



Review

Nanotechnology in medicine revolutionizing drug delivery for cancer and viral infection treatments



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ABSTRACT

Advancements in nanotechnology were vastly applied in medicine and pharmacy, especially in the field of nano-delivery systems. It took a long time for these systems to ensure precise delivery of very delicate molecules, such as RNA, to cells at concentrations that yield remarkable efficiency, with success rates reaching 95.0% and 94.5%. These days, there are several advantages of using nanotechnological solutions in the prevention and treatment of cancer and viral infections. Its interventions improve treatment outcomes both due to increased effectiveness of the drug at target location and by reducing adverse reactions, thereby increasing patient adherence to the therapy. Based on the current knowledge an updated review was made, and perspective, opportunities and challenges in nanomedicine were discussed. The methods employed include comprehensive examination of existing literature and studies on nanoparticles and nano-delivery systems including both *in vitro* tests performed on cell cultures and *in vivo* assessments carried out on appropriate animal models, with a specific emphasis on their applications in oncology and virology. This brings together various aspects including both structure and formation as well as its association with characteristic behaviour in organisms, providing a novel perspective. Furthermore, the practical application of these systems in medicine and pharmacy with a focus on viral diseases and malignancies was explored. This review can serve as a valuable guide for fellow researchers, helping them navigate the abundance of findings in this field. The results indicate that applications of nanotechnological solutions for the delivery of medicinal products improving therapeutic outcomes will continue to expand.

1. Introduction

Nanotechnological improvements in medicine are growing continuously. Nowadays, achievements in the field of nanotechnology are vastly used for increasing efficiency and reducing harmfulness of diagnostic and therapeutic methods resulting in the development of new interdisciplinary scientific and technological fields. Nano molecules (NMs) have physicochemical properties that differ in many ways from materials

built from larger particles of the same chemical composition and can also be adapted to the scope of application, which gives them added value in technological terms (Jeevanandam et al., 2018). It is important to emphasize that nanomaterials can be of natural origin, synthetic or arise as by-products of production (Malakar et al., 2021). Nanomedicine and nanomedical engineering is aimed in improving the formulations of drugs and developing along with improving the systems based on NMs for various applications in medicine and pharmacy (Luo et al., 2015;

Abbreviations: ACE2 receptors, angiotensin-converting enzyme 2 receptors; DOX, doxorubicin; LNP, lipid nanoparticles; LPNPs, lipid-polymer nanoparticles; FDT, photodynamic therapy; mRNA, messenger RNA; NMs, nano molecules; NCs, nano-carriers; NP, nanoparticle; PAMAM, polyamidoamine; PLNE, porphyrin-lipid stabilized paclitaxel nanoemulsion; PTX, paclitaxel; ROS, reactive oxygen species; SLNPs, solid lipid nanoparticles; SPNPs, solid polymer nanoparticles..

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Patra et al., 2018). Breakthroughs in these areas have provided opportunities in prophylaxis, diagnosis and therapy of various diseases which were, until recently, unthinkable. Today, nanotechnological solutions are used in surgery, analytics, dentistry, dermatology, neuroscience, and other branches of medicine to help transfer diagnostic and therapeutic agents through biological barriers, ensure access to certain molecules, mediate certain molecular interactions or detect changes in molecules of interest (Das et al., 2017; Malakar et al., 2021).

The development of nanomedicines, or pharmaceuticals with the size and properties of nanoparticles (diameter ranging from 1 to 100 nm), also known as nano-carriers (NCs), is a result of advances in nano-medical engineering and nanomedicine. These NCs are acting as transport agents that improve the delivery of active substances to place where their action is needed (i.e., to the target structures). The active substance could be conventionally synthesized molecule(s), nanotechnologically enhanced molecule(s), and completely nanotechnology-based new drugs, and the target structure could be tissue, cell or even molecule (Luo et al., 2015). NCs protect the active substances (small molecules, peptides, proteins, or nucleic acids) allowing them to access the target structures in sufficient quantity and enable controlled spatial and temporal release of active substances. This is particularly beneficial for hydrophobic drugs, especially given that 40% of newly synthesized drugs face rejection from pharmaceutical industry for this reason (Sun et al., 2023). In addition, for mRNA, considering that without a carrier, less than 1 in 10,000 initially inputted molecules enter the target cell (Qin et al., 2022). Key property of NCs is their adaptability to the properties of active substance, target and the desired release pattern (Rinoldi et al., 2021). Furthermore, their size is a crucial factor in pharmaceutical applications, as particles—especially those intended for parenteral use—ideally should be smaller than 100 nm (Tenchov et al., 2021). NCs can be chosen based on these factors. For instance, micelles are effective for delivering amphiphilic and water-insoluble drugs, while liposomes enhance cellular uptake of various drug types (Sun et al., 2023).

The time of entrance of nanotechnology into field of delivery of active substances to the target structures was assigned to 1964s and the discovery of liposome structures. It took 30 years until the first clinically available nanomedicines arrived, but the development of this area has brought such improvements in treatment outcomes. Nanotechnology is now considered to be among the technologies with the greatest potential that contribute to the further progress of humanity (Bayda et al., 2019). Still, a small number of medications based on nanoparticles (NPs) have been authorised for use in clinical settings. The development and approval of NP-based drugs face challenges at various stages, including formulation, safety, efficacy, and regulatory considerations, also gap in translation between findings in animal studies and their applicability to humans makes it harder to get approval for the drugs (Mitchell et al., 2021). To address these challenges more research in this field is still necessary. The understanding of NC critical components and their key properties, and interactions with active substances results in the increased effectiveness, reproducibility, and stability of the molecule (Rashid and Ahmad, 2019). Even though some parts of this topic have formerly reviewed, a comprehensive overview like this that brings together various aspects including both structure and formation as well as its association with characteristic behaviour in organisms is still missing. To optimise the transport of active chemicals to target structures, particularly in the treatment of malignant diseases and the prevention and treatment of viral infections, this study seeks to provide an overview of the development and variety of nanotechnological solutions. This information may increase the quantity of clinically approved NP-based medications.

2. Nano solutions for drug delivery

2.1. Challenges in traditional drug development

Pharmaceutical industry has historically concentrated on producing small-molecule medications since they were easier to design and to produce in large quantities than giant molecules. However, clinical application of small-molecule drugs often suffers from weak specificity for targeted structures resulting in the dissipation of active substance to non-targeted structures leading to reduced efficiency, increased applied dose of drug, increased toxicity of the drug, side effects and the need for additional medications which also have their adverse effects, reduced adherence of patients with therapy, further impairment of the patient's health and higher cost of treatment (Al-Nemrawi et al., 2020; Zhang et al., 2018). As an illustration, only a little of the powerful anticancer medication cisplatin reaches the desired cells. According to pharmacokinetic studies, a significant portion of a drug (ranging from 65 to 98%) is therapeutically inactive as it binds to plasma proteins, primarily albumin (Gutierrez-Romero et al., 2024).

Other common examples in treating malignant diseases like doxorubicin (DOX), gemcitabine, fluorouracil and paclitaxel (PTX), are effective but also with numerous serious side effects. To avoid or combat these side effects, it is often necessary to introduce other medicines, e.g., antihistamines and/or corticosteroids (Aldea et al., 2020). According to the magic bullet concept (Zottel et al., 2019), the ideal drug would be the one that goes straight towards its target, and thus effectively attacks the target tissue, cell or molecule, and at the same time would not have any adverse effects on other tissues. Striving for this goal, in the last 10–20 years the use of nanotechnological solutions has surged for targeted drug delivery. Basic research in this field continually develops new nanomaterials with improved capabilities, gradually integrating them into clinical applications (Cryer and Thorley, 2019), (Khalid et al., 2023). Interestingly, the food and drug administration (FDA) and the European medicines agency (EMA) have jointly approved about 80 nanomedicine items for clinical use (Halwani, 2022).

2.2. Goals of nanotechnological improvements

The aims of nanotechnological improvements involve; (a) general improvement of pharmacokinetic and pharmacodynamic properties of the drug without changing its molecular structure, (b) the precise delivery of the drug to the target structure, (c) ensuring the possibility of circumventing biological barriers and (d) simple and easy production (Foulkes et al., 2020; Scioli Montoto et al., 2020), with help of NCs (Mosquera et al., 2018). By using NCs, pharmacokinetic parameters like absorption, distribution, metabolism, and excretion can be improved, which can reduce the frequency of medication delivery. This improvement can contribute to better compliance and ultimately improve clinical outcomes (Fig. 1(a)) (Alghamdi et al., 2022). NCs with a size of less than 100 nm can penetrate cells easily. Substances smaller than 35 nm are able to cross the blood-brain barrier and enter nuclei (Malakar et al., 2021). Various stimuli were examined for their ability to trigger drug release in NCs. These carriers can be made to react to both internal and external stimuli, including changes in pH, hypoxia, different enzymes, and ionic strength, as well as external stimuli like temperature, light, magnetic fields, and ultrasound. Furthermore, they can be tailored to respond to a combination of these stimuli, demonstrating their flexibility in controlled drug release mechanisms (Fig. 1(a)) (Mi, 2020; Patra et al., 2018).

