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Review Article

The Combination of Cutting-edge Strategies in Nano-delivery Systems to Overcome Drawbacks for Malignant Tumor Treatment

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Abstract

The advent of nanoparticle technology has transformed oncology therapeutics through its capacity for accurate drug delivery and regulated pharmaceutical release, boosting treatment effectiveness while minimizing adverse reactions. Various nanostructures, including polymeric carriers, liposomal formulations, and metal-based nanoparticles, can be engineered with tumor-specific targeting molecules to facilitate cellular uptake in malignant cells. Despite these advancements, issues such as production scalability, potential chronic toxicity, and regulatory approval processes still need to be addressed. Viral nanoparticles and virus-like particles (VLPs) represent innovative tools in nanotechnology and biomedicine, offering exceptional potential for targeted therapies, immune modulation, and diagnostic applications. Their natural biocompatibility, precise structural organization, and capacity for surface modification make them highly suitable for developing strategies to treat malignant tumors. Alongside VLP development, other approaches have also been investigated, such as magnetic hyperthermia, where magnetic nanoparticles are used to generate localized heat under an external magnetic field, selectively destroying cancer cells while sparing healthy tissue. This paper presents a brief review of nanocarriers in drug delivery systems and discusses the integration of nanoparticles, viral nanoparticles, and VLPs. Additionally, we explore the challenges and propose cutting-edge solutions, offering a forward-looking perspective on how the combination of these advanced technologies could transform oncology.

Introduction

Nanotechnology applies engineering principles such as electronics and materials, as well as physical science, to fabricating materials at the molecular level, which can be devices, systems, or supramolecular structures with dimensions ranging from 0.1 to 100 nm. Nanotechnology has brought significant advances in medical applications, gene therapy, drug delivery, imaging, and techniques for new approaches to drug therapies.[1,2] In terms of drug delivery, several nano-delivery systems for small molecules, proteins, and DNA have been developed. Physicochemical properties of nanostructures allow them to cross cellular and tissue barriers, making them promising materials for biomedical applications.[3] In the field of cancer research, the problems associated with therapeutic agents involve bioavailability, biodistribution, degradation, elimination, and elimination of the biological activity of nanoparticles and their structures.[4]

In addition, classical and target-directed drugs can kill both healthy and malignant cells, leading to strong side effects.[5] Drug delivery mediated by nanoparticles represents an improvement over conventional methods, enhancing the selective delivery to the target cancer cells, which has already been achieved for several chemotherapeutic drugs.[6] There are still challenges related to nanodelivery of antitumor drugs concerning instability in the biological tract and loss of drugs due to rapid degradation. The tumor-targeting efficiency of nanoparticles is related to several physicochemical, biochemical, and biological features, and the interaction with the cellular surface of the target cells is one of those.

The cellular uptake of nanoparticles is divided into endocytosis-mediated internalization and direct intracellular entry. The first strategy involves endocytosis mediated by clathrin, caveolin,

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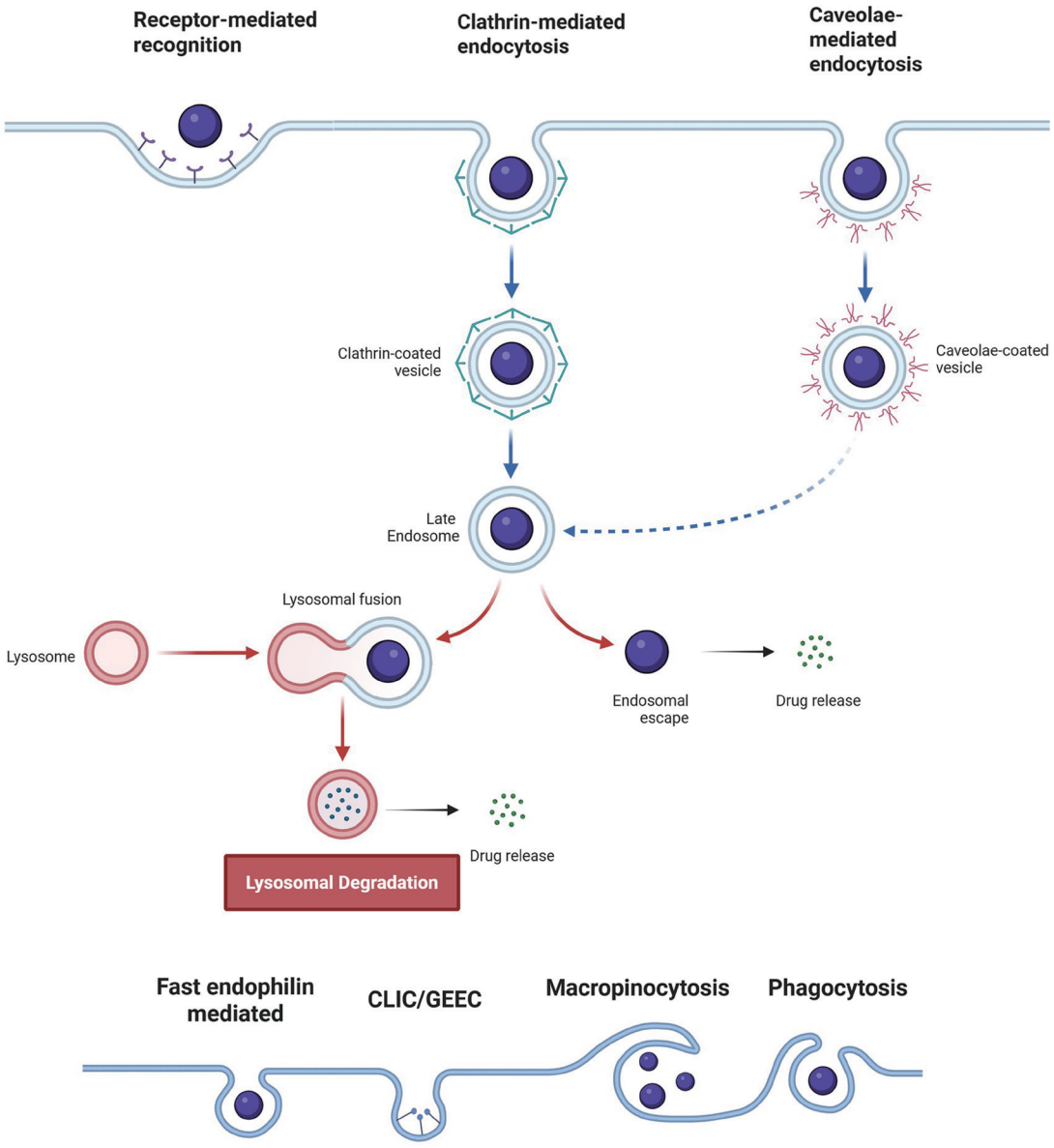

Fig. 1. Nanoparticles endocytosis – In receptor-mediated endocytosis NPs ligands are recognized by cell receptors activating the endocytic pathway, what occurs for clathrin, caveolin, fast endophilin mediated endocytosis, CLIC/GEEC and phagocytosis, while macropinocytosis is not initiated by the binding of specific cargo molecules to receptors on the cell surface. Instead, it involves the non-selective uptake of extracellular fluid and its contents through the formation of large membrane structures and subsequent engulfment. After internalization the NPścargo can be released through endosomal or lysosomal escape. CLIC, clathrin-independent carriers; GEEC, glycosylphosphatidylinositol-anchored protein-enriched endocytic compartment; NPs, nanoparticles.

phagocytosis, and macropinocytosis,[7] while the direct intracellular entry involves lipid fusion and translocation.[8] In addition, artificial strategies such as electroporation and microinjection achieve limited use due to induced deformation of the membrane structure and its destruction.[9] Receptor-mediated endocytosis involves the interaction between surface receptor proteins of the cell with target molecules present on the nanoparticle surface. This interaction leads to the activation of the endocytic pathway, with the nucleation of cytosolic proteins within the nanoparticle entry site, generating a coated pit, followed by an invagination process that will create an intracellular vesicle carrying the nanoparticles (Fig. 1). There are five types of receptor-mediated endocytosis: clathrin-dependent endocytosis, clathrin-independent endocytosis (endophilin-mediated/dynamin-dependent and glycosylphosphatidylinositol-anchored protein-enriched endocytic compartment (GEEC), macropinocytosis, phagocytosis, and caveolin-dependent endocytosis.[7] Clathrin is a protein involved in the formation of a polyhedral lattice in the cell membrane, which forms a coated cavity as the membrane invaginates to create a vesicle during specific endocytic pathways.[10] In clathrin-dependent endocytosis, the nanoparticles bind to cell membrane receptors, e.g., epidermal growth factor receptors. After the formation of the clathrin-coated cavity consisting of receptor-bound nanoparticles within the cavity and the invagination of the cell membrane, the cell membrane's break-

down forms an intracellular vesicle able to entrap nanoparticles of □100 nm in size.[11] The endocytosed nanoparticles are then extracted from the vesicles, where they can reach their target.

In caveolin-mediated endocytosis, this protein that generates the coated vesicles also follows receptor-mediated binding of nanoparticles, generating flask-shaped membrane invaginations known as caveolae.[12] Both clathrin- and caveolin-mediated endocytosis need to constrict and cut the plasma membrane to generate the intracellular vesicles. Dynamin, a GTPase, is thought to perform this role by forming spiral polymers. Even though there are several works showing that this is true for clathrin,[13] serious doubts have been raised regarding dynamin's role in caveolin-mediated endocytosis.[14]

Clathrin- and caveolin-independent endocytosis (Fig. 1) utilizes lipid rafts, structures composed of cholesterol and sphingolipids found in the cell membrane, which are capable of being endocytosed.[15] Endophilin-mediated endocytosis is initiated by cell surface ligand-receptor interaction and is modulated by endophilin A2 recruitment and actin polymerization. The cutting of the membrane neck to generate the vesicles is also dependent on dynamin.[11] GEEC endocytosis, on the other hand, is clathrin- and dynamin-independent, utilizing extracellular galectin proteins, glycoproteins, and glycolipids for vesicle formation and loading. GEEC endocytic vesicles are capable of transporting cargo up to 100 nm in size, whereas vesicles formed during the endophilin-mediated/dynamin-dependent endocytosis pathway transport cargo approximately 60–80 nm in size.[11]

Phagocytosis of nanoparticles can be instigated through interaction with receptors of phagocytic cells such as polymorphonuclear neutrophils, monocytes, and macrophages, but also by non-professional phagocytes, such as Fc receptors and complement receptors.[16,17] Phagocytosis can be utilized for the cellular uptake of larger cargoes, typically exceeding 200 nm, and can therefore facilitate the uptake of larger nanoparticles.[11] Components of the immune system, such as immunoglobulins and complement proteins, are responsible for identifying and removing nanoparticles by phagocytes through opsonization and adsorption onto the nanoparticle surface. When nanoparticles are phagocytosed, they are contained in phagosome vesicles that, in turn, fuse with a lysosome, thus forming the phagolysosome. On the other hand, macropinocytosis is not initiated by the binding of specific cargo molecules to receptors on the cell surface. Instead, it involves the non-selective uptake of extracellular fluid and its contents through the formation of large membrane structures mediated by actin filaments and subsequent engulfment of the molecules interacting with the cell membrane.[18]

Once nanoparticles are endocytosed, the endocytic vesicle becomes the early endosomal compartment that matures into a late endosome that fuses with the lysosome. Due to the enzymatic nature of the lysosomal content, this may lead to degradation of the nanoparticle cargo, reducing therapeutic efficiency. To reduce this effect and ensure the delivery of active therapeutic cargo, a common strategy is an event called lysosomal escape, which uses the proton sponge effect, where nanoparticles induce an influx of ions into the lysosome, leading to swelling and rupture.[19] Other strategies include pH-sensitive linkers that degrade under the acidic conditions of the lysosome, favoring the release of therapeutics into the cytoplasm; and the addition of peptides that promote fusion with the lysosomal membrane and subsequent release of the drug.[20] On the other hand, if the cargo is released from the endosome into the cytoplasm (endosomal escape), the release of the cargo from nanoparticles in the cytosol results in intact therapeutic release, maintaining its bioactivity.[21]

In addition to the engineered synthetic nanoparticles that possess their own advantages and drawbacks (Fig. 2), this technology also takes advantage of nanoparticles of natural origin, such as viral nanoparticles (VNPs). As with synthetic nanoparticles, VNPs are also subject to endocytic pathway entry. In particular, virus-like particles (VLPs) (a subgroup of VNPs) have become a versatile platform that can be explored to solve a variety of problems that arise with the use of synthetic nanocarriers, including biocompatibility and sharper targeting of tumor cells. This class of nanoparticles also has its own issues regarding drug delivery, encapsulation, scalability, stability, and immune response. Studies on the application of both synthetic and natural nanoparticles to treat tumors where conventional and targeted therapy have failed have been increasing at an exponential rate. This review addresses the combination of several nanocarriers with different therapeutic strategies to improve the anticancer response of patients, discusses the main drawbacks, and the innovative solutions to achieve maximum efficiency.

