CANCER THERAPY BY NANOMEDICINE/ NANOTECHNOLOGY

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ABSTRACT

Cancer is still one of the most deadly diseases in the world. Modern immunotherapies and conventional cancer medicines are non-tumor-targeted therapeutic techniques that result in several unwanted side effects since they are unable to discriminate malignant cells from healthy ones. Recent developments in nanotechnology, coupled with our expanding knowledge of cancer biology and nano-bio interactions, have sparked the creation of a number of nanocarriers that target tumour tissues, cells, or organelles specifically in an effort to increase therapeutic efficacy while lowering off-target toxicity of the encapsulated anticancer agents. Unfortunately, most nanocarriers lack the capacity to target hierarchically, and their therapeutic indices are frequently hampered by ineffective cellular internalisation, inadequate tumour accumulation, or incorrect subcellular localisation. In order to maximise therapeutic outcomes, this review summarises current and future approaches for designing cancer nanomedicines that target tumour tissue, cells, or organelles. It also highlights recent advancements in hierarchical targeting technologies, which enable these three stages of static tumour targeting to be dynamically integrated. In conclusion, we provide a brief overview of the present obstacles and forthcoming prospects for the clinical use of cancer nanomedicines.

KEYWORDS: Cancer, Nanoparticles, Treatment, Chemotherapy, Gene therapy

INTRODUCTION

Considering the millions of fatalities caused by cancer annually, it remains a serious public health problem.[1] The Greek physician Hippocrates is credited with coining the name "cancer" because of the finger-like extensions that grow from it that resemble crabs.[2] Galen, a different Greek physician, referred to tumours as "oncos," which meaning swelling.[3]Cancer has long been regarded as one of the most serious illnesses that might endanger human health, and cancer therapy is still one of the biggest obstacles facing scientific applications today.[4]

Therefore, there is an urgent need for effective medical therapies to lower the total cancer death rate. Many individuals have shown an improvement in survival when using traditional cancer therapies such radiation, chemotherapy, and surgery. They are not very effective in treating advanced metastatic tumours, though.[5]

The topic of cancer nanomedicine has seen significant growth in research over the last thirty years.[6,7]Different types of nanoparticles, including as lipid-based, polymeric, and inorganic nanoparticles, have been created to deliver therapeutic nucleic acids, immunotherapeutic drugs, or chemotherapeutic agents to tumours in a targeted manner. At least fifteen cancer nanomedicines are now licensed worldwide, and more than two hundred clinical trials are being conducted to assess over eighty new cancer nanomedicines. However, only ten candidates are now undergoing clinical trials; no actively targeted cancer nanomedicine has achieved regulatory clearance. With the help of recent developments in nanotechnology and our growing understanding of cancer biology and nano-bio interactions, a number of nanocarriers have been developed that can target tumour tissues, cells, and organelles specifically to increase therapeutic efficacy while reducing off-target toxicity.[8,9,10]

Rapid advancements in nanotechnology have made it possible to effectively synthesise a wide range of multifunctional agents at the nanoscale, which have enormous promise as nanomedicines for the detection, prevention, and treatment of illness. The use of nanocarrier-based drug delivery systems (NDDSs) has gained significant traction, particularly in the fields of cancer therapy. The Food and Drug Administration (FDA) has now authorised a variety of nano-formulations for the treatment of cancer in clinical studies. Examples of these include liposomal irinotecan (Onivyde) and paclitaxel albumin-bound nanoparticles (Abraxane). Engineered nanomedicine can selectively or even on-demand release its payload following precise stimulations at the tumour tissues, maximising the therapeutic benefit and minimising hazardous side effects. This is in contrast to molecular chemical medications, which lack specialised targeting capabilities.[11,12,13]

ORIGION AND HISTORY OF NANOMEDICINE

The first recorded instances of nanomedicine trace back to the usage of colloidal gold particles for therapeutic reasons in antiquity. Historical evidence indicates that colloidal gold particles were utilised for medical purposes in a number of ancient civilisations, indicating the long history of nanoparticle usage in medicine. Colloidal gold was used in ancient medical systems including Unani medicine, ancient Chinese Medicine (TCM), and Ayurveda. Colloidal gold is made up of minute gold particles floating in a liquid.[14]Historical medical literature from a variety of civilisations frequently describes processes for preparing drugs that included grinding or pulverising medicinal ingredients. Due to their historical focus on achieving certain particle sizes and consistencies for medicinal applications, these practices might be seen as early examples of nano-scale preparation techniques.[15]

The foundation of nanotechnology was established by Richard Feynman's seminal speech, "There's Plenty of Room at the Bottom," which was given in 1959 at the California Institute of Technology (Caltech). Feynman explored the possibility of atomic and molecular level matter manipulation in this lecture, speculating that it would be able to manipulate individual atoms and molecules to produce novel materials and technologies with extraordinary

capabilities. Nanotechnology emerged as a separate field of study as a result of scientists and researchers exploring the potential of working at the nanoscale, spurred by Feynman's innovative ideas. The idea of nanomedicine originated with the use of nanotechnology in the medical domain.

Indeed, the application of nanotechnology—which deals with materials and structures at the nanoscale scale, usually 1 to 100 nanometers—to medicine and healthcare is known as nanomedicine. It includes the creation, manufacture, characterisation, and use of nanomaterials, nanodevices, and nanoscale phenomena in medicine for prophylactic, therapeutic, and diagnostic objectives. Nanomedicine has great potential in tackling some of the persistent issues in healthcare, including customised treatment plans, early illness diagnosis, and focused medication delivery. Nanomedicine has the potential to transform many facets of healthcare delivery and enhance patient outcomes by using the special qualities of nanomaterials, such as their tiny size, high surface area-to-volume ratio, and programmable surface chemistry.

