)H oxidation in the tumor cell lines (uncoupling effect), which reduced mitochondrial membrane potential  $\Delta\Psi_{\text{m}}$  and intracellular ATP levels. Furthermore,  $\text{TPP}^+\text{C}_{10}$  significantly inhibited the growth of TA3/Ha tumors in vivo (Jara, J. A., *et al*, 2014).

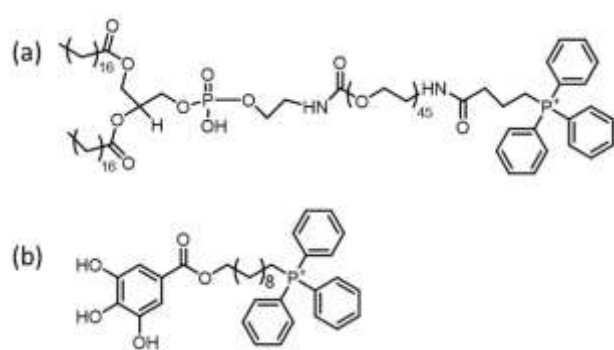


**Figure 4.** The representative TPP conjugate structures used for mitochondrial targeting strategy in cancer therapy. (Biswas, S., *et al*, 2012 and Jara, J. A. *et al*, 2014)

## 2.2 Dequalinium (DQA)

Dequalinium (DQA) is a lipophilic compound first described by Weiss *et al.* in 1987. It is made up of two cationic quinolinium moieties linked by an alkyl chain of ten carbons. It is a delocalized lipophilic cation that targets mitochondria (Weiss, M. J., *et al*, 1987). According to Weiss *et al*, this substance inhibited the proliferation of various cancer cell lines both in vitro and in vivo. The studies show that DQA can induce reactive oxygen species (ROS) by disrupting ATP synthesis which in turn causes cytochrome c expression and mitochondrial membrane potential depolarization. This mechanism activates the endogenous apoptosis pathway through caspase-9 and caspase-3 signaling (Sancho, P., *et al*, 2007). As a result, DQA's cytotoxicity restricts its use in numerous biological investigations, including cell biology research and fluorescent probes. But because of its cytotoxicity, DQA is also a potential drug delivery ligand for anti-cancer treatment. To transport Dox to mitochondria specifically, there are studies wherein DQA chloride has been coupled with Dox (DQA-Dox). The developed compound DQA-Dox demonstrated substantial cytotoxicity to cancer cells and was mostly observed to accumulate in the mitochondria of MCF-7/ADR cells. DQA's (dequalinium) limited endosomal escape and low transfection efficiency are intrinsic barriers that cause therapeutic payloads to remain trapped in

endosomes or lysosomes. This restricts its use as a standalone carrier in mitochondrial gene therapy, though it remains valuable for direct drug conjugation (Ali, M. S., *et al*, 2025). Wang et al. generated a dequalinium polyethylene glycol-distearoylphosphatidylethanolamine (DQA-PEG2000DSPE) conjugate as a mitochondriotropic molecule. Then mitochondrial targeting resveratrol liposomes were developed by modifying DQA-PEG2000-DSPE on the surface of liposomes for overcoming the cancer resistance (Wang, X. X., *et al*, 2011). The cellular uptake was increased by mitochondrial-targeting liposomes and accumulated into mitochondrial, which induced the apoptosis in both non-resistant and resistant cancer cells, which eventually enhanced the anticancer efficacy significantly. Similarly, Zhang et al. generated a kind of mitochondrial targeting daunorubicin plus quinacrine liposomes by physically mixing DQA with lipid components for treatment of breast cancer arising from the cancer stem cells (Zhang, L., *et al*, 2012). The results showed that these mitochondrial targeting liposomes evidently enhanced the mitochondrial uptake of drugs, selectively accumulated into mitochondria, activated the pro-apoptotic Bax protein, disrupted the mitochondrial membrane potential, opened the mitochondrial permeability transition pores, released cytochrome C by translocation, and initiated a cascade of caspase 9 and 3 reactions,

thereby induced apoptosis of MCF-7 cancer stem cells. The mitochondrial targeting liposomes showed the strongest efficacy in treating MCF-7 cancer cells in vitro, and the relapsed tumor in mice. Wang et al. developed functional doxorubicin (DOX) nanoparticles for targeted delivery of the classical cytotoxic anticancer drug DOX to tumor cells, using folate-terminated polytrioxanes along with DQA, which have been proven to be able to overcome the cancer resistance.

### **3. Mitochondrial targeting strategy based on peptides**

The strategies involving mitochondrial targeting peptide in cancer therapy utilise functional peptides to bypass barriers associated with complex cell membranes and directly deliver cytotoxic drugs, apoptosis-inducing sequences, or metabolic disruptors to the mitochondria of cancer cells. This approach exploits the enhanced negative mitochondrial membrane potential unique to cancer cells, which significantly reduces the damage to healthy tissues.