Cancer

Cancer is a major public health problem worldwide and is one of the most prevalent malignant diseases that cause morbidity and mortality.[22] Traditional methods of cancer treatment include surgical resection, chemotherapy, and radiotherapy. Immunotherapy and photothermal therapy have also emerged recently.[23,24] Chemotherapeutic drugs have several types of mechanisms, including affecting the chemical structure of DNA, inhibiting nucleic acid synthesis, acting on nucleic acid transcription and DNA replication, and interfering with mitotic tubulin synthesis.[25] However, these drugs do not distinguish between healthy and malignant cells, leading to side effects during treatment. In addition, conventional drugs for this type of treatment have several problems, such as drug solubility in aqueous media, biodistribution, short half-life, and the resistance of these drugs over time.[26]

Several types of nanoparticles, including liposomes, polymeric nanoparticles (PNPs), solid lipid nanoparticles (SLNs), dendrimers, silica-based materials, and magnetic nanoparticles, constitute an improvement in drug delivery to cancer cells, increasing treatment efficacy and minimizing side effects.[27] Thus, the binding of these drugs to nanoparticles currently presents great advantages, such as targeting the drug to the proper tumor cell (active targeting). Active targeting utilizes molecular recognition: ligands, such as aptamers or monoclonal antibodies, are conjugated to nanocarriers, enabling them to specifically bind to receptors that are overexpressed on the surface of cancer cells. This effect enables the administration of the medication to be more precise and reduces unwanted side effects. On the other hand, passive targeting leverages the enhanced permeability and retention effect,[28] a consequence of the fact that tumor vasculature tends to be leaky and lacks adequate lymphatic drainage, allowing nanoparticles, such as liposomes or polymeric micelles, to accumulate more easily in tumor tissues than in healthy tissues. We can combine both strategies, with passive targeting ensuring that nanocarriers reach the general tumor area, while active targeting enhances targeting down to the cellular level.[28] We have several examples, such as in the case of achieving selective drug accumulation in tumor tissues through antibody-mediated binding, like monoclonal antibodies (trastuzumab) that can guide nanoparticles to human epidermal growth factor receptor-2 (HER2)-positive breast cancer cells,[29] or even the evolution of cancer-targeting therapies (the development

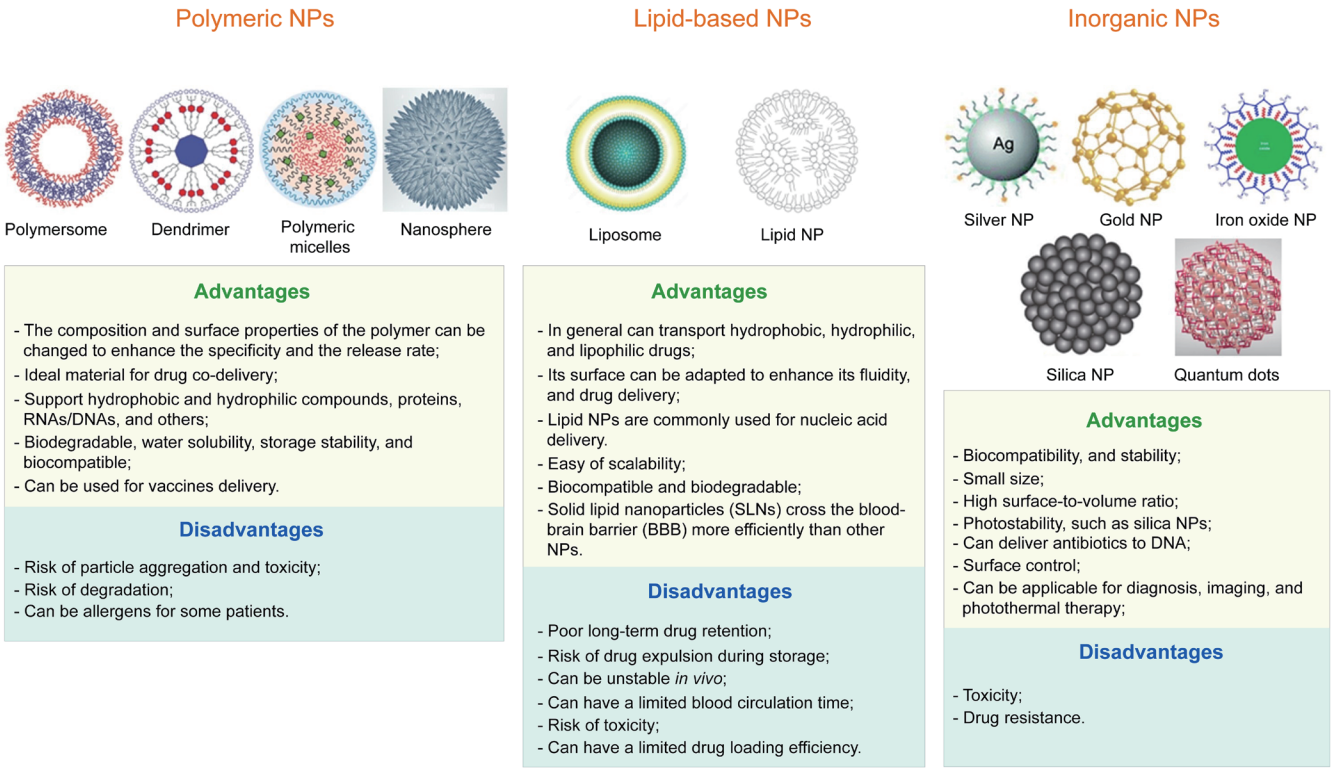

Fig. 2. Types of nanoparticles (NPs) for use in drug delivery, as well as its advantages and disadvantages.

of Accurins), which are programmable nanoparticles containing a therapeutic load, grafted with a ligand targeting the extracellular domain of prostate-specific membrane antigen, designed to target tumors at three levels: tissue, cellular, and molecular.[30] There are approximately 14 drugs with nanoparticles approved by the U.S. Food and Drug Administration for clinical use, the majority of which are in the liposome matrix. These nanoparticles are more efficient vehicles for transport and targeted delivery in a hydrophobic manner without provoking an immune response.[31]

Anticancer drugs are generally lipophilic and behave well within the trapped vesicles, being protected from external reactions.[32] Nanoparticles associated with anticancer drugs act on angiogenesis mechanisms, uncontrolled cell proliferation, and increased tumor mass,[33] affecting only tumor tissues and reducing multidrug resistance.[34] The issue of endocytosis of these tumor cells by these drugs through nanoparticles is an important factor because it reduces the dispersion of the drug outside the cancer cell and can increase the therapeutic potential of the drug.[35] In addition to drugs, nanoparticles can be loaded with peptides, proteins, nucleic acids, and antibodies, improving their pharmacokinetics.[36] There are several challenges for nanoparticles in cancer therapy; among them are the proper delivery and accumulation at the target site and decreased accumulation at off-target sites, problems addressed by those who study the improvement of drug delivery systems.

Nanocarriers in drug-delivery systems for cancer treatment

In the development of nanocarriers (biodegradable or non-biodegradable), the drugs are enveloped, adsorbed, or encapsulated in the nanoparticle matrix and can be prepared in several ways with distinct drug-release properties and characteristics (Fig. 2).

Liposomes

These nanocarriers were the first to be tested as drug carriers. They are spherical vesicles composed of phospholipids and steroids. They may have a bilayer or even surfactants formed when some lipids are dispersed in an aqueous medium and can be prepared by sonication.[37] Liposomes increase the solubility of drugs and improve their pharmacokinetic properties, such as the therapeutic index of chemotherapeutic agents, rapid metabolism, and reduction of harmful side effects.[38] The drug is incorporated into the liposome via an encapsulation process, and its release depends on several factors, such as the composition of the liposome, pH, and osmotic gradient.[38] The interactions between liposomes and cells are mediated by adsorption, fusion, and endocytosis. Several liposomal formulations are available for anticancer drugs such as cisplatin,[38] as well as for other conditions, which use liposomal formulations with neurotransmitters,[39] antibiotics,[40] anti-inflammatories,[41] and antirheumatics.[42]

Nanoparticles based on solid lipids

SLNs, nanostructured lipid carriers, and lipid drug conjugates (LDCs) are carrier systems based on a solid lipid matrix.[43] They have been used in dermal,[44] parenteral,[45] ocular,[46] pulmonary,[47] and rectal administration.[48] SLNs are particles made of solid lipids, e.g., highly purified triglycerides, complex mixtures of glycerides, or waxes stabilized by various surfactants.[38,49] They are characterized by good physical stability, drug-degradation protection, and controlled drug release. However, they have a low drug-loading capacity due to low drug solubility in the lipid. Nanostructured lipid carriers and LDCs are modifications of lipid-based nanoparticles that were developed to overcome the limitations of conventional SLNs, such as low drug-loading capacity, and LDCs were

developed for lipophilic drug delivery.[43] SLN has been extensively studied for application in the treatment of triple-negative breast cancer using docetaxel.[50,51]

Polymeric nanoparticles

PNPs are structures with a diameter ranging from 10 to 100 nm. They are obtained from various synthetic polymers, such as polyacrylamide and polyacrylate,[52,53] or even from natural polymers, for example, albumin,[54] DNA,[55] chitosan,[55] and gelatin.[56] PNPs can be classified as biodegradable—poly(L-lactide),[57] and polyglycolide,[58] and non-biodegradable, such as polyurethane.[59] PNPs have a structure coated with non-ionic surfactants to minimize immunological interactions, as well as molecular interactions between surface chemical groups such as van der Waals forces and hydrogen bonds.[60] Drugs can be immobilized on the surface of PNPs or encapsulated and released into the target tissue by diffusion or desorption.[60–62] PNPs have been evaluated to improve delivery to treat resistant tumors.[63,64]

Dendrimer nanocarriers

They were discovered in 1978 and are macromolecular compounds with a series of branches around an internal core.[65] These systems are interesting for drug delivery because of their nanometric size range, ease of preparation and functionalization, and ability to display multiple copies of surface groups for biological reorganization processes.[55,66] In the structure of the dendrimer, in contrast to the linear polymer, the following elements can be distinguished: a core, dendrons, and surface active groups. The core is a single atom or molecule (only if it has at least two identical functional groups) to which the dendrons are attached. The dendrons (dendrimer arms) are monomer molecules attached to the core that form layers in successive generations. The biocompatibility and physicochemical properties of dendrimers are determined by the presence of surface functional groups.[67] Due to their globular shape and the presence of internal cavities, they have interesting properties, such as encapsulating drugs inside macromolecules or attaching them to surface groups.[68] The encapsulation of drugs inside macromolecules is used when they are toxic, unstable, or poorly soluble. On the surface of dendrimers, the amount of drugs can be controlled through the number of covalent bonds.[58] The surface of dendrimers provides a surface for the binding of specific ligands, which may include folic acid,[69] antibodies,[70] peptides,[71] selective adenosine A3 receptors,[72] antimicrobial agents of silver salt complexes,[73] and poly(ethylene glycol).[74] Among the anticancer drugs conjugated in dendrimers are doxorubicin, camptothecin, cisplatin, and paclitaxel.[75]

Silica materials

Silica materials are used in drug delivery as xerogels through the sol-gel method.[76] This manufacturing process involves temperature, agitation, the proportion of reagents, and drying of this material during the reaction,[77] allowing the formation of an amorphous and porous material with high surface area and biocompatibility that can carry drugs such as doxorubicin and cisplatin.[78,79]