Considering drug release triggered by change in pH, one of the basic properties of the NCs is their ability to "recognize" subtle differences in pH which exist between different parts of the body as well as between the disease-affected and healthy tissue. NCs not only protect the active substance from the place of intake to the target structure but also respond to changes in pH and adjust its size, shape, or hydrophobicity (Patra et al., 2018). An example of such NCs are hydrogels designed as

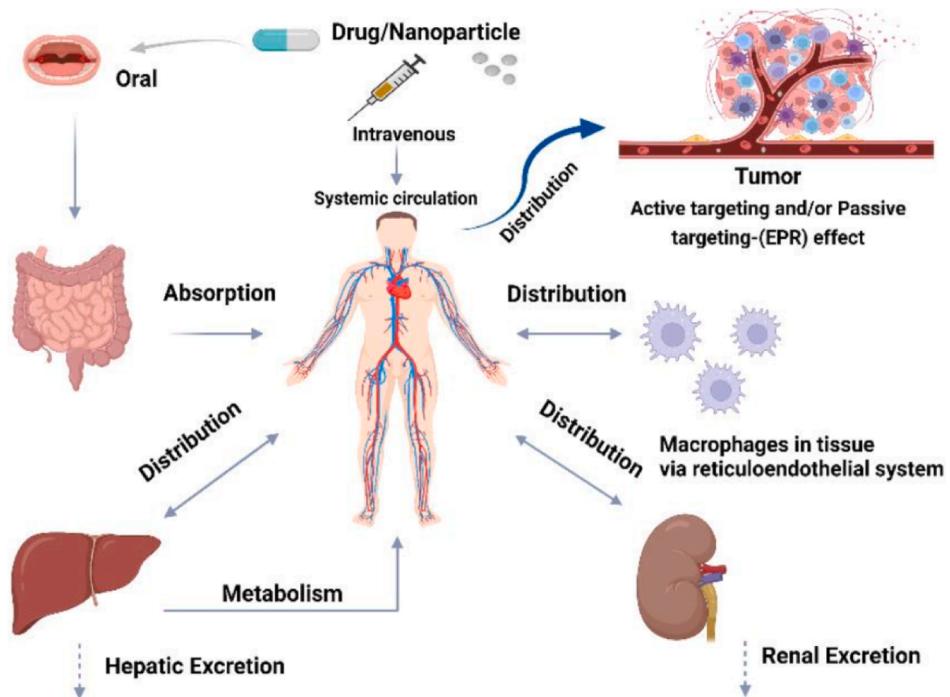


Fig. 1a. Complex goals of nanotechnological improvements in drug delivery systems. These include improvement in absorption- enhancing entry into the blood-stream through various administration routes (e.g., oral or intravenous), distribution – achieving precise drug delivery to the target site via passive or active targeting mechanisms, metabolism- increasing resistance to enzymatic degradation causing prolongation in drug's half-life and ensuring effective delivery of the appropriate dosage to the target site, excretion-facilitating hepatic or renal elimination pathways. Adopted with permission from (Alghamdi et al., 2022).

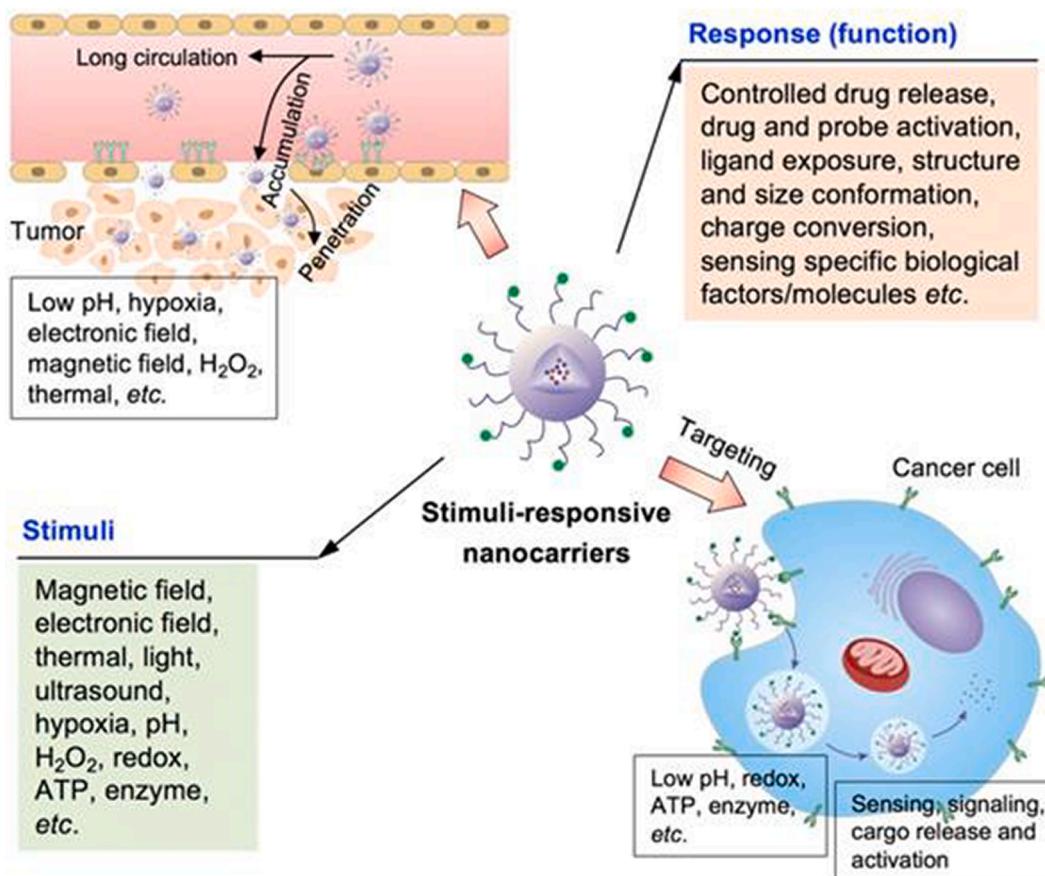


Fig. 1b. Various internal or external stimuli can affect NC accumulation in tumour tissue such as pH, hypoxia, electric field. NC respond in tumour tissue or directly in cancer cells causing controlled drug release, ligand exposure, and activation of other cellular structures. Adopted with permission from (Mi, 2020).

carriers of tetracycline and DOX, which at pH 1.2 and 7.4 show different degrees of biodegradability. At pH 1.2 they demonstrate reversible volume reduction exceeding 80% of the initial volume (Xu et al., 2018). Endocytosis is a mechanism by which NCs might enter cancer cells. To prevent additional breakdown in low-pH late lysosomes, endosomal/lysosomal escape is necessary. To release cargo into cancer cells, a number of intercellular pH-triggered NCs are currently being developed. Commonly found in endosomes (pH~5–6.5) or lysosomes (pH~4.5–5), low pH causes neutral or negatively charged NCs to undergo a positive charge transformation. This process is known as pH-triggered charge conversion NCs. Because of the protonation of cationic molecules, this positive charge conversion plays a role in the disruption of endosomes and lysosomes (Liao et al., 2020).

Certain chemical groups, such as citraconic anhydride, 2,3-dimethylmaleic anhydride, *cis*-aconic anhydride, carboxy dimethylmaleic anhydride, *cis*-4-cyclohexene-1, 2-dicarboxylic anhydride, etc., may be able to cause pH-triggered charge conversion (Mi, 2020). Conversely, bio-irritability can be accommodated by adjusting the gel's pH and level of crosslinking. These changes affect the bonds between the active substance and NC thus enabling the controlled release of the drug under certain environmental pH conditions. In this way, a targeted and gradual delivery of DOX is achieved over 2 weeks (Xu et al., 2018), also the risk of exposure of healthy organs (heart) to side effects of DOX is reduced (Mi, 2020). NMs also can respond to some other physicochemical stimuli such as temperature (40–42 °C in tumour tissue), charge, electric field, glutathione as an antioxidant, magnetic field, etc. Fig. 1(b) (Baig et al., 2021; Mi, 2020; Saleh, 2020; Sun et al., 2023) makes them promising for drug delivery to hypoxic tumours.

2.3. Nanoparticles used for drug delivery

The choice of NP form is a crucial factor in meeting specific application requirements. Various types are presented in Fig. 2. Each form has its characteristics, advantages and limitations which can be used to optimize NC according to the actual requirements (Singh et al., 2023). For example, variations in size can significantly alter the properties of NP, affecting both their physical and chemical characteristics. Due to their size, NPs exhibit an exceptionally elevated surface area relative to their volume making them very reactive. This increased surface area

makes their catalytic activity much stronger. Additionally, smaller NPs can more readily interact with cells and penetrate biological barriers. However, smaller NPs are also prone to agglomeration due to their elevated surface-to-volume ratio (Ogochukwu et al., 2024). Changes in size also influence its loading capacity. In the case of gold NPs size 25 nm drug loading capacity was 900 molecules, while those larger, sized 55 nm loaded about 15,000 molecules. Furthermore, larger particles, measuring 90 nm, demonstrate an even higher loading capacity, capable of carrying up to 55,000 molecules (Gutierrez-Romero et al., 2024). Moreover, the incorporation of specific molecules such as cyclodextrins (cyclic oligomers) into the structure of NCs can significantly enhance their performance in drug delivery systems. The benefits of both cyclodextrins and NPs are combined in cyclodextrin-conjugated NPs, which provide more variation and customisation in the creation of NCs suited to particular applications (Pandey, 2021; Sengupta et al., 2024).