#### **3.1 Mitochondrial targeting signal peptides (MTS)**

The mitochondrial targeting signal peptides (MTS) have the capability to become a useful way for selective and effective delivery of therapeutic proteins to mitochondria. MTS have been successfully working for the mitochondrial delivery of various cargo molecules, including nucleic acids, proteins, and endonucleases (Yu, H.,

*et al*, 2013). Mitochondria-targeting peptides are typically lipophilic and carry a cationic charge which facilitates them to interact positively with hydrophobic mitochondrial membranes and promote mitochondrial accumulation due to mitochondrial highly negative membrane potential. Unlike traditional TPP and pyridinium salts, these peptides do not induce mitochondrial membrane depolarization even at millimolar concentrations. Furthermore, due to their excellent biocompatibility, they are suitable for treating diseases and for targeted drug delivery (Todaro, B., *et al*, 2023). Mitochondria-targeting peptides are designed to interact with specific receptors and proteins on the outer mitochondrial membrane, allowing them to exploit natural mitochondrial import mechanism. Therefore these targeting peptides facilitate selective mitochondrial accumulation (Boddapati, S. V., *et al*. 2008). Y Bae *et al*. reported that mitochondria targeting sequence (MTS)-hybrid cationic oligopeptide, MTS-H<sub>3</sub>R<sub>9</sub>, demonstrated dual functionality as both a mitochondrion targeting vector along with anticancer therapy agent. Compared with MTS alone, MTS-H<sub>3</sub>R<sub>9</sub> exhibited enhanced effectiveness in terms of greater cell-penetrating and internalization capabilities coupled with the effects of more efficient escape from lysosome to the cytosol. They showed efficient targeting of MTS-H<sub>3</sub>R<sub>9</sub> to mitochondria in HeLa cell line. Furthermore, upon accumulation within mitochondria,

MTS-H<sub>3</sub>R<sub>9</sub> triggered cancer cell death by reactive oxygen species generation and loss of mitochondrial membrane potential (Bae, Y., *et al*, 2019). Q Xiao *et al*. showed several new MTPs, which could be easily synthesized by resin-based solid-phase peptide synthesis. In particular, MTP3, consisting of three positively charged arginine and two D- and L- alternating naphthylalanines, was used as a mitochondria-targeting doxorubicin prodrug delivery system. This prodrug selectively accumulated in the mitochondria of cancer cells and released the active drug doxorubicin in response to intracellular glutathione (GSH). The released drug caused mitochondrial membrane depolarization, leading to cancer cell death. Importantly, prodrug exhibited strong anticancer activity against human tumor cells while showing very low toxicity toward normal cells. These findings suggested that MTP3 was a promising carrier for mitochondria-targeted drug delivery and that engineered cell-penetrating peptides can serve as effective tools for targeted cancer therapy (Xiao, Q., *et al*, 2021).

### 3.2 Mitochondria penetrating peptides

Mitochondria-penetrating peptides (MPPs) are emerging mitochondrial targeting ligands characterized by their short peptide sequences and high mitochondrial uptake efficiency. The structure of MPPs is commonly cationic and hydrophobic which

allows them to overcome membrane barriers and preferentially accumulate within the mitochondrial matrix (Lei, E. K., & Kelley, S. O. 2017, Fonseca, S. B., *et al*, 2011, Hidaka, T., *et al*, 2017). Due to their simple peptide structures and excellent biocompatibility, mitochondrial-penetrating peptides (MPPs) consisting fewer than 10 amino acids are expected to exhibit low cytotoxicity, making them attractive agents for the development of novel tools for mitochondrial investigation (Zhao, T., *et al*, 2019). J Yang *et al*. designed a mitochondria-penetrating peptide modified doxorubicin (MPP-Dox) loaded N-(2-hydroxypropyl) methacrylamide (HPMA) copolymer conjugates (PM), as well as a nuclear accumulating HPMA copolymer Dox conjugates (PN). After co-delivering of two organelle-targeted systems (PMN), PM induced cell apoptosis and inhibited tumor metastasis through damaging mitochondria, whereas PN suppressed cell proliferation and triggered apoptosis by destroying nucleus. Importantly, PM and PN demonstrated complementary effects. PN improved PM-induced mitochondrial dysfunction and tumor metastasis, whereas PM induced the suppression of cell proliferation and apoptosis by disrupting the nucleus of PN. As a result, tumor growth of breast cancer 4T1 cells in vivo was significantly inhibited and lung metastasis was markedly reduced and almost eradicated, highlighting the

benefits of organelle targeting combination therapy (Yang, J. *et al*, 2021).

#### **4. Conclusion**

Mitochondria-targeted drug delivery has emerged as a promising strategy for overcoming the limitations of conventional cancer therapeutics by selectively disrupting mitochondrial function, a key regulator of cellular metabolism, apoptosis, and redox homeostasis. Delocalized lipophilic cations, including triphenylphosphonium (TPP), rhodamine 123, dequalinium chloride (DQA), and mitochondrial penetrating peptides (MPPs), have demonstrated remarkable potential as mitochondrial targeting ligands owing to their ability to exploit the elevated mitochondrial membrane potential of cancer cells. These moieties have been successfully integrated into diverse nanocarriers to enhance mitochondrial accumulation of chemotherapeutic agents, photosensitizers, and nucleic acids, resulting in improved intracellular delivery, enhanced reactive oxygen species generation, mitochondrial membrane depolarization, ATP depletion, and activation of apoptosis pathways. Despite encouraging preclinical outcomes, several challenges remain, including limited tumor specificity, off-target accumulation, potential systemic toxicity, formulation complexity, and the need for scalable manufacturing processes. Future research should focus on developing multifunctional and stimuli-responsive mitochondrial-

targeted nanoplateforms capable of precise spatiotemporal drug release while minimizing adverse effects. Furthermore, comprehensive pharmacokinetic, toxicological, and clinical investigations are essential to bridge the gap between laboratory findings and clinical translation. Overall, delocalized lipophilic cations-mediated mitochondrial targeting represents a powerful and versatile approach with significant potential to improve the efficacy of cancer therapy and advance the next generation of precision nanomedicine.

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