Carbon nanomaterials

Carbon nanocarriers used in drug delivery systems are differentiated into nanotubes and nanohorns.[3,80,81] Carbon nanotubes are formed by rolling single (single-walled carbon nanotubes) or multi (multi-walled carbon nanotubes) layers of graphite with an enormous surface area and excellent electronic and thermal conductivity,[81] and their biocompatibility can be implemented with dendrimer anchoring.[81,82] Single-walled carbon nanotubes have been used to improve the properties of other carriers, such as polymeric or non-polymeric composites.[81–83] There are three ways of immobilizing drugs in carbon nanocarriers: encapsulation of a drug in a carbon nanotube,[84,85] chemical adsorption on the surface or in the spaces between the nanotubes (by electrostatic, hydrophobic interactions, and hydrogen bonds),[86,87] and fixation of active agents in functionalized carbon nanotubes. The application of carbon nanomaterials in cancer treatment has expanded to a variety of architectures combined with photodynamic therapy,[88] gene therapy, immunotherapy, and chemotherapy, and has been demonstrated in gastric cancer,[89] liver cancer,[90] pancreatic cancer,[91] ovarian cancer,[92] among others.[93]

Magnetic nanoparticles

Magnetic nanoparticles are highly promising materials that can be used in several areas of nanotechnology. They are relatively easy to manufacture, low-cost, biocompatible, and can be directed by an external magnetic field. They can be visualized by magnetic resonance imaging (MRI).[3,94] Magnetic nanoparticles can be manufactured using family 1B metals with empty orbitals (3d), such as iron, manganese, zinc, cobalt, and nickel. Iron magnetic nanoparticles have been approved for clinical use by the U.S. Food and Drug Administration as an MRI agent and to treat iron deficiency.[95] In the synthesis of magnetic nanoparticles using iron, cobalt, nickel, and zinc, a core can be formed, and various types of coatings can be applied, such as polymers,[96] dendrimers,[97] or silanes.[98]

Nanocarriers and their challenges

In the current pharmaceutical industry, one issue concerns drug delivery systems and the pharmaceutical technologies used, which are less developed than the production of drugs, whether they are of natural or synthetic origin. The industry is seeking new delivery systems, which has shifted the pharmaceutical market in this direction. The therapeutic arsenal of drugs is extensive, and often the application of these delivery systems is minimal, requiring investment and a change in perspective on drugs that are usually already established but whose effectiveness in some diseases is entirely compromised. From a technological point of view, nanocarriers have interesting characteristics, including their surface-to-mass ratio—much higher than that of other particles, their quantum properties, and their ability to absorb and transport drugs to different biological systems. Although nanoparticles are defined as 1–100 nm in size, this size limits the adsorption of drugs, and often, in a disease, a larger quantity of the transported drug is needed. Consequently, the size range (1–100 nm) is, in this case, relative.

Furthermore, differences in size can influence distribution and bioavailability.[99–103] In liposomes with sizes above 100 nm, the clearance rate by the phagocytic system increases with liposome size,[104] whereas liposomes smaller than 100 nm show a more effective charge.[105] However, this varies with nanoparticle composition. The size, composition, surface charge, and shape of the nanoparticles are equally crucial for their performance.[106] Factors such as heating and light can cause or even increase their therapeutic effects, such as cell death or drug release at the drug site. Doxorubicin is an example, as it exhibits increased cytotoxicity when the *in vitro* temperature is 42°C.[107]

The composition of these nanocarriers can be of natural or synthetic origin; in this case, it is essential to consider their biocompatibility. It is important not only to transport nanoparticles to the tissue or organ site and release the drug from the nanoparticle but also to ensure biocompatibility with the biological system and reduce toxicity.[3,108–110]

Table 1. Approved cancer drugs using nanotechnology

Nanocarrier type	Drugs	Drug product name	Agency and year of approval	Treatment indication	Reference
Liposomes	Mitoxantrone	Novantrone	EMA (2016)	Lymphoma and Breast cancer	118
Liposomes	Irinotecan liposome injection	Onivyde	FDA (2015)	Metastatic pancreatic cancer	119,120
Liposomes	Eribulin mesylate	Halaven	FDA (2012), EMA (2011)	Liposarcoma and Breast neoplasms	121
Liposomes	Liposome vincristine sulfate	Marqibo	FDA (2012)	Anticancer alkaloid that binds to tubulin and interferes with cell division	122
Liposomes	Mifamurtide	Mepact	EMA (2009)	Osteosarcoma	123
Liposomes	Paclitaxel Genexal/Cynviloq	Paclitaxel Genexal/ Cynviloq	Korea (2007)	Breast cancer and Non-small cell lung cancer	124
Liposomes	Doxorubicin nonpegylated liposomal	Myocet	FDA (2000)	Breast cancer	125,126
Liposomes	Liposomal cytarabine	Depocyt	FDA (2007)	Lymphomatous meningitis/ antineoplasic agent/ inhibit DNA polymerase	127,128
Liposomes	Diphtheria toxin	Ontak	FDA (1999)	T-cell lymphoma	129,130
Liposomes	Liposomal daunorubicin	DaunoXome	FDA (1996)	HIV-associated Kaposi's Sarcoma (KS) as a chemotherapy drug	131
Liposomes	Liposomal Doxorubicin	Doxil/Caelyx/ Lipidox	FDA (1995)	Treatment of diferent cancers ranging from metastatic ovarian cancer	132,133
Liposomes	Daunorubicin and cytarabine encapsulated in liposomes	Vyxeos	FDA (2017)	Acute myeloid leukemia	134,135
Polymeric NPs	PEGylated-L asparaginase	Oncaspar	FDA (1994)	Acute lymphoblastic leukemia and chronic myelogenous leukemia	136,137
Polymeric NPs	Albumin-NPs bound to paclitaxel	Abraxane	FDA (2005/2012/2013)	Metastatic breast cancer, lung cancer and metastatic pancreatic adenocarcinoma	138
Polymeric NPs	Leuprolide acetate	Eligard	FDA (2002)	Prostate cancer	139

EMA, European medicines agency, FDA, Food and Drug Administration, NPs, nanoparticles.

Formulation challenges

The ideal condition in drug administration is to deliver the drug to the tumor site in the body while minimizing its harmful effects on unaffected tissues, which is a challenge considering the development of metastasis, a feature of resistant tumors. Nanoparticles improve local action related to the affected organ or tissue, increasing the amount of drug at the site and allowing penetration into cell membranes and lysosomal escape after endocytosis.[111] There are several reviews on nanometric formulations of chemotherapeutics.[112–114] In addition to size, the chemistry of the particle surface is crucial for the absorption, distribution, stability, and effects of the particles. However, one problem is that nanoparticles can become trapped in the liver and spleen,[115,116] which can be positive for the treatment of liver tumors. On the other hand, it reduces the circulation of these nanoparticles to target other organs. In the case of nanoparticles for oral administration, this can be critical, as some nanoparticles will be metabolized in the liver (first-pass effect), and much of the carrier and drug will be lost. The ideal use would perhaps be local or intravenous administration to minimize drug loss along with the carrier.[117]

At present, several liposomes and PNPs are approved for use in anticancer treatment (Table 1).[118–139]

Challenge of the brain and its blood-brain barrier (BBB)

The brain poses specific challenges regarding drug delivery. The BBB is well known as the body's best shield against exogenous substances.[140] Pharmaceuticals, including most small molecules, generally do not cross the BBB. The endothelial barrier is particularly narrow at the interface with brain astrocytes and, under normal conditions, can be crossed only using endogenous BBB transporters, resulting in transporter-mediated active efflux transport and/or receptor-mediated transport. However, the barrier properties can be compromised, either intentionally or unintentionally, by drug treatment, allowing the passage of nanoparticles.[141–144] Several studies analyze the toxic effects of nanoparticles on brain endothelial cells (nanoparticles > 200 nm),[145] but contradictory results have been reported in other studies with similar nanoparticles.[142] When nanoparticles with different surface characteristics were evaluated, it was found that neutral nanoparticles and low concentrations of anionic nanoparticles had no effect on BBB integrity, whereas high

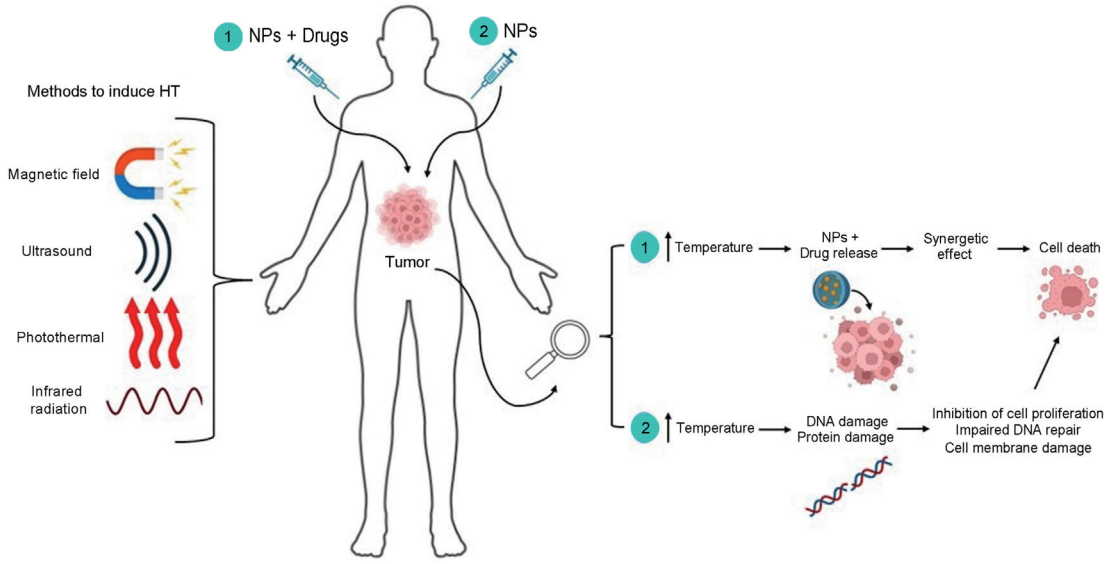

Fig. 3. Overview of viral nanoparticle-based drug delivery and magnetic hyperthermia. This figure shows the various mechanisms of action of VNPs and how they can be combined with magnetic nanoparticles for tumor targeting and drug release. The figure also highlights the role of magnetic hyperthermia in enhancing therapeutic efficacy by localizing heat to the tumor site. HT, hyperthermia; NPs, nanoparticles; VNPs, viral nanoparticles.

concentrations of anionic and cationic nanoparticles were toxic to the BBB. The extent of brain uptake by anionic nanoparticles at lower concentrations was higher than that by neutral or cationic formulations at the same concentration. Therefore, the surface charges of nanoparticles should be considered when determining their toxicity and brain distribution profiles.[143] In particular, coating nanoparticles with surfactants (e.g., Tween) has resulted in drug transport across the BBB. The transport mechanism is suggested to be endocytosis through the low-density lipoprotein receptor of endothelial cells after the adsorption of lipoproteins from blood plasma onto the nanoparticles.[142] The role of apolipoprotein E has been observed in drug transport across the BBB, whereas apolipoprotein E variants that do not recognize lipoprotein receptors fail to transport the drug across the BBB.[146]

It has been suggested that recognition and interaction with lipoprotein receptors on brain capillary endothelial cells are responsible for drug uptake by the brain. BBB passage can also be achieved by masking certain drug characteristics, thereby preventing or limiting binding to cellular efflux systems such as P-glycoprotein, a cellular transporter associated with drug removal from cells. P-glycoprotein is an adenosine triphosphate (ATP)-dependent efflux transporter that plays an important physiological role in limiting drug entry into the brain.[147–149] Other routes to reach the brain, bypassing the BBB, include migration along the olfactory or trigeminal nerve endings after deposition in the olfactory mucosa in the nasal region.[150] Solid nanoparticles, such as manganese oxide, have also been shown to be translocated to the brain via the olfactory pathway,[151] based on measurements of manganese in different parts of the brain. Due to the BBB, a number of brain treatments for cancer with nanoparticles involve intracranial injections, but the search for a non-invasive route to the brain has become a priority among investigators.[152]

Hyperthermia-based anti-cancer treatment

Hyperthermia-based treatment dates back to ancient civilizations such as the Egyptians, Greeks, and Romans, who recognized the healing properties of heat, using thermal baths and saunas not only for relaxation but also to alleviate pain and treat various ailments.