The two most common forms of polymeric NPs are nanospheres and nanocapsules. The drug is embedded in an aqueous or oily core of nanocapsules, which are spheres measuring 5–1000 nm, but most commonly 100–500 nm. The shell of nanocapsules is made of a thin coating of synthetic polymers (poly (lactic acid), poly (lactic-co-glycolic acid) (PLGA), and poly (ϵ -caprolactone)) and natural polysaccharides rich in amino groups or carboxylic acid groups, chitosan, alginate, dextran, and protein-based polymers (Chatterjee et al., 2023). Chitosan is most common as a drug carrier and has proven itself best as a drug delivery system for infectious diseases, given that it binds very well to *S. aureus* (causing 1000 time reduction in intracellular bacterial number compared to classical administration of the same antibiotic) and *M. abscessus* (70 to 80% killing efficacy) (Anversa Dimer et al., 2020; Deng et al., 2020). The small size of nanocapsules enables penetration through basal membranes. Antibodies and cell-surface receptors can be added to their surfaces to enable targeted delivery of biomolecules. Polysaccharides are used as drug carriers due to their biocompatibility and mucoadhesive properties (Deng et al., 2020; Pathak et al., 2019).

Nanospheres are spherical structures with a nucleus composed of a polymer matrix and surrounded by a polymer sheath. The main difference between two most important polymer types of NPs is in the modality of drug loading (Christoforidis et al., 2012). The active substance can be dissolved and adsorbed into a polymer sheath or embedded in a polymer matrix. In addition, by incorporating different antigens or

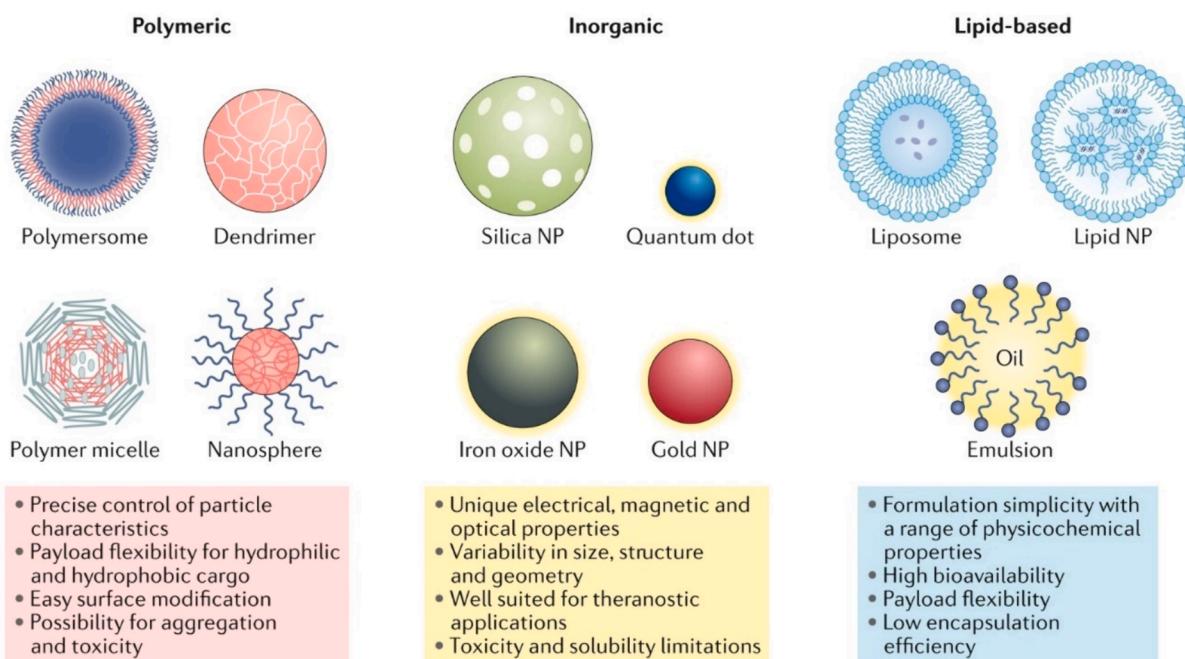


Fig. 2. Features of different nanocarriers: characteristics, advantages and limitations in drug delivery systems. Adopted with permission from (Mitchell et al., 2021).

antibodies as well as a material with magnetic properties on the surface, immunocompetent and magnetic nanospheres have been developed recently. The primary features of nanospheres are their capacity to evade phagocytosis, release the active ingredient gradually and uniformly, and move through intercellular gaps, which enables them to enter tissues that are difficult to access. A nanobiotechnological achievement is represented by nanospheres made of Fe-DNA ligand, where metal ion is regulator of the size and composition of the nanosphere causing loading efficiency of DNA between 50% and 73.8%. These particles facilitate the precise delivery of functional DNA at the cellular level particularly in breast tumour cells, exhibiting a 3.2-fold increase in accumulation within the tumour cells compared to traditional administration without nanocarriers (Li et al., 2019), (Ghosal et al., 2022). Following a 2-hour and 24-hour incubation of diverse cell lines with Fe-DNA nanospheres, a substantial increase of 44-fold and 30-fold, respectively, in cellular uptake was observed, as measured by fluorescence intensity using flow cytometry (Li et al., 2019). Through pH-controlled diffusion, the medication leaves nanosphere and controls the release of capsules containing weak polyelectrolytes. A shift in the polyelectrolyte film's degree of ionisation causes multilayers to swell (Mateos-Maroto et al., 2022).

Polymers with a highly branching structure are called dendrimers (Araújo et al., 2018). Gaps and flexible spaces in the structure of dendrimer facilitate the capture of molecules of active substance, and surface functional groups allow interaction with biological goals (Tripathy and Das, 2013). Their main pharmacological characteristic is the ability to bind different active substances and ligands on their terminal functional branches. This permits controlled release of the active ingredient and accurate distribution to the intended tissues. The overall percentages of apoptotic cells for drug docetaxel alone, docetaxel delivered via dendrimer, and the combination of trastuzumab and docetaxel delivered in dendrimer were 16.5, 32.7, and 42.6%, respectively, in the study that focused on HER2-positive and HER2-negative breast cells (Abedi-Gaballu et al., 2018b). In addition to other properties such as hydrophilicity, biocompatibility, immunological tolerability, and the ability to conjugate or encapsulate the drug, they also exhibit excellent properties of facilitating cell entry, retention in circulation and stability, making them almost ideal NCs (Abedi-Gaballu et al., 2018a).

Spherical shape and amine groups on the surface give them the ability to be modified to suit their purpose and also allow uniform and prolonged release of the active substance. This can be even more fine-tuned usually by using the appropriate bond between NC and active substance (amide and ester bonds are commonly used for smaller molecules and disulfide for larger ones) and also by a selection of hydrolysis mode (enzymatic or pH-dependent) (Ambekar et al., 2020; Markowicz et al., 2022). A polyamidoamine (PAMAM) dendrimers are a large family of dendrimers made of synthetic polymers. It's interesting to note that some PAMAM dendrimers have anti-inflammatory qualities and can boost drug's penetration into the skin by two to four times as compared to when it's administered traditionally (Chauhan, 2018). Moreover, under conditions of elevated temperature, as observed in tumour tissue (43 °C), the drug release rate is significantly increased (95% within 20 h), compared to the release rate at physiological temperature of 12% within the same time frame (Ambekar et al., 2020). The properties of other types of dendrimers like PPI/POPAM, kyral, tecto, hybrid, amphiphilic and peptide dendrimers (among them frechet and polydopamine-organosilicon dendrimers) have been extensively researched recently (Abedi-Gaballu et al., 2018b; Araújo et al., 2018; Surekha et al., 2021).

Amphiphilic copolymers are used to create polymeric micelles, which are designed to serve as a unique colloidal carrier for the delivery of amphiphilic and weakly water-soluble medications. The outer, hydrophilic layer and small size, give basis for pharmacokinetic properties, reduce unwanted decomposition of active substance, and ensure the dispersion of micelle. The internal, hydrophobic, layer serves to sequester the water-insoluble active substances and reduce the removal

of drug from circulation through reticuloendothelial system (Ghezzi et al., 2021; Majumder et al., 2020). Their main characteristic is the survival in solution dependent on the molecules and ions from which they were formed (Han et al., 2013). These micelles, with high water solubility and adaptable applications, have a remarkably low critical micelle concentration ranging from 10^{-6} to 10^{-7} M ensuring stability even in diluted biological fluids (Majumder et al., 2020). A study was conducted that proves the effectiveness of polymer micelles as nanocarriers of drug DOX and PTX. In the study, coumarin and imidazole were used to prepare polymer as shown in Fig. 3. A comparison was made between the drug loading of micelles made from polymer grafted with imidazole and coumarin, polymer grafted with coumarin alone, and polymer alone. Micelles that were grafted with imidazole and coumarin demonstrated a high drug loading of 17.2%, whereas those that were grafted with coumarin alone demonstrated 16.5%. When compared to 9.6% DOX loading achieved with the unaltered polymer, these results were noticeably higher (Kotta et al., 2022). In the case of PTX nanomolecular administration in conjugate polymer carboxymethyl chitosan-rhein (CR) increased drug uptake up to $35.46 \pm 1.07\%$ (Wang et al., 2020b).