With continuous research and development activities aiming at converting nanotechnology-based breakthroughs into clinical applications, nanomedicine has undergone substantial evolution since Feynman's speech. The discipline of nanomedicine continues to expand our knowledge of disease causes and change the face of contemporary healthcare, from drug delivery systems and diagnostic nanoparticles to theranostic nanodevices and regenerative nanomedicine.[16]

The invention of doxorubicin-loaded liposomes for the treatment of breast cancer marked the beginning of nanoparticle-based cancer therapy. Dendrimers and polymers were later used. For targeted therapy and treatment effectiveness, solid lipid nanoparticles and siRNA molecules with various nanoparticles were created between 2000 and 2015, respectively.[17]Afterwards, quantum dots and gold nanoparticles were used in cancer treatment, particularly for bio-imaging. Better therapeutic outcomes are anticipated in the future with the use of nanobots.[18,19]Targeted nano-therapy has shown to be a more successful strategy than traditional anticancer treatments, with less toxicity and improved permeability and retention. It modifies biodistribution and lengthens the plasma half-life of nano-sized medications, which causes differentiable accumulation of nanoparticles in tumour tissues.[20]

LOGICAL DESIGN FOR CHEMOTHERAPY ENSURED BY NANOMEDICINE

Nanomedicines have enormous potential for cancer therapy because of their special physicochemical qualities. This is especially true when it comes to enhancing the effectiveness and reducing the side effects of traditional chemotherapy. With additional engineering, the NDDSs may be further developed into intelligent, multifunctional nanoplatforms that can react to in vivo or in vitro stimuli by reprogramming their inherent characteristics and engineering their surface functionalities. Furthermore, less than ideal clinical results would often result from the disruption of the tumour biological barrier, the intricate tumour microenvironment, and the inadequate absorption of traditional chemical therapeutic molecules, among other factors. To date, an increasing number of nano-agents, such as size/surface charge- or particle shape-transformable nanomedicines, have been

developed to increase the penetration of therapeutic agents to tumour locations.[21]Nanomedicines have proven to be promising drug delivery systems (DDSs) to specifically deliver elevated dosages of drugs into tumour tissues via EPR effects, thereby improving the therapeutic efficacy of tumour chemotherapy and reducing adverse reactions, despite the enhanced permeability and retention (EPR) effect being hotly debated recently.[22]

Nanoparticles for Tumor Targeting and Delivery

A range of materials, including polymers, dendrimers, liposomes, viruses, carbon nanotubes, and metals like iron oxide and gold, can be utilised to create nanoparticles that are employed to deliver anticancer drugs. Currently undergoing clinical trials or FDA approval, nearly all nanoparticle delivery technologies are based on polymers or liposomes.[23]

1. AUGMENTATION OF THE EPR EFFECT

One of the best ways to target a tumour site is through the EPR effect, and in mouse model systems, effective accumulation of nanoparticles at tumour sites is frequently reported. However, just 1% of human clinical investigations have shown that nanoparticulate delivery methods may effectively employ the EPR effect.[24]In reality, increased interstitial fluid pressure inhibits extravasation since the lymph system often progresses poorly in tumours. This impedes the targeted administration of a medication to the tumour location via nanoparticle systems utilising the EPR effect. Other approaches have been developed to improve the EPR effect in order to address this problem and enable the targeted accumulation of medicinal medicines at the locations of tumours. As was previously mentioned, overcoming the high interstitial fluid pressure at the tumour location is an effective delivery system strategy to permit extravasation. This pressure is typically 3–10 mm Hg in normal tissues, but it can reach 40–60 mm Hg in tumour tissue.[25]

Prostaglandin E1 was utilised by Salnikov et al. to regulate fluid pressure, and they observed a 40% increase in 5-FU accumulation in tumour locations.[26]Increasing systolic blood pressure is another tactic. Maeda et al. observed that angiotensin-induced hypertension chemotherapy resulted in enhanced tumour nanoparticle accumulation.[27]It is difficult to specifically regulate blood flow in the tumour vasculature, and using such techniques may have unfavourable systemic implications like a cardiovascular event.[28] A possible answer are nanoparticles that provide regulated release of vasodilators, or drugs that widen blood arteries. To increase the EPR effect, for instance, liposomes encapsulated with spontaneous nitric oxide (NO) releaser (NOC-18) have been studied.[29]Selective vasodilation in cancer neovasculatures is achieved by NOC-18's slow release of NO following liposome absorption by tumour locations through the EPR effect. As a result, medication accumulated more favourably and specifically at the locations of tumours. Similarly, to produce localised vasodilation and two to five times higher particle accumulation at tumour locations, researchers employed S-nitorosothiol-incorporated serum albumin as the macromolecular vasodilator.[30]

2. Carbon based Nanomaterials

Carbon-based nanomaterials (CNMs), with their high loading capacity, high surface-to-mass ratio, and capability to bind hydrophobic molecules through π–π interactions, make them attractive carriers for delivering medicines, genes, and proteins to particular places. Since the graphitic carbon structure gives CNMs a considerable absorption capacity in the near-infrared

spectrum (750–1000 nm for the NIR-I window and 1000–1700 nm for the NIR-II window), they also display unique optical features. Because of these characteristics, CNMs are desirable candidates for deep-tissue fluorescence imaging, photoacoustic imaging, and tumour photothermal treatment.[31] Moreover, CNMs have multifunctional surface chemistry, are immunogenicity-free, and are biocompatible. These characteristics make them a favoured choice for creating composites with high pharmaceutical efficiency, remarkable low toxicity, and targeting capabilities.[32]

Numerous studies have looked at the potential benefits of carbon nanotubes for cancer treatment. In particular, multiwall carbon nanotubes, or MWCNTs, have begun to attract more attention from scientists. As an illustration, Radzi et al. MWCNTs with acid functionalisation, and combined the particles with localised hyperthermia treatment. In tumours treated with hyperthermia treatment, the researchers saw a significant decrease in cell proliferation in comparison to the untreated tumour, along with an increase in Hsp70 expression. Together with a significant increase in tumor-infiltrating CD8+, CD4+ T cells, macrophages, and natural killer cells, the combination therapy also increased dendritic cell infiltration and maturation. Thus, the combination of MWCNTs with hyperthermia therapy is a potentially useful treatment approach for breast cancer.[33]