In the late 19th century, medical practitioners began to observe that cancer patients who experienced high fevers occasionally saw their tumors regress. This observation led to the hypothesis that heat could have a direct therapeutic effect on diseases. This marked one of the earliest scientific acknowledgments of the potential of heat in treating cancer.[153]

By the 1970s, technological advancements allowed for the development of precise equipment, such as microwave and ultrasound devices, enabling controlled heat application. Consequently, in 1975, during the first International Hyperthermia Congress held in Washington, scientists unveiled groundbreaking findings highlighting the effectiveness of combining heat therapy with conventional treatment methods for combating tumors. This announcement marked a pivotal moment in cancer research, establishing hyperthermia as a promising complementary approach to traditional therapies.[154]

In the 21st century, hyperthermia gained recognition as an adjuvant therapy in cancer treatment, particularly when combined with radiotherapy, chemotherapy, and immunotherapy. Ongoing clinical studies and research continue to explore its potential in treating various types of tumors and other diseases. Heat causes direct damage to cancer cells by denaturing proteins and damaging cell membranes, leading to cell death. Cancer cells are particularly vulnerable to this damage due to their less efficient repair systems. Additionally, hyperthermia enhances the effectiveness of other treatments by increasing blood flow to tumors, thereby improving the delivery of chemotherapy drugs and sensitizing cancer cells to radiation. It also stimulates the immune system, activating cells such as lymphocytes and macrophages,[155,156] which promote a more robust antitumor response (Fig. 3).

Modern hyperthermia techniques vary depending on the application. Local hyperthermia targets superficial or accessible tumors using radio waves, microwaves, or ultrasound. Regional hyperthermia is used for larger areas, such as organs or body cavities, often involving the perfusion of heated fluids or radiofrequency

devices. Whole-body hyperthermia, which consists of heating the entire body, is typically reserved for cases of metastatic cancer and can be induced using thermal blankets, hot water baths, or specialized devices.[157] Despite its promising potential, hyperthermia is not without challenges and risks. Precise temperature control is crucial, as excessively high temperatures can damage healthy tissues and cause burns, swelling, or pain in the treated area. In cases of whole-body and regional hyperthermia, for example, there is a risk of overheating and systemic complications, leading to severe side effects like gastrointestinal symptoms and cardiac complications.[157,158]

As an advanced evolution of the technique, magnetic hyperthermia involves injecting magnetic nanoparticles into tumors, which generate localized heat when exposed to an alternating magnetic field (AMF). This approach is highly efficient, noninvasive, and minimizes damage to normal tissues. It is also cost-effective, offers excellent tissue penetration, and effectively destroys cancer cells.

Magnetic hyperthermia

Magnetic hyperthermia has emerged as a revolutionary approach in cancer treatment, offering a unique blend of precision, efficiency, and minimal invasiveness. When exposed to an AMF, this innovative technique leverages magnetic nanoparticles to generate localized heat within tumors. By delivering these nanoparticles directly to the tumor site—either through passive targeting, which exploits the leaky vasculature of tumors through what is known as the enhanced permeability and retention effect,[159] or active targeting using tumor-specific ligands—magnetic hyperthermia ensures that heat is concentrated precisely where needed. When the AMF is applied, two phenomena emerge: Néel relaxation, due to the internal reorientation of the magnetic moments within the magnetic nanoparticle, and Brownian relaxation, due to the rotation of the entire nanoparticle within a fluid caused by Brownian motion. These processes produce heat that raises the local temperature to therapeutic levels, typically between 42–46°C. This localized heating disrupts cancer cell membranes, denatures proteins, and impairs mitochondrial function, leading to cell death or halted proliferation while sparing surrounding healthy tissues.[160]

The development of advanced magnetic nanoparticles has been a driving force behind the success of magnetic hyperthermia. Traditional iron oxide nanoparticles (Fe_3O_4 and/or γ-Fe_2O_3) have been widely used due to their biocompatibility and magnetic properties.[161] These nanoparticles can be tailored to optimize their performance, ensuring they accumulate effectively in tumors and generate sufficient heat under the influence of the AMF.

One of the most compelling aspects of magnetic hyperthermia is its ability to combine this thermal therapy with other treatment modalities.[162] Magnetic nanoparticles can be functionalized to carry chemotherapy drugs or be encapsulated within thermo-responsive materials that release therapeutic agents when heated. This dual approach enhances the direct cytotoxic effects of heat and allows for targeted drug delivery, reducing systemic side effects. Additionally, it can activate thermo-responsive promoters to trigger the expression of therapeutic genes, further amplifying its anticancer effects. The versatility of magnetic hyperthermia extends to its compatibility with existing treatments like chemotherapy and radiotherapy, as the heat generated can sensitize tumor cells, making them more susceptible to these therapies.

Established therapies combined with magnetic hyperthermia

Magnetic hyperthermia exerts its antitumor effects through various interconnected mechanisms. These mechanisms include direct cell damage, structural changes in cells, DNA damage, repair inhibition, apoptosis induction, and modulation of heat shock proteins (HSPs). Together, these processes halt tumor growth and enhance the effectiveness of other cancer therapies.[163,164]

Direct cell damage is the primary mechanism of hyperthermia and depends on the temperature and duration of heat exposure. At moderate temperatures (40–45°C), prolonged exposure of 30–60 min is required to cause irreversible cell damage.[165] At higher temperatures (above 60°C), proteins rapidly denature, leading to immediate cell death through coagulative necrosis. This destabilizes the cytoskeleton and cell membrane structure, impairing motility and intracellular signaling. Mitochondria are particularly sensitive to heat, with high temperatures causing proton leakage, swelling, and structural changes that contribute to cell death. Additionally, heat inhibits DNA replication by denaturing essential enzymes, such as DNA polymerase alpha, further compromising cell survival.[166–170] Hyperthermia also induces significant changes in cellular structure, particularly in the cytoskeleton, which is essential for maintaining cell shape and function.

Another important mechanism is DNA damage and repair inhibition. Hyperthermia directly causes DNA breaks and the formation of apurinic/apyrimidinic sites while promoting the generation of reactive oxygen species that further damage DNA.[171] Heat limits the activity of DNA polymerases, impairing replication and increasing DNA breaks. It also promotes the formation of γH2AX foci, markers of double-strand breaks, and modulates the activity of proteins such as ATM and ATR, which are involved in the DNA damage response. Additionally, hyperthermia disrupts multiple DNA repair mechanisms, including base excision repair, nucleotide excision repair, mismatch repair, and homologous recombination. By inhibiting these repair mechanisms, hyperthermia increases the susceptibility of cancer cells to other treatments, such as chemotherapy and radiotherapy.[172–176]

Finally, hyperthermia also triggers apoptosis, or programmed cell death, and modulates the expression and function of HSPs, which play a dual role in the tumor response. On the one hand, HSPs are overexpressed in response to heat stress, helping cells cope with protein denaturation and preventing irreversible damage. On the other hand, extracellular HSPs released by necrotic tumor cells act as signaling molecules, activating the immune system. Proteins such as HSP70 and HMGB1 enhance antigen presentation and dendritic cell activation, promoting an immune response against the tumor. HSP70, in particular, forms complexes with tumor antigens recognized by immune cells, further amplifying antitumor immunity.

Hyperthermia in clinical applications

The clinical applications of hyperthermia are extensive. It is widely studied in cancer treatment, particularly in combination with radiotherapy, chemotherapy, and immunotherapy (Fig. 3). It has shown promise in treating breast, prostate, head and neck, and melanoma cancers, among others. Clinical studies have demonstrated that hyperthermia can increase tumor response rates and improve patient survival. A summary of clinical studies evaluating the efficacy and outcomes of hyperthermia combined with radiotherapy, chemoradiotherapy, and immunology across various cancer types is presented in Table 2.[177–190]

Magnetic hyperthermia in clinical applications

In 2003, the first clinical feasibility study on magnetic nanoparticle hyperthermia was conducted with 14 glioblastoma multiforme patients, including two with primary tumors and 12 with recur-

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Table 2. Summary of clinical studies evaluating the efficacy and outcomes of hyperthermia combined with radiotherapy, chemoradiotherapy and immunology across various cancer types. Missing values indicate unreported or inapplicable data

Cancer type	Treatment protocol	Sample size	Key outcomes	pCR/CR rate	3–5 years OS (%)	Main conclusion	Study (Ref.)
Rectal cancer	RT + CT + Magnetic HT	78	14% pCR; 50% Dworak 3–4; 3-yr OS: 94%, DFS: 81%	14	94	Magnetic HT is feasible, enhances regression, and maintains QoL	177
LACC (IB2–IVA)	RT (46–50.4 Gy) + BT + Weekly RHT	378	CR: 77%; 5-yr LC: 53%, DSS: 47%, Late Toxicity: 12%	77	-	RHT improves outcomes; supports use in LACC as alternative to chemoradiation	178
Locally advanced prostate cancer	EBRT (70 Gy) + Regional/Interstitial HT	26	3-yr bNED: 70% overall; 79% (regional), 57% (interstitial)	-	100	Combined therapy favorable; minimal toxicity	179
Bladder, cervical, rectal cancer	RT ± HT (median dose: 65 Gy)	358	CR: 55% (RT+HT) vs. 39% (RT); 3-yr OS: 51% vs. 27%	55	51	HT improves CR and LC; especially effective in cervical cancer	180
Advanced prostate cancer (C2–D1)	EBRT (median 68 Gy) + 1–2 HT sessions	26	5-yr OS: 73%; bNED: 35%; PSA nadir significant	-	73	HT feasible, but limited outcome improvement	181
HNSCC (recurrent)	Re-irradiation + Weekly FRWBH	10	No excess toxicity; partial protocol adherence	-	86	FRWBH potentially beneficial, but challenging to implement	182
Locally advanced rectal cancer	Preop RCT (RT + 5-FU/Leucovorin) + Weekly HT	37	pCR: 14%; R0 resection: 86%; 38-mo OS: 86%	14	-	HRCT is effective, safe, and improves locoregional control	183
Prostate cancer (T2b–T3b)	EBRT ± Androgen Therapy + 2 TRUS HT sessions	30	Rectal toxicity correlated with Tmax; GI toxicity ≤ Grade 2	-	-	Rectal wall temperature strongly predicts acute toxicity	184
Bladder	CHT (MMC) vs. BCG (1-year regimen)	190	24-mo RFS (PP): 81.8% (CHT) vs. 64.8% (BCG); p = 0.02	-	-	CHT demonstrated superior RFS in PP analysis; both had <2% progression. Study underpowered but supports CHT as viable alternative.	185
Breast	Low-dose ICB (nivolumab, ipilimumab), regional HT, systemic fever-range HT (IL-2)	Case report	Complete remission of pulmonary metastases	100	alive at 27 mo	Combined ICB + HT + IL-2 induced durable remission with minimal toxicity; promising protocol for further TNBC research.	186
Breast, ovary, colon, prostate	Locoregional & whole-body HT, IL-2, low-dose ipilimumab + nivolumab	131	ORR: 31.3%, median PFS: 10 mo, OS: 36.6% at 24 mo; Grade 3–4 irAEs: 8.4%	31.3	36.6	Novel ICI-HT combination therapy showed favorable safety and efficacy; further optimization with viral/bacterial agents suggested.	187
High-risk Soft Tissue Sarcoma	Neoadjuvant CT + Regional HT	341	HR for local PFS = 0.65 (p=0.002); HR for OS = 0.73 (p=0.04); 10-yr OS: 52.6% (HT) vs. 42.7% (CT)	Not reported	62.7% (HT) vs. 51.3% (control)	Regional HT significantly improves local PFS and OS in high-risk sarcoma.	188
Colorectal Peritoneal Metastases	CRS ± Oxaliplatin-based HIPEC	265	No OS benefit (HR=1.00, p=0.99); Grade ≥3 AEs higher at 60 days in HIPEC group (26% vs. 15%)	Not reported	no improvement	HIPEC did not improve OS; CRS alone should remain standard for peritoneal metastases.	189
Stage III Epithelial Ovarian Cancer	CRS ± Cisplatin-based HIPEC	245	RFS: 14.2 mo (HIPEC) vs. 10.7 mo (CRS); HR for death = 0.67 (p=0.02); No significant increase in Grade 3–4 AEs	CR not specified, but improved RFS	45.7 mo (HIPEC) vs. 33.9 mo	HIPEC added to interval CRS significantly improves RFS and OS without increasing toxicity.	190