Liposomes, or lipid-based NPs, are emulsion particles that have found use in pharmaceutical industry for several reasons, including targeted drug administration, extended drug release, and enhanced drug solubility and bioavailability at the site of action (Shah et al., 2020). They are sphere-shaped vesicles of microscopic dimensions with a hollow core filled with liquid surrounded by a membrane built of phospholipid bilayer. Because of their structure, they can incorporate both liposoluble and hydrophilic active substances (liposoluble active substances are incorporated into phospholipid membrane, and hydrophilic substances are incorporated into nucleus). Prior research has confirmed that they can incorporate molecules of different sizes, ranging from 243 to 1278 g/mol (Shah et al., 2020). Because of excellent qualities that all of the aforementioned produce, including low toxicity, biocompatibility, and biodegradability, liposomes are the most frequently FDA-approved type of NPs (Mitchell et al., 2021). The results revealed a significantly higher cardiotoxicity risk in patients undergoing traditional administration of DOX compared to those receiving liposomal administration (HR = 3.16; 95%, CI 1.58–6.31, $p < 0.001$). Traditional DOX administration caused a greater incidence of adverse effects, including alopecia (66% compared to 20%), nausea (53% compared to 37%), vomiting (31% compared to 19%), and neutropenia (10% compared to 4%), when contrasted with the liposomal administration (Jiang et al., 2023). Liposomes are most often used in the production of drugs for rare and serious diseases (gene therapy, monoclonal antibodies, peptides and proteins), oncological drugs and drugs for neurodegenerative diseases and diabetes (Shah et al., 2020).

On the other side, liposomes have certain limitations that suppress their widespread application. They are rapidly cleared from circulation, unstable, have low incapacitation efficiency, high price and also, an unpredictable tendency towards gelatinization and insufficiently improved incorporation efficiency (Naseri et al., 2015; Paliwal et al., 2020). Since 1990s, liposome systems have continuously been replaced by solid lipid nanoparticles (SLNPs) (Duan et al., 2020b). These NPs are synthesized from solid lipids at room temperature and additionally stabilized with emulsifiers. The core composed of solid-state lipids (triglycerides, complex mixtures of glycerolipids and waxes) is bounded by a surfactant layer forming a spherically shaped structure sizing 40–1000 nm in diameter. The combination of lipids and surfactants affects physicochemical properties as well as stability and encapsulation efficiency. The active substance is incorporated by dissolution in lipid component (stearic acid, oleic acid, compritol 888) heated to 5–10 °C above its melting point. Due to the absence of inflammatory lipid components, they could be considered appropriate for delivering drugs to the eyes. Tobramycin was encapsulated in SLNPs and demonstrated a 1.5-fold increase in c_{max} and an 8-fold increase in t_{max} compared to a reference eye drop solution (Duan et al., 2020a). They can also be

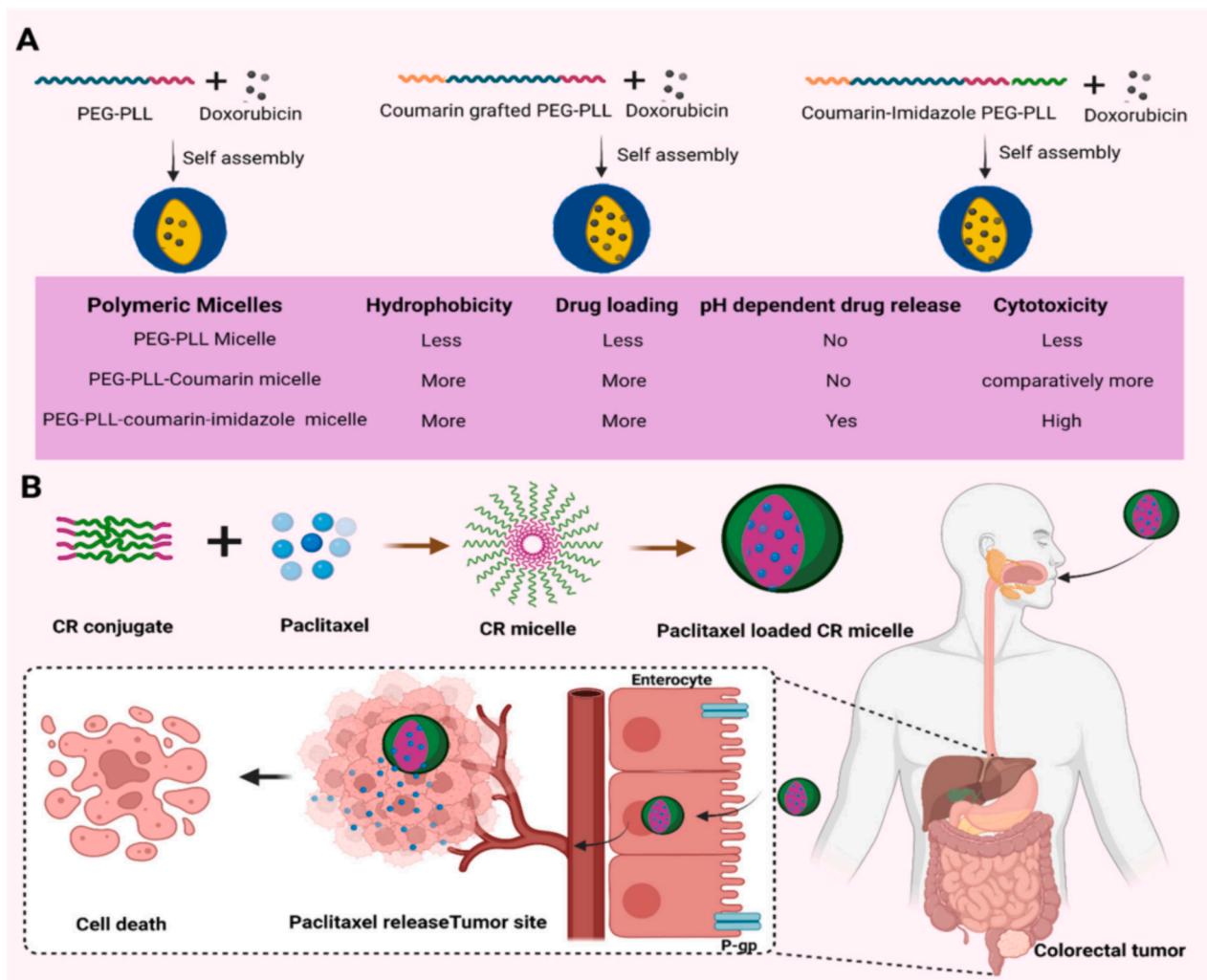


Fig. 3. (A) Doxorubicin-loaded polymeric micelles grafted with imidazole and coumarin demonstrate pH-dependent drug release and (B) Conjugate polymer carboxymethyl chitosan-rhein (CR) application in colorectal tumour treatment. Adopted with permission from (Kotta et al., 2022).

modified to release the drug according to desired pattern by changing their composition and matrix structure, the composition and concentration of surfactants, and the place of implantation of active substance into the carrier (Duan et al., 2020a). SLNPs have been used in the delivery of anticancer medications, mRNA vaccines, and gene therapy because of their pharmacokinetic qualities and suitability for large-scale manufacture (Naseri et al., 2015; Palival et al., 2020).

The more recent class of NC, known as lipid-polymer nanoparticles (LPNPs), was developed to fulfil the need for delivering two or more medications with various physicochemical characteristics to the intended structure. Usually, core is made of polymer, and it is surrounded by a layer of lipids. Another layer of lipids, most often polyethylene glycol (PEG), is usually deposited on the surface of structure. Their structure consists of three blocks (Mukherjee et al., 2019). The outer layer serves as protection against immune mediation and clearance, the middle layer serves to protect the core from penetration of water and to secure the active substance integrated into the nucleus from precocious release. They demonstrate usefulness for targeted drug delivery in chronic obstructive pulmonary disease and lung cancer, leading to a significant reduction in tumour size in mice, decreasing from 1486 to 263 mm³ (Chikuma et al., 2020; Wang et al., 2018). The ability to modify multiple properties, including the amount of encapsulated drug, kinetics of the drug's release, stability of the drug in serum, and accuracy of delivery to the target tissue, cell, or molecule, suggests that NC structured in this way has a bright future in the delivery of oncology drugs as well as DNA

or RNA materials, even though their use is not yet very widespread. The amphiphilic properties of polymers and lipids have made it possible to execute stable nanosystems for the delivery of various hydrophilic and/or hydrophobic medications (Dave et al., 2019; Mukherjee et al., 2019).

3. Gateways for nanocarriers' entry into cells

Once a suitable NC has been synthesized, one of the primary challenges is effective delivery to target cells. However, the success of this delivery is significantly influenced by the chosen administration route. As previously mentioned, absorption is defined as the entry of nanomolecules into the bloodstream through various administration routes (e.g., oral or intravenous). Oral type of administration is without discomfort and leads to increased compliance among patients with various conditions, and it is the most common type of nano-drug administration (Vitulo et al., 2022). However, certain orally administered drugs confront various biochemical, biological, and physical barriers before absorption into systemic circulation, resulting in a decrease in therapeutic effectiveness (Alghamdi et al., 2022), (Sahoo et al., 2021). Unpleasant conditions in our digestive system like low pH in the stomach, various enzymes that can cause degradation or simply drugs insoluble in our digestive systems are problems in drug administration that decrease therapeutic effectiveness. Nanodrugs are designed in a way that the drug is encapsulated into NC and protected from these conditions, so the process of absorption is affected by structure of NC

itself. They can be absorbed within the gastrointestinal tract through diverse mechanisms; uptake by M cells, passive diffusion across cell membranes, carrier-mediated transcytosis or paracellular transport (Tashima, 2021). This enables NPs to access the systemic bloodstream either through portal vein or via intestinal lymph nodes. When NC is absorbed through M cells, the bioavailability of drug is increased due to the evading of efflux mediated by P-glycoprotein, hepatic first-pass and metabolism of CYP450 (Alghamdi et al., 2022).