3. Metal based Nanoparticles

Due to a number of benefits, including their relatively narrow size and shape distribution, long activity period, potential for dense surface functionalisation, and capacity to remodel TME by transforming unfavourable conditions into therapeutically accessible ones, metallic nanoparticles have also attracted a lot of interest for the development of tumor-targeted systems.[34,35,36]In this regard, several in vitro and in vivo investigations have explored the application of metallic nanoparticles against various cancer types, taking advantage of their controlled-release capability under a variety of internal and external stimuli.[37,38,39,40]
To deliver doxorubicin to tumours in a pH-responsive manner, Jin et al.synthesised hollow silica nanoparticles modified with an aptamer and featuring a pollen structure. At a pH of five, the authors found an 87.5% release efficiency, and the unique spikes of the nanoconstruct served as "entry claws." In contrast to healthy cells, which internalised nearly no nanoparticles, target cells internalised more of the drug nanocarriers due to the improved connection between the two. Furthermore, these nanoplatforms' superior cell survival and biocompatibility make them suitable for targeted tumour treatment.[41]

As an alternative, a US-responsive drug release mechanism was created by Kim and colleagues. The researchers encapsulated polymeric phenyboronic acid using titanium dioxide nanoparticles coordinated with doxorubicin. The nanosystem as built demonstrated significant tumour accumulation and effective suppression of tumour development, enabling medication release via reactive oxygen species (ROS) produced during US irradiation. The promising outcomes of this sonodynamic chemotherapy indicate that the recently created particles could be a helpful treatment option for malignancies that are resistant to conventional treatments.[42]

Glucose was connected to liquid metal nanoparticles created by Ding et al. in the recent past. The nanoparticles were then mineralised using amorphous calcium carbonate and embellished with poly l-aspartic acid-grafted copolymer PEG-PAsp. The objective of the study was to combine photothermal treatment with adenosine triphosphate production inhibition to enhance tumour therapy. Following the breakdown of calcium carbonate at the tumour site, the suggested nanosystem might effectively oxidise glucose to produce hydrogen peroxide and gluconic acid, further driving calcium ions to impact mitochondrial activity towards a reduction in ATP generation.[43]

4. LIPOSOMES

One of the most studied structures for creating effective drug carriers is the liposome.[44]Because of their special design, which consists of an aqueous core and a phospholipid bilayer surrounding it, they may administer both hydrophilic and hydrophobic medications.[45]Other advantageous characteristics of liposomes include their biocompatibility, effective drug encapsulation, size controllability, and simplicity of functionalisation. PEGylation helps compensate for the short circulation half-life of liposomes, which is a known drawback. The potential to create multifunctional liposome-based nanoparticles with improved tumour site targeting is also made possible by the ease of surface modification.[46,47]

Wu et al. created liposomes modified with low molecular weight heparin and alendronate to deliver doxorubicin in this way. Heparin has the ability to increase liposome blood circulation time and demonstrate anti-metastasis efficacy, whereas alendronate serves as both a bone target and an antiosteoporosis therapeutic drug. The effectiveness of the nanosystem against orthotopic osteosarcoma and breast cancer bone metastases was demonstrated by its impressive decrease of tumour development and blockage of tumour metastasis. Furthermore, there is a great deal of practical potential for the liposomal formulation as proposed, as each part of the system has FDA approval.[48]

Large, anionic liposomes delivered intraperitoneally have the potential to target TAMs for the release of resiquimoid, according to a research by Kang et al. By means of this specific administration, the medication facilitated the infiltration of T cells and the activation of M1 macrophages, hence diminishing the proportion of Tregs in TME and augmenting the effectiveness of PD1 inhibition against syngeneic ovarian tumours. The scientists are optimistic that more liposomal nanovehicle optimisation might result in a therapeutically applicable strategy for improved immunotherapy for patients with ovarian cancer, based on these encouraging findings.[49]

5. CUBOSOMES

Another type of nanocarrier that shows promise for theranostic effectiveness is the cubosome.[50]These materials are three-dimensional, self-assembling structures in the bicontinuous cubic liquid crystalline phase that resemble honeycombs and have favourable features for creating cutting-edge delivery systems. Large interfacial area, a comparatively easy manufacturing process, the capacity to encapsulate hydrophobic, hydrophilic, and

amphiphilic moieties, biodegradability, and a targeted and controlled release of bioactive goods are some of these advantageous qualities. It follows that the use of cubosomes to create tumor-targeted vehicles with various internal cubic shapes, compositions, and drug-loading mechanisms has begun to garner growing scientific attention.[51,52,53]

Patil et al., for example, created inhalable cubosomes loaded with bedaquiline as nanomedicines against non-small cell lung cancer. The cubosomal formulation showed a persistent release pattern for 72 hours after an initial burst release in vitro. Nevertheless, cubosomes may experience endocytosis and enzymatic breakdown in vivo, which helps to release the medication more quickly. In vitro, these nanostructures were seen to exhibit improved anticancer efficacy when compared to free medicines, as well as reduce cell proliferation, colony formation, and cancer spread. Additionally, this formulation demonstrated a fast cell internalisation rate, an ideal aerodynamic diameter, and good deep lung deposition following nebulisation.[54]

Faria et al. presented an intriguing method in which they encapsulated elesclomol (ELC) into cubosomes based on monoolein and stabilised with Pluronic F127. Submicrometer-distance nanostructures collected near the mitochondria, causing ROS-mediated cytotoxicity. Additionally, the investigators examined the performance of cubosomes containing pre-complexed copper-ELC, noting enhanced cytotoxicity and encouraging characteristics for systemic delivery.[55]

6. Lipid Nanoparticles

Lipid nanoparticles provide attractive characteristics for developing tumor-targeting nanosystems with diverse uses, regardless of their form (solid-lipid nanoparticles, lipid-drug complexes, nanostructured lipid carriers, polymer-lipid conjugates, etc.).[56]Lipid nanoparticles provide a number of benefits, including as biocompatibility, biodegradability, bioavailable colloidal carriers, simplicity of synthesis using safe, straightforward methods, desired drug encapsulation, controlled and prolonged cargo release, and the potential for active targeting.[57,58]