BCG, bacillus Calmette-Guérin; bNED, biochemical no evidence of disease; BT, brachytherapy; CR, complete Response; CRS, cytoreductive surgery; CT, chemotherapy; DFS, disease-free survival; DSS, disease-specific survival; EBRT, external beam radiotherapy; FRWBH, fever-range whole-body; GI, gastrointestinal; HIPEC, hyperthermic intraperitoneal chemotherapy hyperthermia; HT, hyperthermia; ICB, immune checkpoint blockade; IL, interleukin; LACC, locally advanced cervical carcinoma; LC, local control; MMC, mitomycin C; mo, months; OS, overall survival; pCR, pathologic complete response; RCT, randomized controlled trial; RFS, recurrence-free survival; RHT, regional hyperthermia; RT, radiotherapy; TRUS, transrectal ultrasound; yr, year.

rences.[191] Magnetic fluid was injected into the tumors using neuronavigation guidance, ensuring a nearly atraumatic procedure with no complications. Slow injection prevented increased intracranial pressure. Patients underwent four to ten thermotherapy sessions (median: 6.5), each lasting 1 h and administered twice weekly, combined with external beam radiation. The median injected fluid volume was 3 mL (range: 1.0–5.5 mL), corresponding to 0.1–0.7 mL per mL of tumor volume. Treatment was well tolerated at magnetic field strengths of 3.8 to 13.5 kA/m (median: 8.5 kA/m), with only minor side effects reported. Intratumoral temperatures reached 42.4–49.5°C, with 90% of tumor volumes achieving 39.3–45.5°C (median: 40.5°C). Approximately 55% of tumor volumes exceeded 42°C, and the median CEM43 T90 was 7.7 min (range: 3.2–502 min). These results demonstrate the feasibility and tolerability of magnetic nanoparticle hyperthermia in treating glioblastoma multiforme.

A prospective feasibility study, launched in February 2004, included 22 patients with recurrent or residual tumors (non-resectable and pre-treated, such as prostate and cervix carcinoma, and soft tissue sarcoma). All patients received additional radiotherapy and/or chemotherapy in conjunction with the experimental treatment. All patients tolerated the nanoparticle instillation well, although pre-irradiated tumor tissue in some cases posed mechanical resistance to injection and fluid diffusion. Median infiltration volumes were 3 mL (range: 1.5–5 mL) for chemotherapy/transrectal ultrasound (CT/TRUS)-guided procedures and 8.5 mL (range: 6–12.5 mL) for TRUS-guided prostate treatments, equating to approximately 0.3–0.4 mL of magnetic fluid per mL of tumor volume. Intraoperative infiltration volumes averaged 7 mL per patient (range: 2.3–10 mL). Magnetic field strengths were limited by patient discomfort (e.g., at skin folds or bone surfaces) to 3–5 kA/m in the pelvic region and up to 8.5 kA/m in the upper thorax, resulting in a median CEM43 T90 of 10.5 min (range: 1–106 min). Treatments were generally well tolerated, with minor to moderate side effects such as sensations of heat, superficial skin burns, increased pulse rate, and elevated blood pressure. Two patients experienced grade 1 to 2 perineal pain lasting up to 4 months. Overall, the study demonstrated the feasibility and tolerability of magnetic nanoparticle hyperthermia in treating recurrent and residual tumors.[191]

The first clinical use of interstitial hyperthermia with magnetic nanoparticles in human cancer was performed by Johannsen *et al*.[192] A pilot study investigated the potential of magnetic hyperthermia as a minimally invasive treatment for locally recurrent prostate cancer. Treatment planning involved CT imaging to determine the optimal number and placement of magnetic fluid depots in the prostate, ensuring adequate heat delivery while protecting the rectum and urethra. Magnetic nanoparticles were injected transperineally under ultrasound and fluoroscopy guidance, and treatments were administered using a magnetic field applicator operating at 100 kHz with a field strength ranging from 0 to 18 kA/m. Invasive temperature measurements were taken during the first and last of six weekly 60-min magnetic hyperthermia sessions. CT scans were repeated to track nanoparticle distribution and the positioning of temperature probes. The nanoparticles remained in the prostate throughout the six-week treatment period, allowing for non-invasive temperature estimation using AMIRA software, which correlated well with direct invasive measurements. A cooling device was used to ensure patient comfort without the need for anesthesia. In the first patient treated, intra-prostatic temperatures ranged from 40.0°C to 48.5°C at a field strength of 4.0–5.0 kA/m, demonstrating effective and controlled heating. These encouraging findings prompted the initiation of a phase I study to evaluate the feasibility, toxicity, and impact on quality of life in patients with biopsy-confirmed local recurrence following radiotherapy.[192]

Viruses as nanocarriers

Viruses are infectious agents ranging in size from 17 to 1,500 nanometers.[193] Since they are obligatory intracellular parasites incapable of generating energy, they do not feed or grow. Their fundamental structure includes a viral genome, which can be either DNA or RNA, but not both simultaneously, and a protein capsid, which protects this genetic material. In addition to the capsid, some viruses may possess a lipid envelope derived from the host cell membrane. Virus-encoded proteins at the surface of the capsid or envelope are used for the recognition and infection of host cells through several pathways, including the endocytic pathway or direct injection of the genetic material into the host cell.[194] The life cycle of a virus comprises several stages: attachment to the cell surface, cell entry, uncoating (release of genetic material into the cell), expression of the early genes, replication of the viral genome, expression of late genes (virus structural proteins), viral assembly (formation of new virion particles), and release from the host cell, leading to or not leading to host cell lysis.[194]

Compared to cellular organisms, viruses are structurally simple, allowing them to be highly efficient at replicating and generating viral burst values, which refers to the number of viruses released by an infected cell during its life cycle.[195] These values can range from 50 to 100 viruses per infected cell in bacteriophages to 50,000 particles per cell in HIV.[196–198] Much of this efficiency is related to how viruses assemble their structures and escape from the cell. In terms of morphology, viruses can present icosahedral symmetry or helical symmetry. Non-enveloped icosahedral viruses have higher viral bursts.[199] This efficiency is also related to self-assembly, the process that allowed the development of natural nanocarriers of viral origin.

Self-assembly of viral capsids

The viral particles assemble spontaneously from their protein subunits and nucleic acid genomes in a process known as self-assembly, defined as “The autonomous organization of individual components into patterns or structures without human intervention”.[200] The viral genome encodes the information that determines their three-dimensional structures in a way that the protein subunits bind to each other. The length of the viral genome, and consequently the number of unique proteins it can encode, is limited by the necessity of being enclosed within its capsid; thus, the capsid must be composed of a large number of identical protein subunits to avoid exhausting the coding capacity of the genome.[201] While for some viruses, the capsid grows around the genome, others build an empty capsid, and the genome is later packed using packaging motors dependent on ATP hydrolysis.[202]

The interactions between neighboring subunits are specific. With all subunits on the capsid surface identical, their interactions will be nearly identical, resulting in a compact, closed, and symmetrical structure.[203] Viral capsids are supramolecular structures, whose assembly results from various noncovalent interactions, including van der Waals forces, electrostatic and hydrophobic interactions, hydrogen bonding, among others.[204] As a consequence of the self-assembly strategy, non-infective virus particles (lacking viral genome) may be naturally produced, generating empty shells. This phenomenon was observed in 1968 by Bayer and collaborators.[205] Since then, it has been observed that these characteristics of viral capsids could make them suitable for the delivery of drugs

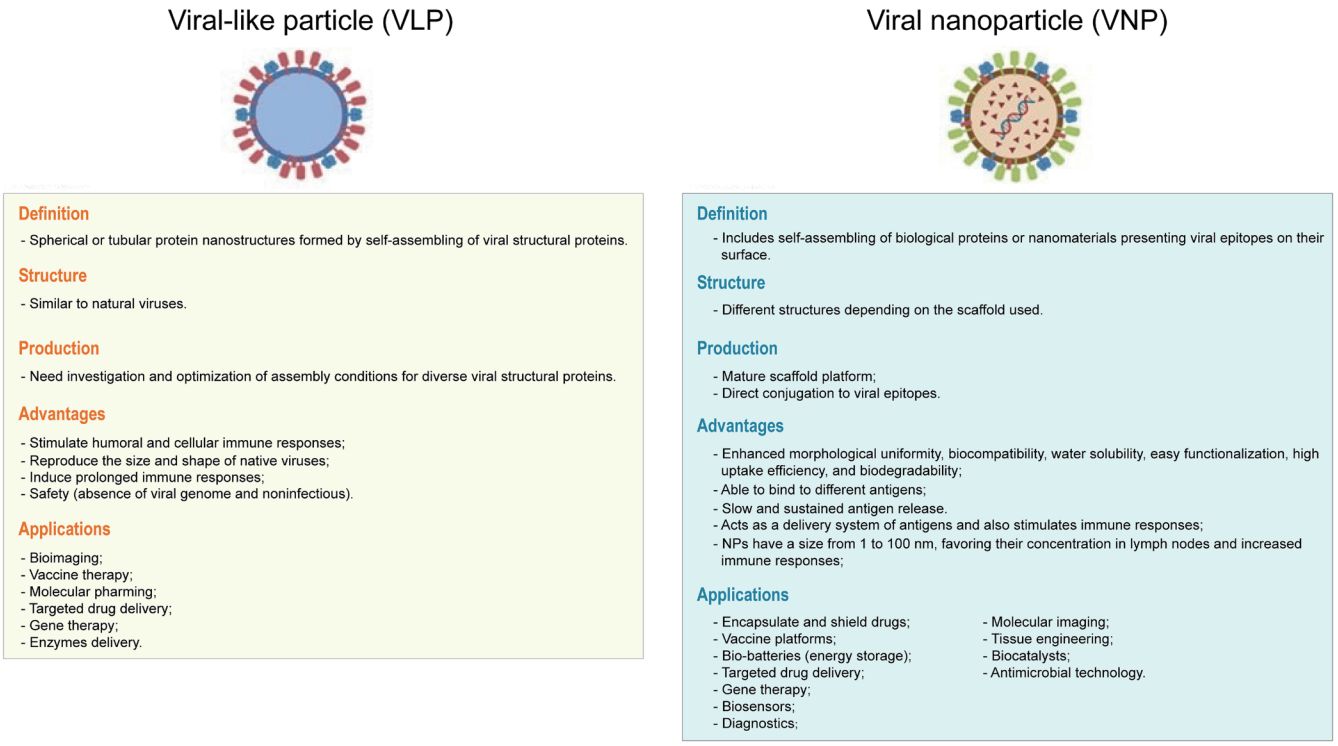

Fig. 4. Comparison between virus-like particles (VLPs) and viral nanoparticles (VNPs). VLPs is a subgroup of VNPs that lacks genetic material and therefore is non-infectious. Generally, is composed by only structural proteins and used as empty shells. On the other hand, the viral genome of the VNPs may be present, inactivated or modified and thus, retains partially its infectivity.

and other therapeutic alternatives, leading to the development of what is now known as VNPs and VLPs.

VNPs and VLPs

As mentioned in previous sections, synthetic nanocarriers offer several benefits but also some drawbacks, such as toxicity, pharmacokinetics, and lack of tissue specificity. VNPs are defined as nanomaterials derived from plants, bacteriophages, and mammalian viruses. VNPs are the version that contains the viral genome,[206] while VLPs constitute a subgroup of VNPs, whose structures are composed of natural viruses lacking their genomes, making them incapable of replication and non-infectious, thus safe for use in vaccines, diagnostics, and research.[207] Since the obligatory parasite features of the virus are essential to its propagation strategy, their components present intrinsic biocompatibility and biodegradability, an advantage over synthetic nanocarriers.[208] Furthermore, co-evolution with their hosts generates tissue specificity, defining the viral tropism toward tissues and organs.