3.1. Enhancing target delivery through modifications in nanocarrier membranes

By delivering active substance to the cell, NCs influence various cellular processes, including ATP-ase activity, mitochondria, membrane transport proteins, the transmission of apoptotic signals, and gene expression. Therefore, optimal NC should enable preservation of drug properties in circulation, make it possible to pass through barriers like the liver and spleen, and also prevent the loss of drug through intercellular spaces of endothelia into extravascular space. This addresses the importance of paying special attention to size and surface area in the design of NCs. They should be both large enough to stop the medication from spreading throughout the body and small enough to evade macrophages, which are mostly found in the liver and spleen's reticuloendothelial system (Rinoldi et al., 2021). In addition, interventions on their surface affect the NC's half-life (Ghosh and Biswas, 2021). For instance, hydrophilic polymer coatings like PEG combined with plasma protein repulsion can inhibit opsonization and thereby NC phagocytosis by macrophages. The data indicate that within 5 min 66% of non-PEGylated NPs is cleared from circulation, while in the case of PEGylated NPs less than 30% accumulates in liver 2 h post-injection, highlighting prolonged stability in circulation. Therefore it became one of the basic ways to prepare surface of NC (Harris et al., 2001).

Additionally, by applying positive charges or active ligands to the

surface that would subsequently react with a negatively charged cell membrane or particular proteins on the surface of target cells, it is possible to promote first interaction of NC with the target cell membrane (Park et al., 2017). In addition, one of the properties of great importance is to make NC resistant to non-target tissue cell takeover. This is extremely important for oncologic drugs because their high toxicity urges precise delivery to the tumour tissue. There are two basic approaches to accommodate this scope. The first, passive approach uses a universal property of the tumours to retain macromolecules that pass through more permeable tumour blood vessels. This retention of molecules is due to an increase in interstitial pressure in tumour tissue that prevents the formation of a functional lymphatic system that would return accumulated molecules to circulation (Wu, 2021). Polymeric micelles with a cross-linked anionic core serve as an example. At pH 7.4, they exhibit a significant negative charge (zeta potential – 18 mV), which decreases to – 7 mV at pH 5, causing micelles' size to contract from 150–160 nm to approximately 110 nm. These NCs use caveolae-mediated endocytosis to specifically enter cancer cells. Because this form of endocytosis cannot occur on apical side of epithelial cells, NCs cannot enter healthy cells. However, in tumour cells, they efficiently reach lysosomes within 30 min and release cargo due to changes in pH (Sahay et al., 2010).

However, this approach is limited by its dependency on the type, perfusion characteristics and localization of tumor as well as by physicochemical properties of the drug (Rinoldi et al., 2021; Wu, 2021). The second, active, approach, demands equipping NC with the specific ligands which will then be recognized by receptors on the surface of cells of the target tissue. Tumour cells display a range of specific receptors on their surface, for example, more than 40% of cancers in humans exhibit an overexpression of folate receptors. For this purpose, NS are equipped with, antibodies, polypeptides, aptamers, transferin and folic acid Fig. 4 (Sun et al., 2023), (Liang et al., 2017). This step is crucial for effectiveness and precision of delivery because the internalization is limited

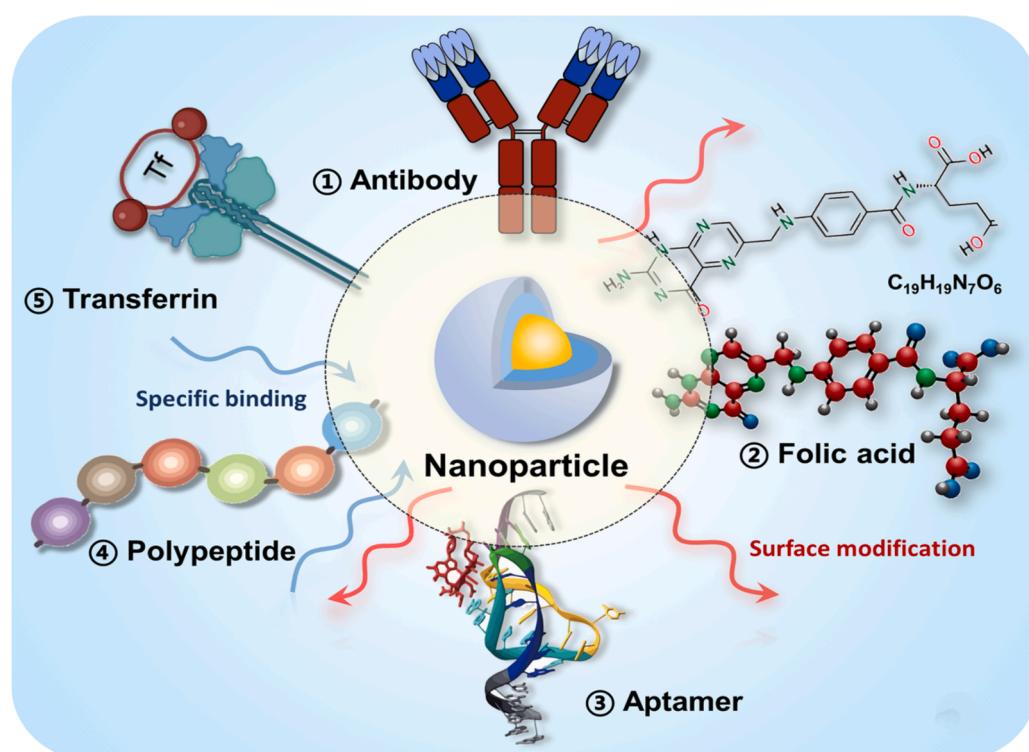


Fig. 4. Surface modification of nanoparticles with specific ligands enables active targeted drug delivery through specific binding with corresponding receptors. 1-monoclonal antibodies, 2-folic acid; increased uptake due to interaction with overexpressed folate receptors on cancer cells, 3-aptamers; consist of short sequences of nucleic acids (RNA, double-stranded DNA or single-stranded DNA) 4- polypeptides; which binds to specific receptors with high affinity, 5-transferin; increase uptake due to interaction with overexpressed transferrin receptor on cancer cells. Adopted with permission from (Sun et al., 2023).

by the physical capacity of internalization mechanism (Rennick et al., 2021).

3.2. Diverse endocytosis mechanisms for targeted delivery

Two main cytoplasm receptor-mediated internalization mechanisms; direct fusion with the membrane of cell and endocytosis demonstrate effective uptake when nanoparticles of about 50 nm are utilized (Mitchell et al., 2021; Rennick et al., 2021). Direct fusion is used by some encapsulated viruses but also some NCs (Tang et al., 2013). However, for most of NCs, endocytosis is the main internalization mechanism and a key step to achieving the biology effect of drug within the cell. At least five primary forms of endocytosis exist: The three types of endocytosis are as follows: (1) clathrin-coated pit-mediated endocytosis, which is dependent on both clathrin and dynamin; (2) fast endophilin-mediated endocytosis, which is independent of both clathrin and dynamin; (3) clathrin-independent carrier/glycosylphosphatidylinositol-anchored protein-enriched early endocytic compartment endocytosis, which is dependent on both clathrin and dynamin; (4) micropinocytosis (creation of macropinosomes sized 0.2–5 μm), and (5) phagocytosis (for particles ≥ 0.5 μm). These processes take place in nearly all eukaryotic cells (Sousa de Almeida et al., 2021). Noteworthy, different mechanisms could be applied to introduce the same nanosystem into different cells. This emphasizes the importance of understanding diversity of internalization mechanisms and their interdependencies for the development of NC with optimal performances (Das et al., 2017; Rennick et al., 2021; Rinoldi et al., 2021).

Some of the processes of entry of nanomedicines into cell are shown

in Fig. 5 (Sahay et al., 2010). It is also important to notice that the introduction of NCs into a cellular medium or their *in vivo* application into circulation causes serum proteins to adhere to their surface, creating a conglomerate that alters the initial properties of NCs. This may lead to aggregation and deposition before reaching targeted structure. In addition, serum proteins can induce attachment to the self-specific proteins of the cell membrane that could lead to the activation of biological effects in non-targeted location (Rennick et al., 2021). The pathway of introduction of drug into organism significantly determines the properties that NC needs to have for the specific situation. Thus, for oral administration, NCs should be stable during passage through gastrointestinal system; in those for percutaneous, nasal and inhaled administration, it will be sought unclerical transport through epithelial membranes; of those expected to act in central nervous system – the ability to pass the blood-brain barrier, and from oncology drugs high specificity and adaptability to the conditions of tumour tissue (Goyal et al., 2019). Nanotechnological improvements for delivery ensure the recognition of target tissues according to their physicochemical characteristics and in this regard, they are becoming more efficient every day.

4. Advanced solutions for delivery in oncology

According to world health organization (WHO), malignant diseases demonstrate an elevated mortality rate, resulting in 10 million global deaths annually (Mattiuzzi and Lippi, 2019; Nakhaei et al., 2021; Qiu et al., 2021; Siegel et al., 2023; Sun et al., 2023). The development of malignant cells is caused by unique features of uncontrolled cell growth.