Wang et al. created paclitaxel- and naringenin-loaded solid-lipid nanoparticles (SLNs) as a novel therapy for glioblastoma multiforme, taking into consideration their beneficial features. Furthermore, the authors functionalised the cyclic RGD peptide sequence (Arg-Gly-Asp) on the surface of SLNs. The sustained drug release behaviour of the nanocarrier was seen to be aided by its matrix structure, and the absorption of the nanosystem through paracellular and intercellular routes was made easier by its nano-size and lipohilic properties. As a result, the as-designed particles had stronger chemoprotective effects, increased oral bioavailability, improved cellular absorption, and higher toxicity than free medicines.[59]In a similar vein, Arduino and colleagues functionalised SLNs for the targeted release of paclitaxel by including a tumor-homing peptide, or iRGD. Additionally, improved cellular absorption, increased anticancer activity, and more effective tumour targeting and penetration were made possible by this surface alteration.[60]

Jang et al.'s second investigation showed that SLNs are appropriate camptothecin (CPT) carriers as well. Pegylated phospholipids were used to stabilise the nanoparticles before they were prepared for intravenous delivery. These nanomedicines demonstrated exceptional tumour targeting, extended circulation, and suppression of tumour development. Furthermore, the pre-injection of bare SLNs prior to drug-loaded particles decreased the accumulation of CPT-SLNs in tissues and organs rich in reticuloendothelial system, improving pharmacokinetic parameters, improving tumour targeting, and boosting the antitumor efficacy of CPT-encapsulated delivery systems, according to the researchers.[61]

7. Polymeric Nanoparticles

Researchers are becoming more interested in creating effective nanocarriers for a wide range of cargos due to the diversity and adaptability of polymers. Tumor-targeting vehicles may be realised with the help of polymeric-based nanoparticles, which have the beneficial ability to encapsulate, protect, and distribute various loads, such as active medicinal components, nucleic acids, imaging moieties, and other biomolecules.[62]Polymeric nanoparticles can reduce drug clearance, improve load stability and solubility, and extend the half-life of the transported agents by a variety of surface functionalisation methods, enabling ideal target site accumulation.[63]

Wang et al. have also addressed the possibilities of pH-responsive polymeric systems in more recent times. Using Mal-PAH-PEG-DMMA/poly (ethylene imine)—poly(ε-caprolactone) block polymers, the researchers created nanocarriers and filled them with IR825 photosensitiser and docetaxel. These intricate delivery methods improved photothermal conversion efficiency, boosted drug release in response to acidic environments and near-infrared light, and improved cellular absorption. In addition to demonstrating better safety and biocompatibility than either therapy alone, the combination chemo-photothermal therapy demonstrated more effective tumour ablation.[64]

Yakati et al. offered yet another cutting-edge medication delivery method in recent times. The scientists used PLGA nanoparticles functionalised with a tumor-homing peptide (CPKSNNGVC, or CPK for short) to encapsulate paclitaxel. These polymeric nanocarriers exhibit preferential cellular uptake and induce MCT1 receptor-overexpressing colorectal cancer cells to undergo apoptosis-mediated cell death. They can also target angiogenic endothelial cells and cancer cells that express the MCT1 receptor. Additionally, they prevent the growth of new blood vessels. The effects that have been mentioned also play a part in the cargo's prolonged release. The cargo profile exhibits an initial burst followed by a constant release over the analysis period of eight days.[65]

Dendrimers are a unique class of polymers that are being studied more and more in the development of tailored medication and gene delivery systems. Compared to traditional polymers, dendrimers have a distinct three-dimensional structure. Their size, functionality, and spherical form may all be precisely customised to meet the needs of individual applications. As a result, these unique nanomaterials enable covalent conjugation with a cleavable linker for TME-targeting or the encapsulation of desirable molecules inside their cavities.[66,67,68,69]

8. Virus-like and Virus- based Nanoparticles

Multimeric nanostructures known as virus-like particles (VLPs) have also piqued attention for targeted delivery approaches. They are made up of self-assembling, non-replicating, and non-contagious protein particles that resemble authentic, wild-type viruses but lack the whole viral genome, or only a portion of it. Because they don't have the potential to replicate, recombine, or go back to virulent phases, these nanoparticles are safe substitutes for developing medication and vaccine carriers.[70]

Liu and colleagues incorporated CRISPR/Cas9 technology and small molecule medicines into a lipid-coated mesoporous silica nanoparticle (MSN) core. The reductive TME caused the freight to be released, which in turn coordinated the regulation of several cancer-associated pathways and inhibited the formation of melanoma in vivo (Figure 11). The created method may serve as a general framework for developing synergistic treatments against a variety of malignant tumours as virus-like nanoparticles have the ability to co-deliver nearly any combination of sgRNAs and small molecule medications to tumours.[71]

A viable VLP-based approach was put out by Simons et al. The scientists engineered the bovine papillomavirus L1 protein to display surface docking sites and decorated it with peptides encoding T cell epitopes from two tumour antigens associated with prostate cancer as well as a neo-antigen stimulator of T cells that are specific to prostatic adenocarcinoma. This resulted in the creation of a VLP vaccine. In animal models of advanced prostate cancer, this therapy boosted the infiltration of CD3+ and CD8+ T cells into the tumour tissue while also considerably reducing the tumour burden.[72]

Recently, plant viruses have also been seen as a potential and safe substitute for medicine delivery.[73,74]Additionally, plant virus nanoparticles are being studied as immune adjuvants to improve the antitumor immune response since they have inherent immuno-stimulatory properties.[75]

9. EXOSOMES

Exosomes have been the subject of recent research as potential nanomaterials for cancer treatment and diagnostics. These nanostructures are naturally occurring particles that are released by different cells and taken up by recipient cells. Because of their special structural and compositional characteristics, these particles have minimal cytotoxicity, the capacity to cross biological barriers, and the ability to evade immune surveillance. Exosomes have the ability to cross cell membranes, release their cargo at the intended location, and stabilise encapsulated proteins, nucleic acids, or other therapeutic substances.[76]Exosomes can participate in a wide range of physiological processes because of the many protein molecules, nucleic acids, proinflammatory agents, cytokines, and transcription factor receptors that are present on the surface of the exosomal membrane.[77,78,79]