VNPs are made by expressing viral proteins in host systems like bacteria, yeast, insects, or mammalian cells, where the proteins self-assemble into nanoparticles. These particles are then purified and often engineered for specific tasks, such as displaying targeting ligands, encapsulating drugs, or carrying genetic material.[209] In VNPs, the viral genome remains inside the capsid, and the resulting product can be either replication-competent or replication-defective vectors. Examples include adenovirus nanoparticles for gene therapy, where specific regions essential for gene expression of its double-stranded DNA genome are replaced by a therapeutic gene that, when expressed, can lead to defect corrections (gene therapy).[210] In adenovirus vaccine applications, the genes inserted are from antigens that stimulate the immune system.[211] In cancer gene therapy, genes related to the activation of the cell death pathway are activated to induce tumor cell death.[212] Plant virus nanoparticles for cancer therapy have been extensively studied, also due to their safety, since, with or without their genomes, plant viruses do not replicate in mammalian cells.[213]

While for some viruses the capsid can self-assemble with or without the presence of its genome, other VNPs are derived from viruses that can only assemble in the presence of their genomes. Thus, those with this limitation need to carry their loads exclusively at the surface of the VNP, such as the potato virus X.[214] VNPs are highly versatile due to their uniform size, self-assembly properties, and ability to be modified for targeted applications.

Chimeric VNPs combine components from different viruses or are engineered to display foreign peptides or proteins.[215] Functionalized VNPs involve modification with chemical groups,[216] targeting ligands,[217] or imaging agents for specific applications, such as the use of cowpea mosaic virus particles functionalized with fluorescent dyes for imaging (Fig. 4).[218]

The generation of VLPs involves the use of yeast-based (among others) expression systems, since yeast can efficiently express and assemble viral proteins. The process begins by cloning the gene(s) encoding the viral structural protein(s) into a yeast expression vector, which is then introduced into yeast cells like *Saccharomyces cerevisiae* or *Pichia pastoris*.[219] The yeast cells are cultured under conditions that induce the expression of the viral proteins, which then self-assemble into VLPs. These VLPs can be harvested from yeast cells or the culture medium and purified using techniques like centrifugation or chromatography. Yeast is particularly advantageous for VLP production due to its cost-effective, scalable

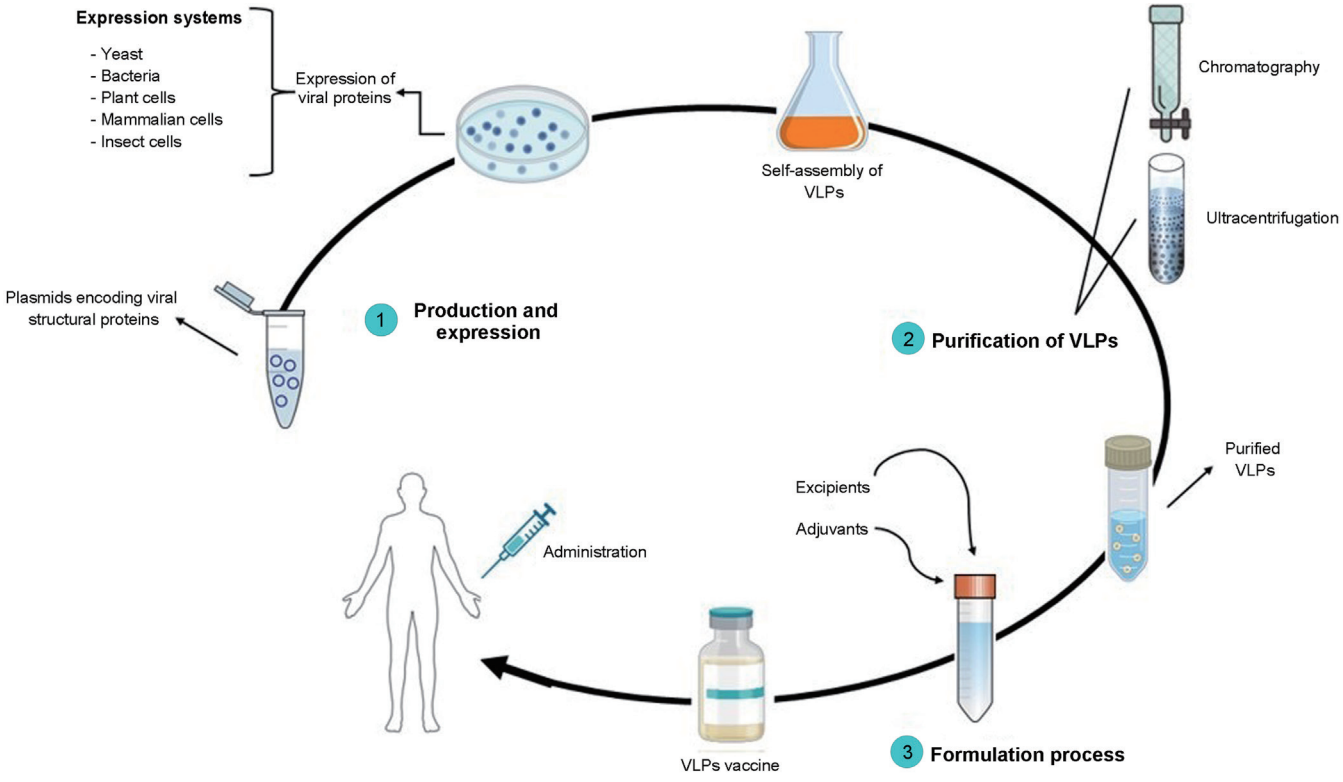

Fig. 5. Steps of virus-like particles (VLPs) production. 1. Production and expression: the viral structural genes are cloned, and after the viral proteins are expressed in different expression systems, including yeast, bacteria, plant cells, mammalian cells, and insect cells. 2. Purification of VLPs: to obtain VLPs with high purity and integrity, techniques like chromatography and ultracentrifugation are employed to purify the VLPs. 3. Formulation: in this last step, adjuvants and excipients are added to VLPs, enabling the production of VLPs vaccine, which will be administered to patients.

nature and its capacity for performing post-translational modifications necessary for proper protein folding and assembly.[220] Examples of VLP vaccines produced in yeast include the hepatitis B vaccine and the human papillomavirus (HPV) vaccine.[221,222] Despite some challenges, such as differences in glycosylation patterns compared to mammalian cells and the production of VLPs derived from enveloped viruses,[223] yeast remains a powerful and widely used platform for VLP production (Fig. 5). The development of VNPs and VLPs to treat cancer is related, among other things, to enhancing drug targeting against tumor cells. Thus, the efficiency of each model (VNPs or VLPs) depends on the targeted tumor.

The use of VLPs in cancer research

Regarding the use of VLPs in cancer therapeutics, several approaches have been developed to both prevent and treat tumors. In the first case, VLPs are used in cancer vaccines to stimulate strong immune responses and long-term immunological memory. When injected, VLPs are taken up by immune cells, such as dendritic cells, activating both adaptive and innate immune responses (Fig. 6).[224] In this respect, preventive vaccines based on VLPs have been developed for hepatitis B virus (HBV) and HPV.[225] When VLPs are generated with structural proteins from HPV, eliciting strong immune responses against HPV infection, preventing the development of cervical cancer. These vaccines were approved by international regulatory agencies for human use, with names such as Engerix-B, Recombivax HB, Euvax, among others (for HBV),[226] and Cervarix, Gardasil, and Gardasil 9 (for HPV).[227] In breast cancer, HER2 is overexpressed in 20–30% of invasive breast tumors. This epitope is used to generate an immune response against HER2, inducing prophylactic vaccination so as to reduce the proliferation of tumors when already established.[228] Other cancer vaccines using VLPs are those developed to treat pancreatic cancer,[229] melanoma,[230] and brain tumors.[231] Another approach involves the generation of VLPs to display tumor-specific antigens, which train the immune system to recognize and attack established tumors, reducing their mass and contributing to overcoming resistance to conventional therapies. Challenges include identifying effective antigens, overcoming immune suppression in tumors, and the development of neo-antigens – antigens derived from tumor mutations.[232]

In addition, a widely studied approach is the use of VLPs loaded with chemotherapeutic drugs using the VLP's surface specificity, which can be engineered to target tumoral tissue instead of normal tissue, also reducing systemic toxicity. Several works have demonstrated the efficiency of VLPs loaded with doxorubicin, showing enhanced efficiency against glioblastoma multiforme, among others.[233,234] Monomethyl auristatin (MMAE) belongs to the group of the Auristatins, synthetic analogs of dolastatin 10 (D10), a highly cytotoxic antineoplastic agent derived from *Dolabella auricularia*. MMAE is usually conjugated with antibodies to treat lymphoma due to its high systemic toxicity,[235] being administered as a prodrug, Val-Cit linked MMAE. Shukla and co-workers evaluated the potato virus X VLPs conjugated with Val-Cit linked MMAE *in vivo* and *in vitro*, observing enhanced cytotoxicity *in vitro* and improved percent survival rates *in vivo*.[236]

Cisplatin, a platinum derivative used in chemotherapy for the last 30 years, was tested as cargo for VLPs by Hu and Steinmetz. In

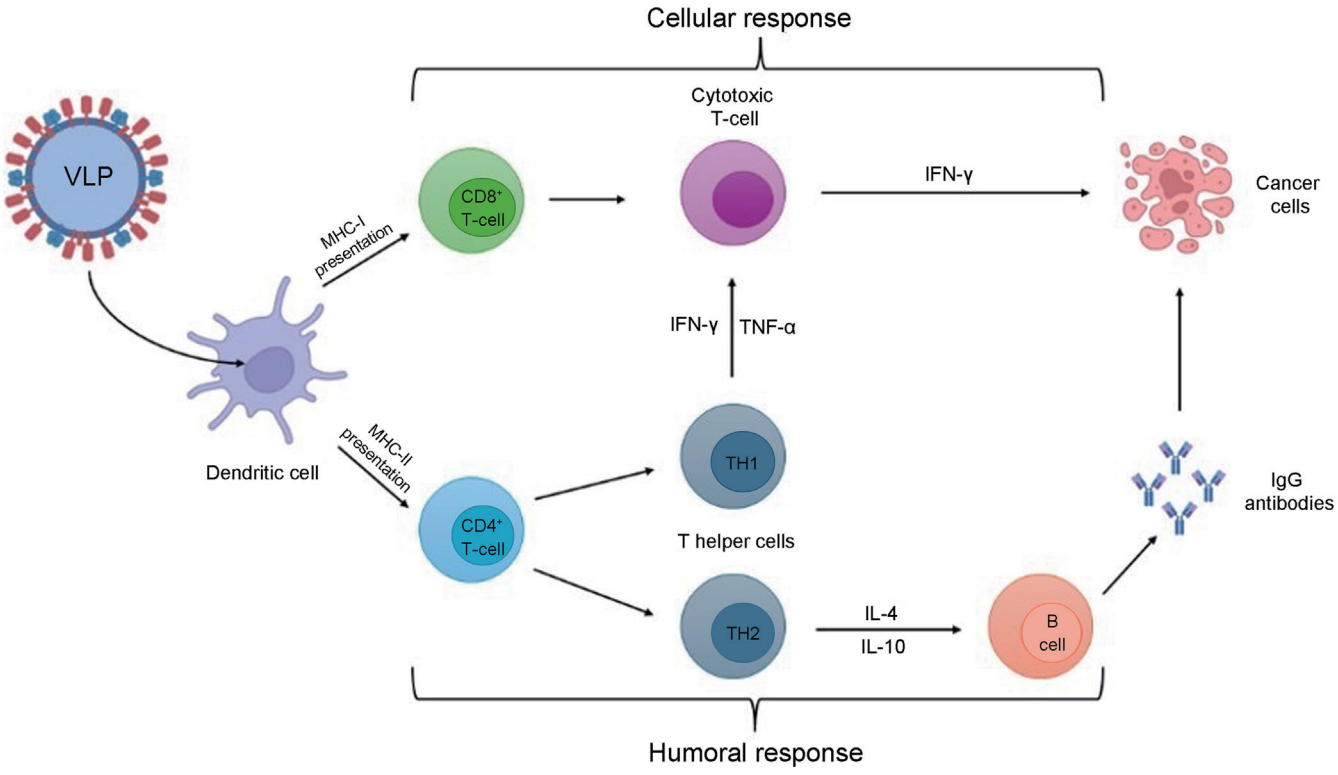

Fig. 6. VLPs-inducing immunity. Upon administration, VLPs are uptake by APC, like dendritic cells. VLPs can be presented by MHC-I or MHC-II, which are recognized by CD8+ and CD4+ T cells, respectively. For cellular response, CD8+ cells differentiate in cytotoxic T cells, releasing IFN-γ to exert their cytotoxicity activity in cancer cells. In humoral response, CD4+ cells differentiate into T helper cells (TH1/TH2), TH1 maintains the activity of cytotoxic T cells, and TH2 releases IL-4 and IL-10, inducing B cell activation. Once activated, B cells release IgG antibodies, enabling their antineoplasic effects. APC, antigen-presenting cells; IFN- γ, interferon-gamma; IgG, immunoglobulin G; IL-4/-10, interleukin-4/-10; MHC-I/II, major histocompatibility complex class I/II; TH, T helper cells; TNF-α, tumor necrosis factor-α; VLP, virus-like particles.