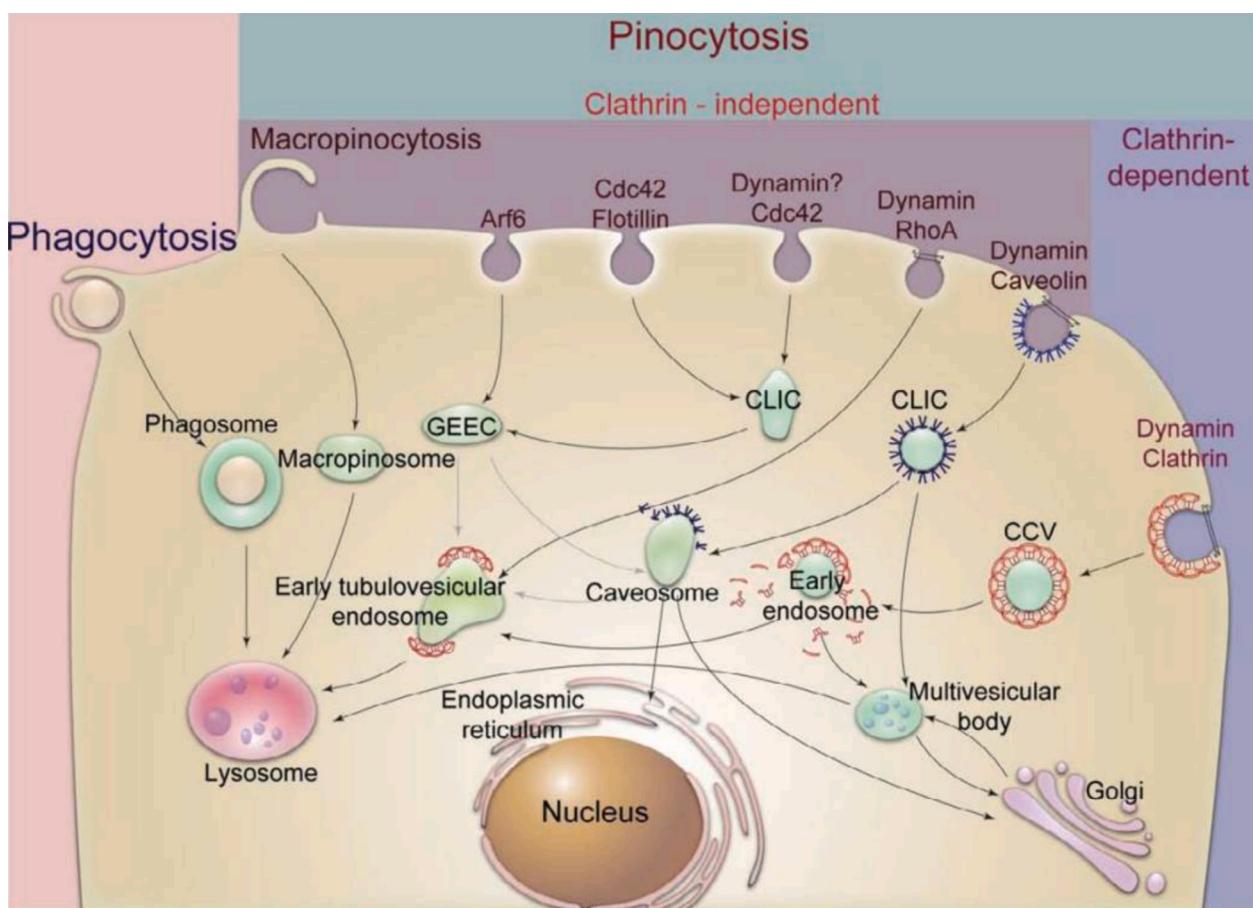


Fig. 5. Types of endocytosis – important mechanisms for entry of nano drugs into cells. The first step is cellular entry via different internalization mechanisms. The second phase typically includes sorting of early and late endosomes. Subsequently, the last step involves delivery of the drug to its final destination. Adopted with permission from (Sahay et al., 2010).

Consequently, they can damage surrounding tissues and spread all over the body through blood and lymph systems. Malignant development is also caused by incapacity to stop excessive cell proliferation, the lack of apoptosis, and capacity to invade nearby and distant tissues. Traditional tumour treatments cause significant side effects, mainly due to toxicity of healthy tissues, causing cardiovascular complications, neurotoxicology and sub-/infertility. Cardiovascular diseases stand out as the most prevalent cause of mortality among tumour survivors. Out of 3.23 million oncological patients in USA, 38% passed from cancer, while 11.3% passed from cardiovascular disease. This indicates the growing importance of cardio-oncology field in medicine, where nanotechnological solutions can be promising alternatives in pursuit of newer therapeutic options (Jiang et al., 2023).

The primary goal is the development of NCs that would upgrade therapeutic efficiency and safety profile of conventional anticancer drugs. This is important because more than 40% of these drugs have low water solubility (Tenchov et al., 2021). As previously said, medication-loaded NCs have the ability to deliver anticancer medications to the intended locations by either loading them with ligands unique to targeted region or taking advantage of pathophysiology of tumours. For example, accelerated growth of tumour blood vessels results in larger fenestrations (>100 nm), enhancing their permeability to NPs (Tenchov et al., 2021). As an illustration, when imatinib is administered via NP, it accumulates more in tumour causing its regression. This resulted in an increased survival rate of up to 40% after 60 days, in a melanoma mouse model (Mitchell et al., 2021). For the delivery of a single or combination of multiple drugs incorporated into one NC, LPNP has recently been increasingly investigated aiming to overcome two main concerns of treatment: (1) poor drug accumulation in the target tissues, and (2) tumour hypoxia induction that accelerates the development of drug resistance and increases tumour invasiveness (Table 1) (Mukherjee et al., 2019). As nanotechnology brings solutions for targeted drug delivery, many companies nowadays trying to protect their authorship rights for developed systems and to ensure a return on investment as well. That is the reason why most of them go for patent registration. Table 2 gives list of recent patents on nanoformulation solutions used in oncology and virology. It is obvious that cancer is much more in focus compared to other viral diseases.

4.1. Paclitaxel as nanomolecular therapeutics

Paclitaxel (PTX) is an antineoplastic drug that has been used individually or in combination with other drugs for the treatment of ovarian, breast, advanced microcellular lung cancer and Kaposi sarcoma associated with acquired immunodeficiency syndrome for about twenty years. However, it might result in major side effects such as hypersensitivity reactions, haematological diseases, peripheral sensory neuropathy, myalgia, and arthralgia, patients typically tolerate it poorly (Chou et al., 2020). To minimize the effects of these serious side effects, several nanotechnological solutions have been designed to improve bioavailability, stability and pharmacokinetics of active substance and increase its delivery to the target tissues that consequently leads to an increase in patient adherence to treatment and, ultimately, improves overall treatment outcomes (Jiang et al., 2023), (Džidić-Krivić et al., 2023). PTX is a hydrophobic molecule (solubility <0.01 mg/mL), and first objective was to increase water solubility. Therefore, bioavailability of PTX by conjugation with hydrophilic molecules – mostly polyvinyl alcohol. Moreover, conjugation with PEG, polystyrene-comaleic acid, and cellular-penetrating peptide tLyP-1 improved treatment outcomes in terms of reducing toxicity and increasing safety, adding pH sensitivity and tumour cell identification, respectively (Peng et al., 2019). Binding of PTX to albumin NPs (Nab-PTX) improves the passage through endothelial cells by using active conveyors activated by albumin binding to glycoprotein 60. In addition, albumin also binds to SPARC protein secreted in certain types of tumours, which facilitates the accumulation of Nab-PTX in tumour tissue (33% higher AUC compared to an

equivalent dose of solvent-paclitaxel) (Montana et al., 2011).

The research on the application of liposomal double-layer protection to PTX liposomes goes back to early 1990s (Liu et al., 2019; Pascual-Pasto et al., 2022; Wang et al., 2020a). In newer formulations of liposomal PTX (L-PTX) stability and cellular uptake of L-PTX were improved by coating with PEG to avoid rapid aggregation and collapse of liposomal two-layer (Nakhaei et al., 2021). Moreover, PEGylated liposomes significantly reduced monocyte phagocytosis resulting in significant elongation of drug half-life (Münster et al., 2022). However, PEGylation also has its disadvantages. As PEG is a synthetic polymer, mammalian cells cannot decompose it and resulting accumulation can harm their function. In addition, PEGylated liposomes interact poorly with tumour cells due to watery layer on their surface attributed to PEG (Caddeo et al., 2018; Mohamed et al., 2019). Therefore, coating of the liposomes was attempted with other polymers and peptides. A recent study compared properties of L-PTX coated with gelatin that is a natural protein containing arginine, glycine and aspartate sequences that are ligands for integrin receptors in cancer cells (Battogtokh et al., 2022; Niebler et al., 2017; Teede et al., 2018). Small and physically stable gelatin-coated liposomes have proven good not only for PTX encapsulation but also for controlling PTX release as it has been shown that the rate of release depends on degree of gelatin coating. In addition, they seem to be superior to PEGylated liposomes in targeting cancer tissue (Battogtokh et al., 2022). The gelatin coating mechanism increased cell uptake of liposomes by 2.50 to 3.58 times compared to PEGylated liposomes. It consists of two stages; firstly, the loose structure of vascular endothelial cells surrounding cancer facilitates the accumulation of liposomes, primarily due to enhanced permeability and retention (EPR) effect. It is considered to increase NP accumulation up to 10–15%, compared to 0.1% accumulation of free drugs (Mitchell et al., 2021). Following this, gelatin binds to integrin receptors on cancer cells, initiating endocytosis (Battogtokh et al., 2022).