Wang and colleagues proposed the combination use of chemo/gene/photothermal treatment and designer exosomes, recognising the immense potential of these nanostructures. To enable responsive molecular imaging, the researchers coated exosomes with magnetic nanoparticles coupled with molecular beacons that may target miR-21. The exosomes were then loaded with doxorubicin. By using an external magnetic field to direct them to the tumour site, the nanocarriers generate localised hyperthermia and release the medication when exposed to near-infrared radiation. This combination therapy is a viable approach for creating next-generation precision cancer nanomedicines, since it was demonstrated to significantly reduce tumour size (97.57%).[77]

As an alternative, Zhou et al. developed an exosome-based delivery method to boost immunotherapy for pancreatic ductal adenocarcinoma and reverse the tumour immunosuppression of M2-like TAMs when the galectin-9/dectin 1 axis is disrupted. Exosomes of bone marrow mesenchymal stem cells were used to produce the platform, which was then surface-modified with an oxaliplatin prodrug and loaded with galectin-9 siRNA. The nanosystem demonstrated remarkable efficiency in targeting tumours and produced anticancer effects through the polarisation of tumor-suppressive macrophages, the recruitment of cytotoxic T cells, and the downregulation of Tregs.[80]

Huang and associates have recently used exosome technology in conjunction with lncRNA MEG3 to target tumours in osteosarcoma patients. In order to more successfully transport MEG3 to the target bone cancer cells both in vitro and in vivo, the authors specifically loaded MEG3 into exosomes that had been altered with the c(RGDyK) peptide. As a result, these systems show promise as osteosarcoma treatments.[81]

CONCLUSION

Cancer is a global health crisis that poses a significant challenge to the scientific community and sufferers alike. Currently, a number of adjuvant and conventional anticancer therapy are being employed in clinical practice, with varying degrees of efficacy. Regretfully, nevertheless, the majority of these therapy approaches could have serious side effects or inadequate therapeutic results.

Nanoparticle-based drug and gene delivery technologies provide significant potential for delivering therapeutic or diagnostic agents. However, due to inadequate technique, instability, biocompatibility, degradability, complex formulations, and a lack of standardisation, there are still problems with clinical applications. Furthermore, nanoparticle systems might exhibit unforeseen toxicity or inefficiency. In fact, despite their advantages over conventional therapies in mouse models, several systems have failed human trials because of unanticipated instability or a lack of tumor-specific targeting. The development of novel drug carrier materials and innovative techniques for assessment are essential elements in the ongoing progress of human tumour targeting.

Numerous materials have been studied: exosomes, carbon-based and metal-based nanomaterials, cubosomes, lipid nanoparticles, polymeric nanoparticles, virus-like and virus-based nanomaterials.

Various chemotherapeutic medicines, nucleic acids, imaging moieties, photosensitisers, photothermal agents, and other biomolecules may be efficiently and effectively delivered by these nanoparticles. Their delivery of their payload to the tumour site can be altered by means of diverse surface functionalizations, TME-response mechanisms, or innate targeting capabilities. Therefore, the use of tumor-targeting nanoparticles leads to increased therapeutic action, cancer cell penetration, and drug accumulation at the targeted region, resulting in increased cytotoxicity against tumour cells and minimal damage in healthy tissues.

In summary, tumor-targeting nanoparticles are a well researched subject whose application in clinical practice would herald a paradigm change in the management of cancer while concurrently permitting more aggressive and targeted therapies. However, as most of the present investigations have just reached the in vitro and in vivo testing stages, further study is needed to clarify the safety and efficacy of the produced nanosystems for human usage before going to the clinic.

References

1. Torre L. A. Siegel R. L. Ward E. M. Jemal A. Global Cancer Incidence and Mortality Rates and Trends—An Update. Cancer Epidemiol. Biomark. Prev. 2016;25(1):16–27.
2. Faguet G. B. A brief history of cancer: age-old milestones underlying our current knowledge database: a brief history of cancer. Int. J. Cancer. 2015;136(9):2022–2036.
3. Stathopoulos P. Galen's Contribution to Head and Neck Surgery. J. Oral Maxillofac. Surg. 2017;75(6):1095–1096.
4. Chabner BA, Roberts TG. Chemotherapy and the war on cancer. Nat Rev Cancer. 2005;5:65–72.
5. Gotwals, P. et al. Prospects for combining targeted and conventional cancer therapy with immunotherapy. Nat. Rev. Cancer 17, 286–301 (2017).
6. Bangham, A. D. & Horne, R. W. Negative staining of phospholipids and their structural modification by surface-active agents as observed in the electron microscope. J. Mol. Biol. 8, 660-IN610 (1964).
7. Folkman, J. & Long, D. M. The use of silicone rubber as a carrier for prolonged drug therapy. J. Surg. Res. 4, 139–142 (1964).
8. Shi, J., Kantoff, P. W., Wooster, R. &Farokhzad, O. C. Cancer nanomedicine: progress, challenges and opportunities. Nat. Rev. Cancer 17, 20–37 (2017).
9. Manzari, M. T. et al. Targeted drug delivery strategies for precision medicines. Nat. Rev. Mater. 6, 351–370 (2021).
10. Mitchell, M. J. et al. Engineering precision nanoparticles for drug delivery. Nat. Rev. Drug Discov. 20, 101–124 (2021).
11. Martin JD, Cabral H, Stylianopoulos T, Jain RK. Improving cancer immunotherapy using nanomedicines: progress, opportunities and challenges. Nat Rev Clin Oncol. 2020;17(4):251–66.
12. Yao VJ, D'Angelo S, Butler KS, Theron C, Smith TL, Marchiò S, Gelovani JG, Sidman RL, Dobroff AS, Brinker CJ, Bradbury ARM, Arap W, Pasqualini R. Ligand-targeted theranostic nanomedicines against cancer. J Control Release. 2016;240:267–86.