their work, VLPs of the physalis mottle virus were conjugated with maleimide-functionalized cisplatin, a prodrug that, upon cellular pH changes, generates cisplatin. They linked the prodrug to both the internal and external surfaces of physalis mottle virus-derived VLPs, and with this approach, they were able to carry cisplatin into cancer cells.[237]

Merging strategies

Most of the strategies discussed have their own advantages and drawbacks. To leverage the strengths of each, they have been combined to maximize their benefits, enhancing delivery efficiency and improving the overall treatment outcomes.

Synergistic combination of VLPs and hyperthermia

VLPs, hyperthermia, and magnetic hyperthermia represent cutting-edge technologies in the fields of nanomedicine and cancer therapy. Their combination offers a promising approach for targeted drug delivery, imaging, and thermal ablation of tumors.

Magnetic nanoparticles, typically composed of iron oxides like magnetite (Fe_3O_4) or maghemite (γ-Fe_2O_3), are injected into the tumor site and activated by an external AMF.[160] The controlled heating induces apoptosis or necrosis in cancer cells while sparing surrounding healthy tissue.

Several groups have explored combinations of both techniques by adding one approach to another. Hoopes and co-workers evaluated the effect of intra-tumoral magnetic nanoparticle hyperthermia in an *in vivo* model for MTG-B mammary adenocarcinoma. They treated the tumor with iron oxide nanoparticles, applying an AMF, and added a modified version of the cowpea mosaic virus VLPs to induce a stronger immune response. In fact, this combined treatment enhanced the expression of pro-inflammatory cytokines like tumor necrosis factor-alpha, interleukin-6, enhanced the immunogenicity against the tumor, and reduced the tumor mass through cell death.[238]

The generation of VLPs with a magnetic core can be used in a series of applications, such as targeted drug delivery,[239] magnetic bioseparation,[240] and MRI contrast agents,[241] among others.[242] The use of superparamagnetic nanoparticles is preferred due to their reversible magnetization, which avoids NP aggregation.

It was already well established that synthetic nanocarriers can be thermally responsive, leading to chemotherapy drug delivery controlled by temperature,[243] but in 2019, Thong and co-workers developed a multifunctional nanovehicle based on the VLP of Macrobrachium rosenbergii nodavirus. In this work, they covalently conjugated folic acid to lysine residues located on the surface of Macrobrachium rosenbergii nodavirus, while doxorubicin was loaded inside the VLP. The objective was to deliver the cargo (doxorubicin) to tumor cells (HT29 colorectal cancer) rich in folic acid receptor (FR) using hyperthermia. They also tested two other cell lines with lower FR expression, and they concluded that, in fact, in the cells with higher FR receptors, the VLP uptake was higher.[244]

Intranasal delivery using different combinations for brain tumors

Primary brain tumors are classified as primary central nervous system (CNS) lymphoma, malignant ependymomas, meningiomas, lower-grade gliomas (I-III), and glioblastomas (Grade IV glioma). In addition, secondary brain tumors derived from metastasis from lung and breast tumors can also pose a threat to the patient's life. Glioblastoma is the most aggressive brain tumor, characterized by necrosis, microvascular proliferation, and rapid, infiltrative growth. Glioblastoma can arise as a primary tumor or develop secondarily from lower-grade gliomas. Treatment for patients with good performance status includes surgery, radiation, and chemotherapy, and even with the development of targeted therapy, the prognosis remains poor, with a median survival of 14–16 months and a five-year overall survival rate of 9.8%.[245]

Developing drugs whose action occurs in the brain is challenging, largely because of the BBB: endothelial cells in capillaries and other microvasculature of cerebral tissue, which function to protect the CNS against xenobiotics and maintain homeostasis, but impair the satisfactory delivery of pharmacological agents to the CNS.[246] A promising solution is intranasal drug delivery, which bypasses this barrier noninvasively by transporting drugs directly to the brain via the olfactory and trigeminal nerves.

The olfactory neurons extend axons through the cribriform plate. These axons are wrapped in the olfactory ensheathing cells and neural fibroblasts that form a protective sheath connected to the brain's protective layers (meninges), allowing drugs to move directly into the brain. These neurons are unmyelinated and bipolar, meaning they have two extensions. They can carry drugs to the CNS through the intracellular pathway, where drugs are taken up by olfactory sensory cells, transported along their axons to the olfactory bulb in the brain, and then spread to other brain regions through a process called transynaptic transport; and the extracellular pathway, where the drugs move through the spaces between cells in the nasal epithelium, then travel along the outside of nerve fibers to reach the brain's cerebrospinal fluid.[247]

Intranasal delivery is a promising method for treating brain-related conditions because it bypasses the BBB, a major obstacle for many drugs. It is non-invasive and allows drugs to reach the brain directly. Furthermore, other benefits include bypassing liver drug metabolism, reducing systemic toxicity.[248]

Problems with intranasal administration

Despite these advantages, intranasal administration of drugs also faces drawbacks, such as the reduction of drug penetration within the nasal epithelial membrane in the nasal chamber due to efflux transporters (P-glycoprotein),[249] metabolic enzymes, and mucociliary clearance.[250] Other side effects include sneezing, bleeding, among others.[251] Thus, alternatives for delivering drugs to the brain via the intranasal route using nanotechnology have been investigated.

Viral oncolysis through intranasal delivery

While in VLPs, natural viruses lacking genomes (replication-incompetent) are used, in viral oncolysis (VO), natural or engineered viruses that maintain their replication capacity are used. They have an intrinsic or induced capacity to replicate only in tumor tissue, leaving normal cells intact. This feature is related to the defective antiviral response of tumor cells (e.g., type I interferon response), dysfunctional tumor suppressor proteins (e.g., p53 or pRb), and overexpression of tumor survival factors in cancer cells. Normal cells are spared because their antiviral defense systems and tumor suppressor pathways remain intact.[252] There are a few naturally occurring oncolytic viruses; in addition, pathogenic viruses can be genetically modified to enhance tumor selectivity by removing virulence factors critical for infecting normal cells. Viral infection relies on cell surface receptors and intracellular interactions, with tumor-specific tropism. Once infected, these cells undergo strong proliferation, inducing tumor cell lysis. In normal cells, interferon activation inhibits viral replication, providing an additional layer of selectivity.[253] Therefore, this therapeutic modality depends on the ability of the virus to maintain its intact replication capacity.

Several studies have shown the capacity of viral strains to infect and kill brain tumors *in vivo*, *in vitro*, and in clinical studies.[254] Oncolytic viruses already studied for brain tumors include oncolytic H-1 parvovirus, herpes simplex virus-1, Reovirus, among others, with non-standardized delivery methods, including intratumoral injection, intravenous,[255] and also intranasal routes, using vesicular stomatitis virus.[256] However, this approach has a limited effect as monotherapy.[257]

To improve the efficiency of viral delivery for viral oncolysis, this method was combined with intranasal cellular delivery of oncolytic viruses. This promising approach involves the use of mesenchymal stem cells (MSCs) as anticancer therapeutics, as they are able to deliver proteins, genes, or oncolytic vectors.[258] This strategy is based on the observation that MSCs can cross the cribriform plate and migrate through the olfactory bulb to other parts of the brain, representing a non-invasive method for cell delivery to the CNS (Fig. 7).[259] Thus, this strategy uses MSCs loaded with oncolytic viruses to directly reach the brain,[260,261] avoiding the side effects related to direct intranasal drug delivery.

Using neurotropic viruses to generate VLPs

The VLPs under investigation to treat brain tumors mostly use the intravenous route or intratumoral injection, but data on the intranasal route through olfactory neurons have not been explored, as evidenced by the lack of literature data. Even though VLPs derived from non-neurotropic viruses can be modified to target neural cells,[262] one way to improve the specificity of these VLPs is to use viruses that have natural neurotropism.

In 2018, Chao and collaborators developed VLPs derived from the neurotropic JC polyomavirus, which infects glial cells and oligodendrocytes and causes fatal progressive multifocal leukoencephalopathy in patients with AIDS. They investigated the feasibility of a gene therapy strategy for glioblastoma using JC polyomavirus VLPs as a gene delivery vector.[263]

In contrast to non-replicating VLPs, oncolytic viruses are replicating viruses designed to destroy tumor cells. Examples include adenoviruses, herpes simplex virus, and rotaviruses, some of which are approved or under clinical trials for cancer therapy.[264] Notably, the Zika virus (ZIKV) has emerged as a promising oncolytic virus for treating glioblastoma due to its neurotropic nature and ability to infect glioma stem cells, which are resistant to conventional therapies like chemotherapy and radiation. ZIKV's specificity for glioma stem cells is linked to the expression of the AXL receptor, SOX2, and αVβ5 integrin, which are highly expressed in these cells.[265] Additionally, the Musashi-1 protein, which is overexpressed in tumors but not in most healthy tissues, enhances ZIKV replication in cancer cells while limiting side effects in patients due to restricted viral replication in normal tissues.

VLPs combined with other nanocarriers

Even though VNPs and VLPs represent an innovation in cancer

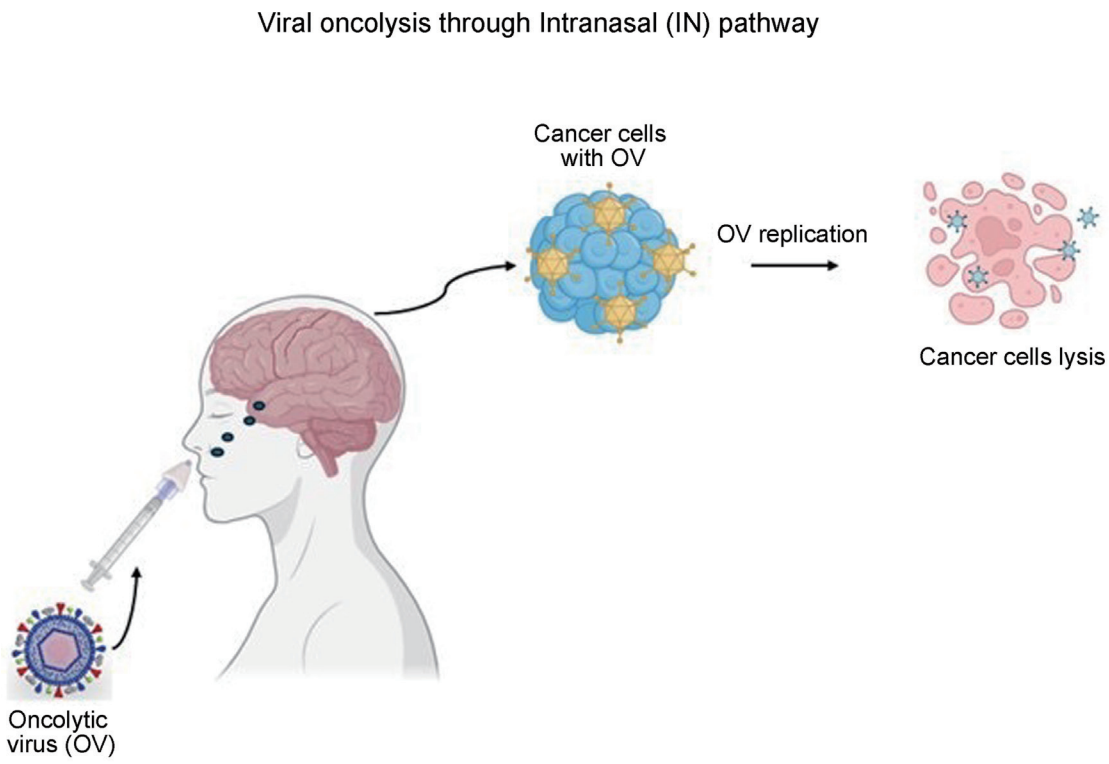

Fig. 7. Representation of viral oncolysis via intranasal pathway (IN). Intranasal inoculation of the oncolytic virus leads to olfactory nerve transport into the brain, infecting and killing tumors, while leaving normal cells intact, reinforcing the viral selectivity against tumor.