To improve properties of NCs, the formulations are getting more and more complex. Another NCs for PTX (FA-BSA-LC/DOPE-PTX) combined 1,2-dioleo soleil-sn-glycerol-3-phosphoethanolamine (DOPE) for pH-sensitivity, and oleic acid, folic acid, and bovine serum conjugate (FA-BSA) for PTX sheath. FA-BSA-LC/DOPE NC has been shown to significantly contribute to improving the delivery of PTX to tumour cells. Folic acid when incorporated into NC structure, binds to folic acid receptors on cancer cells, facilitating endocytosis. This enhancement in the delivery of PTX results in a remarkable tumour growth inhibition rate of 79.3%. In comparison, the same NC without folic acid achieved a rate of 68.6%, while rates of 46.9% and 58.7% were observed for other simpler NC structures, respectively ($p < 0.01$) (Chen et al., 2015).

Recent improvements are also aimed at enabling more therapeutic modalities and combining multiple types of drugs into a single system. Thus, porphyrin-lipid stabilized paclitaxel nanoemulsion (PLNE-PTX) was created to combine photodynamic therapy (PDT) and antineoplastic PTX treatment. PDT is a minimally invasive therapeutic option that uses photosensitive substances that accumulate in tumour tissue to produce reactive oxygen species (ROS) after they are exposed to the light source. ROS then induces necrosis and apoptosis of tumour tissue, damages tumour blood vessels, reduces the supply of oxygen and micronutrients to tumours, and activates immune response resulting in tumour regression. However, PDT has its limitations arising from unavailability of tumour tissue for illumination or dissemination of malignant disease (Avci et al., 2013). On the other hand, anticancer drugs are effective in eradicating tumours and often cause damage in other tissues as well. The carrier is derived from a shell made up of porphyrin-lipid, which is amphiphilic due to the phosphate hydrophilic head of the molecule and carbohydrate, hydrophobic tail. The core consists of an oil phase, glyceryl-tri octanoate in which hydrophobic PTX is integrated. A stable nanoemulsion with spherical PLNE particles with a uniform diameter of 119.7 ± 0.6 nm suitable for longer-term storage was obtained. The animal model showed stability in circulation with a half-time decay of 3.67 ± 0.22 h and rapid intracellular transition of PLNE to tumour cells.

Table 1

Clinically approved nanocarriers loaded by anticancer drugs along with nanocarriers currently under evaluation for drug delivery (Sun et al., 2023).

Company and brand name	Particle type/drug	Approved application/indication	Approval (year)	Investigated application/indication
Janssen, –Doxil Caelyx	Liposomesdoxorubicin (PEGylated)	Ovarian cancer (secondary to platinum-based therapies) HIV-associated Kaposi's sarcoma (secondary to chemotherapy), multiple myeloma (secondary)	FDA (1995) EMA (1996)	Various cancers including solid malignancies, ovarian, breast, leukaemia, lymphomas, prostate, metastatic, or liver
Galen, –DaunoXome	Liposomesdaunorubicin (non-PEGylated)	HIV-associated Kaposi's sarcoma (primary)	FDA (1996)	Various leukemias
Teva UK, –Myocet	Liposomesdoxorubicin (non-PEGylated)	Treatment of metastatic breast cancer (primary)	EMA (2000)	Various cancers including breast, lymphoma, and ovarian
Celgene, –Abraxane	Albumin-particle bound paclitaxel	Advanced non-small cell lung cancer (surgery or radiation is not an option), metastatic breast cancer (secondary), metastatic pancreatic cancer (primary)	FDA (2005) EMA (2008)	Various cancers including solid malignancies, breast, lymphomas, bladder, lung, pancreatic, head and neck, prostate, melanoma, or liver
Spectrum, –Marqibo	Liposomes vincristine (non-PEGylated)	Philadelphia chromosome-negative acute lymphoblastic leukaemia (tertiary)	FDA (2012)	Various cancers including lymphoma, brain, leukaemia, or melanoma
Millennium, Mepacet	Liposomesmifamurtide (non-PEGylated)	Treatment for osteosarcoma (primary following surgery)	EMA (2009)	Osteosarcomas
Merrimack, –Onivyde MM-398	Liposomes irinotecan (PEGylated)	Metastatic pancreatic cancer (secondary)	FDA (2015)	Various cancers including: solid malignancies, breast, pancreatic, sarcomas, or brain
Jazz Pharmaceuticals, –Vyxeos CPX-351	Liposomesformulation of cytarabine: daunorubicin (5:1 M ratio)	Acute myeloid leukemia	FDA (2017) EMA (2018)	Various leukemias
Nanobiotix, –Nbtxr3 Hensify	Hafnium oxide nanoparticles stimulated with external radiation to enhance tumor cell death via electron production	Locally advanced squamous cell carcinoma	CE (Conformité Européene) Mark (2019)	Locally advanced soft tissue sarcoma
AMAG, Feraheme; Takeda, Rieno	Ferumoxytol- Iron polyglucose sorbitol carboxymethyl ether colloid	Iron deficiency in patients with chronic kidney disease	FDA (2009)	Iron deficient anemia Imaging: brain metastases, lymph node metastases, neuroinflammation in epilepsy, head and neck cancer, myocardial infarction, or multiple sclerosis
Lantheus Medical Imaging, –Definity	Perflutren lipid microspheres	Ultrasound contrast agent	FDA (2001)	Ultrasound enhancement for: liver or breast or intraocular or pancreatic tumors, pulmonary diseases, heart function, transcranial injuries, strokes, or liver cirrhosis
Magforce Nanotech AG, –NanoTherm	Amino silane-coated iron oxide NPs in magnetite form	Local ablation in glioblastoma	EMA (2010)	Thermal ablation, hyperthermia therapy, local ablation in glioblastoma
Endomagnetics Ltd, Sienna	Carboxydextran coated iron oxide NPs	Detection of cancerous sentinel lymphnodes in breast cancer; rectal cancer	EMA (2011)	Detection of cancerous sentinel lymphnodes in breast cancer; rectal cancer
American Regent, –Venofer	Iron sucrose colloid	Epithelial ovarian cancer; gynecologic cancer; treatment of iron deficiency anemia in adult patients with chronic kidney disease	FDA (2010)	Anemia; pregnancy; postural orthostatic tachycardia syndrome; chronic heart failure; inflammatory bowel disease; postpartum anemia; surgical intervention; hip fracture; hematological malignancies; renal failure; restless legs syndrome; perioperative blood conservation; colorectal neoplasm; puerperal disorders; critical illness; hypertension; premature birth
Vifor, –Injectafer, Ferinject	Iron carboxymaltose colloid	Iron deficiency anemia in pancreatic cancer; cancer and chemotherapy related anemia; metastatic colorectal cancer; solid cancer metastatic disease	FDA (2013)	Fibromyalgia; heart failure; restless legs syndrome; postoperative anemia; CKD; colorectal neoplasm; inflammatory bowel disease; thrombocytosis; postpartum anemia; diabetes mellitus
Sichuan Enray Pharmaceutical Sciences Company	Carbon nanoparticle-loaded iron [CNSI-Fe(II)]	-	Clinical trial NCT06048367	Patients with advanced solid tumours. Tumour types include colorectal, pancreatic, breast, gastric, cervical, lung, head and neck, and prostate cancers.
Ahmed A. H. Abdellatif, Al-Azhar University	Polymeric nanoparticles loaded with cetuximab, with somatostatin analogue	-	Clinical trial NCT03774680	-
Allegheny Singer research institute	Iron oxide, nanoparticles (SPION)	-	Clinical trial NCT04682847	-
Shanghai Henlius Biotech	Carboplatin-nanoparticle albumin bound (Nab) paclitaxel	-	Clinical trial NCT04033354	Locally advanced or metastatic squamous NSCLC
Roswell Park cancer institute	Liposomal irinotecan, fluorouracil and leucovorin	-	Clinical trial NCT03736720	Refractory advanced high grade neuroendocrine cancer of gastrointestinal, unknown, or pancreatic origin

Table 2

Recent patents highlight advanced nanoformulations for use in oncology and virology.