13. Zhou L, Wang H, Li Y. Stimuli-responsive nanomedicines for overcoming cancer multidrug resistance. Theranostics. 2018;8:1059–74.
14. Mohan Bhagyaraj S. and Oluwafemi O. S., Nanotechnology: The Science of the Invisible, in Synthesis of Inorganic Nanomaterials [Internet], Elsevier, 2018. [cited 2022 Oct 7], p. 1–18.
15. Klemm D. Cranston E. D. Fischer D. Gama M. Kedzior S. A. Kralisch D. et al., Nanocellulose as a natural source for groundbreaking applications in materials science: today's state. Mater. Today. 2018;21(7):720–748.
16. Bodunde O. P. Ikumapayi O. M. Akinlabi E. T. Oladapo B. I. Adeoye A. O. M. Fatoba S. O. A futuristic insight into a “nano-doctor”: a clinical review on medical diagnosis and devices using nanotechnology. Mater. Today Proc. 2021;44:1144–1153.
17. Senapati S. Mahanta A. K. Kumar S. Maiti P. Controlled drug delivery vehicles for cancer treatment and their performance. Signal Transduction Targeted Ther. 2018;3(1):7.
18. Quader S. Kataoka K. Nanomaterial-Enabled Cancer Therapy. Mol. Ther. 2017;25(7):1501–1513.
19. Alshehri S. Imam S. S. Rizwanullah M. Akhter S. Mahdi W. Kazi M. et al., Progress of Cancer Nanotechnology as Diagnostics, Therapeutics, and Theranostics Nanomedicine: Preclinical Promise and Translational Challenges. Pharmaceutics. 2020;13(1):24.
20. Vllasaliu D. Thanou M. Stolnik S. Fowler R. Recent advances in oral delivery of biologics: nanomedicine and physical modes of delivery. ExpetOpin. Drug Deliv. 2018;15(8):759–770.
21. Ding J, Chen J, Gao L, Jiang Z, Zhang Y, Li M, Xiao Q, Lee SS, Chen X. Engineered nanomedicines with enhanced tumor penetration. Nano Today. 2019;29:100800.
22. Fan W, Yung B, Huang P, Chen X. Nanotechnology for multimodal synergistic cancer therapy. Chem Rev. 2017;117:13, 566–638.
23. Qiu LY, Bae YH. Polymer architecture and drug delivery. Pharm Res. 2006;23:1-30.
24. Wilhelm S, Tavares AJ, Dai Q, Ohta S, Audet J, Dvorak HF, Chan WCW. 2016. Analysisof nanoparticle delivery to tumours. Nat Rev Mater. 1(5): 14
25. Omidi Y, Barar J. 2014. Targeting tumor microenvironment: crossing tumor interstitial fluid by multifunctional nanomedicines. Bioimpacts. 455–67.
26. Salnikov AV, Iversen VV, Koisti M, Sundberg C, Johansson L, Stuhr LB, Sjöquist M, Ahlstr öm H, Reed RK, Rubin K. 2003. Lowering of tumor interstitial fluid pressure specifically augments efficacy of chemotherapy. FASEB j.. 17(12):1756-1758.
27. Fang J, Nakamura H, Maeda H. 2011. The EPR effect: Unique features of tumor blood vessels for drug delivery, factors involved, and limitations and augmentation of the effect. Advanced Drug Delivery Reviews. 63(3):136-151.
28. Lewis AB, Freed MD, Heymann MA, Roehl SL, Kensey RC. 1981. Side effects of therapy with prostaglandin E1 in infants with critical congenital heart disease.. Circulation. 64(5):893-898.
Tahara Y, Yoshikawa T, Sato H, Mori Y, Zahangir MH, Kishimura A, Mori T, Katayama Y. Encapsulation of a nitric oxide donor into a liposome to boost the enhanced permeation and retention (EPR) effect. Med. Chem. Commun.. 8(2):415-421.

29. Kinoshita R, Ishima Y, Chuang VT, Nakamura H, Fang J, Watanabe H, Shimizu T, Okuhira K, Ishida T, Maeda H, et al. 2017. Improved anticancer effects of albumin-bound paclitaxel nanoparticle via augmentation of EPR effect and albumin-protein interactions using S-nitrosated human serum albumin dimer. Biomaterials. 140162-169.
30. Saleem J., Wang L.M., Chen C.Y. Carbon-Based Nanomaterials for Cancer Therapy via Targeting Tumor Microenvironment. Adv. Healthc. Mater. 2018;7:18,5-25.
31. Mohajeri M., Behnam B., Sahebkar A. Biomedical applications of carbon nanomaterials: Drug and gene delivery potentials. J. Cell. Physiol. 2019;234:298–319.
32. Radzi M.R.M., Johari N.A., Zawawi W.F.A.W.M., Zawawi N.A., Latiff N.A., Malek N.A.N.N., Wahab A.A., Salim M.I., Jemon K. In vivo evaluation of oxidized multiwalled-carbon nanotubes-mediated hyperthermia treatment for breast cancer. Mater. Sci. Eng. C. 2021:11,25-86.
33. Shang L., Zhou X., Zhang J., Shi Y., Zhong L. Metal Nanoparticles for Photodynamic Therapy: A Potential Treatment for Breast Cancer. Molecules. 2021;26:6532.
34. 62. Evans E.R., Bugga P., Asthana V., Drezek R. Metallic nanoparticles for cancer immunotherapy. Mater.Today. 2018;21:673–685.
35. Tinajero-Díaz E., Salado-Leza D., Gonzalez C., Martínez Velázquez M., López Z., Bravo-Madrigal J., Knauth P., Flores-Hernández F.Y., Herrera-Rodríguez S.E., Navarro R.E., et al. Green Metallic Nanoparticles for Cancer Therapy: Evaluation Models and Cancer Applications. Pharmaceutics. 2021;13:17-19.
36. Păduraru D.N., Ion D., Niculescu A.-G., Mușat F., Andronic O., Grumezescu A.M., Bolocan A. Recent Developments in Metallic Nanomaterials for Cancer Therapy, Diagnosing and Imaging Applications. Pharmaceutics. 2022;14:435.
37. Mohapatra A., Uthaman S., Park I.-K. External and Internal Stimuli-Responsive Metallic Nanotherapeutics for Enhanced Anticancer Therapy. Front. Mol. Biosci. 2021;7:437.
38. Liu D., Li J., Wang C., An L., Lin J., Tian Q., Yang S. Ultrasmall Fe@Fe3O4 nanoparticles as T1–T2 dual-mode MRI contrast agents for targeted tumor imaging. Nanomed. Nanotechnol. Biol. Med. 2021;32:102335.
39. Liu Y., Wu P.-C., Guo S., Chou P.-T., Deng C., Chou S.-W., Yuan Z., Liu T.-M. Low-toxicity FePt nanoparticles for the targeted and enhanced diagnosis of breast tumors using few centimeters deep whole-body photoacoustic imaging. Photoacoustics. 2020;19:100179.
40. Jin R., Wang J., Gao M., Zhang X. Pollen-like silica nanoparticles as a nanocarrier for tumor targeted and pH-responsive drug delivery. Talanta. 2021;231:122402.
41. Kim S., Im S., Park E.-Y., Lee J., Kim C., Kim T.-I., Kim W.J. Drug-loaded titanium dioxide nanoparticle coated with tumor targeting polymer as a sonodynamic chemotherapeutic agent for anti-cancer therapy. Nanomed. Nanotechnol. Biol. Med. 2020;24:102110.
42. Ding X.-L., Liu M.-D., Cheng Q., Guo W.-H., Niu M.-T., Huang Q.-X., Zeng X., Zhang X.-Z. Multifunctional liquid metal-based nanoparticles with glycolysis and mitochondrial metabolism inhibition for tumor photothermal therapy. Biomaterials. 2022;281:12,13-69.
43. Yousefi M., Shadnoush M., Sohrabvandi S., Khorshidian N., Mortazavian A.M. Encapsulation Systems for Delivery of Flavonoids: A Review. Biointerface Res. Appl. Chem. 2021;11:13934–13951.