research and treatment, there are some issues that limit their efficiency. Among the limitations of VLPs regarding drug delivery are: payload capacity, pre-existing immunity, difficulty in crossing biological barriers, penetrating solid tumors, and physical instability. As can be seen below, and in Table 3, some combinations of VLPs with other nanocarriers have the potential to solve some of these problems.[206,266–273]

Payload capacity

VLPs may present low payload capacity. They have limited internal space, restricting the amount of drugs they can carry. Among the recent solutions to improve the delivery of VLPs' payload, Mg-based micromotors have been designed. This strategy utilizes the autonomous motion of biocompatible micromotors to actively deliver Qβ VLPs' payloads within the tumor area, enhancing the local distribution and retention time.[266] These micromotors utilize a core made of biocompatible and biodegradable Mg microparticle 'engine' covered with gold. The gold layer allows the micromotor chemical reaction with the water fuel, generating hydrogen bubbles in biological media. This method was evaluated to treat ovarian cancer *in vivo*.[266]

Pre-existing immunity

For the VLP to successfully reach the target tissues, it needs to avoid immune neutralization. The immunological response towards VLPs in cancer can reduce their efficiency, since those used for the prevention of cancer development (vaccines against oncoviruses) mostly use VLPs built of human viruses (such as HBV or HPV VLPs).[274] For the treatment of established tumors such as breast cancer and melanoma, human viruses are also used. In both cases, this can lead to the development of antibodies against VLP components, leading to neutralization and reducing the therapeutic response.[275] A solution in this case is the use of plant-based VLPs for targeting human tumor tissues; they can be targeted to the tumor tissue, but since they are derived from a plant virus, there's no off-target binding or immunological clearance. In addition, compared to the generation of synthetic or animal-derived nanoparticles, the synthesis of these plant-based VLPs is scalable, cost-effective, and environmentally sustainable. Even though a weak immunological response was observed, no signs of allergy were detected.[267]

Low permeability in the BBB

Improving the permeability of the BBB is critical for the treatment of brain tumors, and several cutting-edge strategies have been designed to achieve this goal. Parsamian *et al*.[268] engineered gold nanoparticles conjugated to Qβ VLPs, generating a polyvalent VLP-gold nanosystem, where the VLPs are decorated with gold nanoparticles to generate photothermal-induced nanobubbles. The transient nanobubble cavitation and collapse can temporarily induce openings in the blood–brain barrier.[268] Without conjugation with VLPs, gold nanostructures can induce tissue damage. This combination enhanced the efficiency of photothermal therapy.

VLPs' physical instability

Among the strategies where VLPs are used, there is antigen presentation. The size of the inserts in viral surface proteins is associated with increased instability.[276] Different viruses need different optimization protocols to reduce VLP instability.[277] More recent

Table 3. Limitations and cutting-edge solutions achieved with the combinations of different nanocarriers with VLPs

Strategy	Problems solved	Remainder challenges	Ref
VLP + Drug	Enhanced drug specificity towards the tumoral tissue.	Payload capacity, Low cell uptake, rapid clearance, pre-existing immunity, difficulty in cross biological barriers (BBB) and penetrate solid tumors and physical instability.	206
VLP + micromotors	Enhanced distribution and delivery of the payload.	NP Agregation	266
VLPs of plant origin	Evade immune neutralization, cost- effective and environmentally sustainable	Weak and transient immunological responses (IgG and IgE)	267
VLP + GoldNp	Enhanced photothermal efficiency using plasmon nanobubles (potential to induce transient BBB opening)	N.D	268
VLP + drug + GoldNp	Enhanced drug delivery	N.D	270
VLP + Metalic NPs	Enhanced physical stability of the VLPs	N.D	269
VLP + Magnetic NP	Enhanced payload capacity; Enhanced biocompatibility of magnetic NPs	Irregular aggregates and a large fraction of empty capsids	271,272
VLP + Silica NP (biomimetic)	Enhanced silica NP´cell uptake, improved immune Responses against Cancer	N.D.	273

IgE, immunoglobulin E; N.D., not detected or not discussed; NP, nanoparticle; VLP, virus-like particle.

approaches to reduce VLP instability use metallic nanoparticles coated with VLPs,[269] also enhancing drug delivery.[270]

Magnetic nanoparticles coated with VLPs

Magnetic nanoparticles have been developed for MRI contrast agents and cancer treatment, but among the issues detected was dispersibility in human fluids such as serum and blood.[271] They also have the potential to enhance payload delivery.[278] Coating magnetic nanoparticles with VLPs improved the dispersibility, and the conjugation with tumor-specific ligands (such as epidermal growth factor) efficiently targets tumor cells.[272]

Topology mimicking strategy

The topology of organic VLPs led researchers to develop methods to synthesize inorganic VLPs (viral-mimicking topography), to enhance internalization and efficiency of silica nanoparticles.[279] Kim *et al*.[273] developed a method where organic VLPs are used as a template to build silica nanoparticles. In their work, they produced VLPs made of HPV16 structural protein, encapsulated doxorubicin, and then performed controlled silicification of HPV16 VLPs, creating a silica nanocage.[273] Their results showed higher biocompatibility and cellular uptake than conventional mesoporous silica nanoparticles. However, the long-term toxicity of inorganic nanoparticles caused by accumulation in the reticuloendothelial system remains a challenge for clinical application.[280]

Limitations of this review

While this review provides an overview of the advancements in combining conventional anticancer therapies (drugs and antibodies) with nanoparticles, magnetic hyperthermia, and VLPs, it has certain limitations. We focused on innovative approaches and challenges but did not extensively cover all possible combinations of these therapies, potentially omitting some emerging or niche approaches. Given the fast evolution of this field, some recent studies or alternative viewpoints might not be included.

Future directions

Technological progress has allowed the integration of multiple strategies that individually enhance anti-tumor treatment efficacy. Synthetic nanoparticles, VNPs, and VLPs, when combined with chemotherapy and hyperthermia, improve targeting accuracy and minimize drug exposure to healthy tissues, particularly in resistant cancers. Intranasal drug delivery, which bypasses the BBB, also offers a promising approach for treating brain tumors. Despite these advancements, cancer remains a critical global health challenge, and widespread access to these innovative therapies continues to be a major barrier.

Magnetic hyperthermia is a promising technique for treating cancer, but it still faces several important limitations that hinder its widespread clinical use. One of the main challenges is the efficacy of delivering magnetic nanoparticles specifically to the tumor site. It is difficult to ensure that enough particles reach the tumor without affecting healthy tissue and to ensure uniform distribution. This uneven distribution can cause inconsistent heating, which reduces the effectiveness of the treatment and increases the risk of damage to nearby healthy tissue. Controlling and monitoring the temperature during treatment is also a major issue. Since heating depends on the concentration and distribution of nanoparticles, it is difficult to predict or regulate the temperature rise. In addition, accurately measuring the internal temperature in real time during treatment remains a technical challenge. There are also concerns about the materials used. Some nanoparticles can be toxic, especially if they are not biocompatible or if they remain in the body for a long time. Their long-term effects are not fully understood, and there is still no standard for what types of particles, coatings, or doses should be used. Another limitation is efficiency. Not all nanoparticles produce sufficient heat, especially when limited by the safe range of magnetic fields that can be used in humans. Stronger fields can increase heating, but they risk causing harm, such as nerve stimulation or tissue damage. From a clinical and practical perspective, magnetic hyperthermia is not yet widely available. The equipment is expensive, clinical trials are limited, and few nanoparticle for-

mulations have been approved for routine use. It is also primarily suited for more localized tumors, which limits its use in the treatment of disseminated or metastatic cancers.

Despite its challenges and limitations, the technique offers a fundamentally different mechanism of action than biochemical or molecular approaches. This makes it particularly useful for overcoming certain forms of drug resistance and for treating tumors that are less responsive to traditional therapies. As demonstrated, a major advantage lies in its strong potential for synergistic use with other treatment modalities. When combined with chemotherapy or radiotherapy, magnetic hyperthermia can enhance therapeutic outcomes by sensitizing tumor cells, increasing drug uptake, improving tissue oxygenation, and activating temperature-sensitive drug delivery systems. This multimodal capability makes it a versatile tool in personalized cancer therapy. In addition, the repeatability of magnetic hyperthermia treatments, made possible by the permanent presence of nanoparticles and the non-invasive nature of magnetic field application, adds a practical dimension to its appeal. Patients can undergo multiple treatment sessions without the need for additional invasive procedures or systemic drug administration.

In summary, while magnetic hyperthermia has real potential, issues related to targeting, control, safety, efficiency, and clinical readiness need to be addressed before it becomes a standard cancer therapy.

The application of VLPs faces several challenges, such as the complexity of large-scale production with high purity and stability. The variation in the immunogenicity of VLPs may affect their efficacy, while improvements in surface modifications, with special focus on tumor neo-antigens, may be considered to ensure efficient delivery to cancer cells, minimizing uptake by healthy tissues. Among magnetic hyperthermia challenges, there are difficulties in controlling heat distribution in target tissues, which can lead to damage to healthy cells, tumor heterogeneity and variations in nanoparticle concentration, and the development of nanoparticles with optimized magnetic properties, capable of generating sufficient heat in clinically acceptable magnetic fields.

Conclusions

Nanoparticles-based anticancer drug delivery improves cancer treatment, but tumors such as gliomas, imposes challenges that require alternative approaches. Even though intratumoral injection of nanoparticles to deliver drugs, therapeutic molecules or induce hyperthermia, improved the response to treatment, variable drug distribution within the tumor and potential leakage into surrounding non-tumoral tissue, uneven heat distribution (for hyperthermia), may reduce efficiency and increase toxicity.

The targeting capacity of VNPs and VLPs dramatically reduced toxicity and improved the antitumor response. The approval of VLPs for prophylactic vaccines and for cancer treatment, such as melanoma and breast cancer, has proven the success of this approach.

However, VLPs as monotherapy are less effective than when combined with conventional immunotherapy. Furthermore, the complex production of VLPs limits its scalability. Drug-loading efficiency, expensive cell culture systems, purification steps, batch-to-batch variability, and structural stability remain significant issues.

Thus, associating the targeting capacity of VNPs and VLPs with the efficiency of traditional drugs, immunotherapy, photothermal, gene therapies, and other nanocarriers may improve the results, leading to a concentrated effort to optimize VNPs and VLPs production, enhancing technical and economic viability, even though most of the optimization studies and their outcomes remain in the pre-clinical stage.

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Conflict of interest

Dr. Janaina Fernandes has been an editorial board member of the *Journal of Exploratory Research in Pharmacology* since November 2021. The authors have no other conflicts of interest to declare.

Author contributions

Study concept and design (RRB, LASO, JF), acquisition of the data (RRB, LASO, GSP, JF), assay performance and data analysis (RRB, LASO, GSP, JF), drafting of the manuscript (RRB, LASO, GSP, JF), and critical revision of the manuscript (RRB, LASO, JF). All authors have approved the final version and publication of the manuscript.

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