44. Sabir F., Barani M., Randar A., Bilal M., Zafar M.N., Bungau S., Kyzas G.Z. How to Face Skin Cancer with Nanomaterials: A Review. Biointerface Res. Appl. Chem. 2021;11:11931–11955.
45. Alavi M., Hamidi M. Passive and active targeting in cancer therapy by liposomes and lipid nanoparticles. Drug Metab. Pers. Ther. 2019;34:20180032.
46. Belfiore L., Saunders D.N., Ranson M., Thurecht K.J., Storm G., Vine K.L. Towards clinical translation of ligand-functionalized liposomes in targeted cancer therapy: Challenges and opportunities. J. Control. Release. 2018;277:1–13.
47. Wu H., Luo Y., Xu D., Ke X., Ci T. Low molecular weight heparin modified bone targeting liposomes for orthotopic osteosarcoma and breast cancer bone metastatic tumors. Int. J. Biol. Macromol. 2020;164:2583–2597.
48. Kang Y., Flores L., Ngai H.W., Cornejo Y.R., Haber T., McDonald M., Moreira D.F., Gonzaga J.M., Abidi W., Zhang Y., et al. Large, Anionic Liposomes Enable Targeted Intraperitoneal Delivery of a TLR 7/8 Agonist To Repolarize Ovarian Tumors' Microenvironment. Bioconjug. Chem. 2021;32:1581–1592.
49. Chettupalli A.K., Ananthula M., Amarachinta P.R., Bakshi V., Yata V.K. Design, Formulation, In-Vitro and Ex-Vivo Evaluation of Atazanavir Loaded CubosomalGel. Biointerface Res. Appl. Chem. 2021;11:12037–12054.
50. Alavi M., Nokhodchi A. Micro- and nanoformulations of paclitaxel based on micelles, liposomes, cubosomes, and lipid nanoparticles: Recent advances and challenges. Drug Discov. Today. 2022;27:576–584.
51. Varghese R., Salvi S., Sood P., Kulkarni B., Kumar D. Cubosomes in cancer drug delivery: A review. Colloid Interface Sci. Commun. 2022;46:100561.
52. Bhosale R.R., Osmani R.A.M., Harkare B.R., Ghodake P.P. Cubosomes: The Inimitable Nanoparticulate Drug Carriers. Sch. Acad. J. Pharm. 2013;2:481–486.
53. Patil S.M., Sawant S.S., Kunda N.K. Inhalable bedaquiline-loaded cubosomes for the treatment of non-small cell lung cancer (NSCLC) Int. J. Pharm. 2021;607:121046.
54. Faria A.R., Silvestre O.F., Maibohm C., Adão R.M.R., Silva B.F.B., Nieder J.B. Cubosome nanoparticles for enhanced delivery of mitochondria anticancer drug elesclomol and therapeutic monitoring via sub-cellular NAD(P)H multi-photon fluorescence lifetime imaging. Nano Res. 2019;12:991–998.
55. Aghazadeh T., Bakhtiari N., Rad I.A., Ramezani F. Formulation of Kaempferol in Nanostructured Lipid Carriers (NLCs): A Delivery Platform to Sensitization of MDA-MB468 Breast Cancer Cells to Paclitaxel. Biointerface Res. Appl. Chem. 2021;11:14591–14601.
56. Alavi M., Nokhodchi A. Micro- and nanoformulations of paclitaxel based on micelles, liposomes, cubosomes, and lipid nanoparticles: Recent advances and challenges. Drug Discov. Today. 2022;27:576–584.
57. Mohamed M.I., Kassem M.A., Khalil R.M., Younis M.M., Danvish A.B., Salama A., Wagdi M.A. Enhancement of the Anti-inflammatory Efficacy of Betamethasone Valerate via Niosomal Encapsulation. Biointerface Res. Appl. Chem. 2021;11:14640–14660.
58. Wang L., Wang X., Shen L., Alrobaian M., Panda S.K., Almasmoum H.A., Ghaith M.M., Almaimani R.A., Ibrahim I.A.A., Singh T., et al. Paclitaxel and naringenin-loaded solid lipid nanoparticles surface modified with cyclic peptides with improved tumor targeting ability in glioblastoma multiforme. Biomed. Pharmacother. 2021;138:111461.

59. Arduino I., Liu Z., Iacobazzi R.M., Lopedota A.A., Lopalco A., Cutrignelli A., Laquintana V., Porcelli L., Azzariti A., Franco M., et al. Microfluidic preparation and in vitro evaluation of iRGD-functionalized solid lipid nanoparticles for targeted delivery of paclitaxel to tumor cells. Int. J. Pharm. 2021;6,10:121-246.
60. Jang D.-J., Moon C., Oh E. Improved tumor targeting and antitumor activity of camptothecin loaded solid lipid nanoparticles by preinjection of blank solid lipid nanoparticles. Biomed. Pharmacother. 2016;80:162–172.
61. Grewal I.K., Singh S., Arora S., Sharma N. Polymeric Nanoparticles for Breast Cancer Therapy: A Comprehensive Review. Biointerface Res. Appl. Chem. 2021;11:11151–11171.
62. Niculescu A.-G., Grumezescu A.M. Polymer-Based Nanosystems—A Versatile Delivery Approach. Materials. 2021;14:68-72.
63. Wang X., Gu Y., Li Q., Xu Y., Shi Y., Wang Z., Xia M., Li J., Wang D. Synergistic chemo-photothermal cancer therapy of pH-responsive polymeric nanoparticles loaded IR825 and DTX with charge-reversal property. Colloids Surf. B Biointerfaces. 2022;209:112-164.
64. Yakati V., Vangala S., Madamsetty V.S., Banerjee R., Moku G. Enhancing the anticancer effect of paclitaxel by using polymeric nanoparticles decorated with colorectal cancer targeting CPKSNNGVC-peptide. J. Drug Deliv. Sci. Technol. 2022;68:103-125.
65. Sharma R., Liaw K., Sharma A., Jimenez A., Chang M., Salazar S., Amlani I., Kannan S., Kannan R.M. Glycosylation of PAMAM dendrimers significantly improves tumor macrophage targeting and specificity in glioblastoma. J. Control. Release. 2021;337:179–192.
66. Liaw K., Sharma R., Sharma A., Salazar S., Appiani La Rosa S., Kannan R.M. Systemic dendrimer delivery of triptolide to tumor-associated macrophages improves anti-tumor efficacy and reduces systemic toxicity in glioblastoma. J. Control. Release. 2021;329:434–444.
67. Sharma A., Liaw K., Sharma R., Spriggs T., Appiani La Rosa S., Kannan S., Kannan R.M. Dendrimer-Mediated Targeted Delivery of Rapamycin to Tumor-Associated Macrophages Improves Systemic Treatment of Glioblastoma. Biomacromolecules. 2020;21:5148–5161.
68. Mignani S., Shi X., Ceña V., Rodrigues J., Tomas H., Majoral J.-P. Engineered non-invasive functionalized dendrimer/dendron-entrapped/complexed gold nanoparticles as a novel class of theranostic (radio)pharmaceuticals in cancer therapy. J. Control. Release. 2021;332:346–366.
69. Suffian I.F.B.M., Al-Jamal K.T. Bioengineering of virus-like particles as dynamic nanocarriers for in vivo delivery and targeting to solid tumours. Adv. Drug Deliv. Rev. 2022;180:114030.
70. Liu Q., Wang C., Zheng Y., Zhao Y., Wang Y., Hao J., Zhao X., Yi K., Shi L., Kang C., et al. Virus-like nanoparticle as a co-delivery system to enhance efficacy of CRISPR/Cas9-based cancer immunotherapy. Biomaterials. 2020;258:120-275.
71. Simons B.W., Cannella F., Rowley D.T., Viscidi R.P. Bovine papillomavirus prostate cancer antigen virus-like particle vaccines are efficacious in advanced cancers in the TRAMP mouse spontaneous prostate cancer model. Cancer Immunol. Immunother. 2020;69:641–651.
72. Alemzadeh E., Dehshahri A., Dehghanian A.R., Afsharifar A., Behjatnia A.A., Izadpanah K., Ahmadi F. Enhanced anti-tumor efficacy and reduced cardiotoxicity of doxorubicin delivered in a novel plant virus nanoparticle. Colloids Surf. B Biointerfaces. 2019;174:80–86.

73. Chung Y.H., Cai H., Steinmetz N.F. Viral nanoparticles for drug delivery, imaging, immunotherapy, and theranostic applications. Adv. Drug Deliv. Rev. 2020;156:214–235.
74. Bahardoust M., Baghoi-Hosseinabadi Z. Role of Adipose-Derived Mesenchymal Stem Cells in the Regeneration of Cardiac Tissue and Improvement of Cardiac Function: A Narrative Review. Biointerface Res. Appl. Chem. 2021;11:8446–8456.
75. Wang J., Chen P., Dong Y., Xie H., Wang Y., Soto F., Ma P., Feng X., Du W., Liu B.-F. Designer exosomes enabling tumor targeted efficient chemo/gene/photothermal therapy. Biomaterials. 2021;276:12,10-56.
76. Kwon S.-H., Faruque H.A., Kee H., Kim E., Park S. Exosome-based hybrid nanostructures for enhanced tumor targeting and hyperthermia therapy. Colloids Surf. B Biointerfaces. 2021;205:11,1,9-15.
77. Zhang F., Guo J., Zhang Z., Qian Y., Wang G., Duan M., Zhao H., Yang Z., Jiang X. Mesenchymal stem cell-derived exosome: A tumor regulator and carrier for targeted tumor therapy. CancerLett. 2022;526:29–40.
78. Zhou W., Zhou Y., Chen X., Ning T., Chen H., Guo Q., Zhang Y., Liu P., Zhang Y., Li C., et al. Pancreatic cancer-targeting exosomes for enhancing immunotherapy and reprogramming tumor microenvironment. Biomaterials. 2021;268:120,5-46.

79. Huang X., Wu W., Jing D., Yang L., Guo H., Wang L., Zhang W., Pu F., Shao Z. Engineered exosome as targeted lncRNA MEG3 delivery vehicles for osteosarcoma therapy. J.Control.Release. 2022;343:107-117.