Patent number	Title	Publication date	Description	Reference
EP4119126A1	Nanoformulation with diverse functional molecules from turmeric and process for the preparation of same	18.01.2023	The invention aims to create encapsulated nanoparticles with turmeric's bioactive, including curcuminoids and turmeric, using nano globulins and surfactants/emulsifiers. These nano-sized, high-bioavailability formulations are enhanced with plant alkaloids, flavonoids and volatiles.	(Ravikanti and Chitrabhanu, 2023)
WO2022035843A1	Topoisomerase inhibitors	17.02.2022	The multi-arm polymeric conjugates of 7-ethyl-10-hydroxy-camptothecin are being used for the treatment of various cancers including breast, colorectal, pancreatic, ovarian, and lung.	(Moody Rebecca et al., 2022)
US 11998616 B2	Nanoparticles for crossing the blood brain barrier and methods of treatment using the same	04.06.2024	Application outlines the use of nanoparticles containing therapeutic agents, including chemotherapeutic agents, and targeting ligands for delivering these agents through blood-brain barrier.	(Mark and Wyent Emily, 2024)
US 20240173265 A1	Extracellular vesicles from microalgae, their preparation, and uses	30.5.2024	MEVs have diverse therapeutic applications, including vaccines, anti-cancer therapeutics, and diagnostics.	(Drittanti et al., 2024)
US 20240165263 A1	Targeting multiple T-cell types using spherical nucleic acid vaccine architecture	23.05.2024	Spherical nucleic acids (SNAs), nanostructures with a core surrounded by oligonucleotides, can target various immune cell classes, potentially aiding in cancer immunotherapy.	(Mirkin Chad et al., 2024)
US 20240166682 A1	Novel compositions and methods for ribosomal synthesis of nucleobase amino acid polymers and their conversion into nucleic acids	23.05.2024	The process involves synthesizing a nucleic acid polymer using a nucleobase amino acid (NAA) polymer, a mRNA template, ribosomes, NAA-tRNA, and non-NAA-tRNA, and adding a polymerase and primer.	(Bishop Bryan and Berry, 2024)
US 20240165241 A1	Targeted delivery of drug molecules with drug ligands conjugated to rna nanoparticle motion elements	23.05.2024	The patent involves the creation of various ligand-conjugated nanoparticles, including camptothecin, PTX, podophyllotoxin, SN38, BMS1, BMS8, BMS27, BMS242, LY294002, PI3K-IN-20, and methotrexate.	(Guo et al., 2024)
US 20240156746 A1	Virus-like particles for preventing the spreading and lowering infection rate of viruses	16.05.2024	The application pertains to nano- and/or micromaterials-based carriers designed to reduce the spread of pathogens and infectious agents, including viruses, bacteria, parasites, antigens, and other disease-causing agents.	(Niemelä, 2024)
US 20240148858 A1	A three-component vaccine for COVID-19	09.05.2024	The patent presents complexes, compositions, and methods for a COVID-19 vaccine, including cell-penetrating complexes, ribonucleic acid sequences, nucleic acid adjuvants, and cationic amphiphatic polymers, which are useful in vaccines containing viral proteins.	(Levy et al., 2024)
US 20240150466 A1	Anti-igfbp7 constructs and uses thereof	09.05.2024	The application offers anti-IGFBP7 constructs, nucleic acid molecules, vectors, host cells, preparation methods, pharmaceutical compositions, and usage methods for binding to IGFBP7.	(Chen et al., 2024)
US 20240148888 A1	Intercellular adhesion molecule 1 (icam1) antibody-drug conjugate and uses thereof	09.05.2024	The patent outlines compositions of an intercellular adhesion molecule 1 (ICAM1) antibody and methods for therapeutic applications, including treating triple-negative breast cancer and predicting drug response.	(Guo et al., 2024)
US 20240150456 A1	Engineered immune cells and uses thereof	09.05.2024	The disclosure introduces immune effector cells that express a functional exogenous receptor, such as a CAR, and a tumor-homing peptide, enhancing tumor infiltration and anti-tumor efficacy.	(Xu et al., 2024)
US 20240148881 A1	Carrier-free curcumin nanoparticles for EGFR-positive cancer therapy	09.05.2024	A carrier-free nanoparticle with curcumin-erlotinib conjugate (EPC) shows stronger cell killing, anti-migration, and anti-invasion effects for pancreatic cancer cells compared to free curcumin and erlotinib.	(Xu, 2024)
US 11976125 B2	B cell maturation antigen binding proteins	07.05.2024	The disclosure outlines improved B cell maturation antigen binding proteins, pharmaceutical compositions, and methods for treating cancer or metastasis using these binding proteins.	(Wesche et al., 2024)
US 20240141345 A1	Cd70-targeted micelles enhance hif2? Sirna delivery and inhibit oncogenic functions in patient-derived clear cell renal carcinoma cells	02.05.2024	A drug delivery system for treating renal cancer, specifically clear cell renal carcinoma, consists of nanoparticles containing CD70-targeting peptides and anti-HIF2 siRNAs.	(Trac and Chung Yoo Eun, 2024)
US 20240141382 A1	Gene editing components, systems, and methods of use	02.05.2024	The disclosure presents novel Cas TypeV programmable nucleases and lipid nanoparticles for therapeutic, plant, and industrial biotechnology applications, including genome editing systems.	(Gasiunas et al., 2024)
US 20240139334 A1	Engineered liposomes for neutralization of sars-cov-2 and other enveloped viruses	02.05.2024	The present disclosure is directed to engineered nanoparticles/liposomes that inhibit enveloped viruses and methods for use thereof.	(King Michael and Zhang, 2024)
US 11969506 B2	Lipid nanoparticle formulation	30.04.2024	Nanoparticles, composed of lipids, phospholipids, sterols, and optional second sterols, are used to deliver therapeutic or prophylactics like RNA to regulate gene expression in mammalian cells.	(Patel et al., 2024)
US 11969438 B1	Polyols and polyol-based hydrogels with anti-cancer activity	30.04.2024	The invention offers methods for selectively treating cancer or tumours using vegetable oil-derived polyol or hydrogel particles containing vegetable oil-derived polyol.	(Vashist et al., 2024)
US 20240131184 A1	Compositions and methods for delivering nucleic acids to cells	25.04.2024	The invention presents a non-viral polyplex particle for delivering nucleic acid to cells, consisting of polyethylenimine	(Pearson and Chakraborty, 2024)

(continued on next page)

Table 2 (continued)

Patent number	Title	Publication date	Description	Reference
US 20240131158 A1	Cell therapy compositions and methods for modulating TGF-B signalling	25.04.2024	complexed with nucleic acid and an anionic biomaterial enveloping it. The invention provides antigen-binding agents, pharmaceutical compositions, and methods for treating diseases involving TGF activity, as well as therapeutic methods for using TGF signalling modulators.	(Kuhn and Shapiro, 2024)
20240132916 A1	Nuclease-guided non-ltr retrotransposons and uses thereof	25.04.2024	The novel nucleic acid-targeting systems, including CRISPR systems and non-LTR retrotransposon elements, enable targeted gene modification, insertion, gene transcript perturbation, and nucleic acid editing.	(Zhang et al., 2024)
US 20240131120 A1	Zip-in technology for antiviral therapeutic nanoformulations	25.04.2024	Nanoparticles deliver active pharmaceutical compounds into cells by ionizing and combining with opposite-charge polymer ions. This creates an initial molecular assembly, followed by a secondary molecular assembly, trapping payload. The non-conjugated charged segments are combined with additional polymer ions to extend and branch the assembly, forming a nanoparticle.	(Nepotchatykh et al., 2024)
US 11965178 B2	Platelets loaded with anti-cancer agents	23.04.2024	The method involves treating platelets with cargo and a loading buffer, including salt, base, loading agent, and optionally ethanol, to form cargo-loaded platelets.	(Moskowitz Keith et al., 2024)
US 20240122867 A1	Coronal protein-coated nanoparticles and uses thereof	18.04.2024	The disclosure outlines nanoparticle compositions and methods for cancer treatment, including hyperbranched polyester (HBPE) nanoparticles containing coronal proteins.	(Khaled et al., 2024)

Compared to both therapeutic mono-modalities, the combined approach demonstrated superior antitumor properties in an additive manner, achieving a 78% inhibition of tumour growth. In contrast, monotherapy with PTX resulted in a 46% inhibition and PDT alone yielded a 44% inhibition, as observed 16 days post-treatment. Additionally, the combined approach demonstrated a lower incidence of side effects (Chang et al., 2021).

A combined approach was employed in the case of PTX and P-glycoprotein inhibitor zosuquidar. Both drugs were incorporated into nanoliposome conjugated with the programmed death ligand 1 to address the drug resistance, often occurring in the treatment of hepatocellular carcinoma. The drug developed in this way exhibited a high encapsulation capacity and a significant synergistic effect of active substances, promising antitumor effectiveness and low toxicity (Gu et al., 2022). When PTX is integrated into albumin, it results in the formation of NPs with albumin serving as the carrier. This structure has a diameter of 130 nm and is referred as "abraxane" (Senapati et al., 2018). In a trial involving patients with breast cancer, abraxane outperformed PTX alone in terms of response rate (33% vs. 19%, p=0.001) and duration of time to tumour progression (23.0 vs. 16.9 weeks, p=0.006). Consequently, FDA has approved abraxane for therapeutic treatment of pancreatic adenocarcinoma, lung cancer, and metastatic breast cancer (Shi, 2020).

4.2. Gemcitabine as nanomolecular therapeutics

Nanotechnological solutions are also used to improve the delivery of other antitumor drugs to target tissues. When it comes to treating various resistant malignant conditions, such as the incurable stage of microcellular lung cancer, gemcitabine—either alone or in conjunction with other antineoplastic medications—became the medication of choice. Originally researched as an antiviral (Conroy et al., 2018; Ebata et al., 2018; Melisi et al., 2018; Zhang et al., 2019). Due to its effectiveness, it is a common choice in treatment, but rapid metabolism and excretion in urine demand high-dose administration leading to unpleasant side effects and treatment withdrawal (Habib and Singh, 2021). In addition, in some cancers, drug resistance ensues due to the loss of transport proteins and inability to phosphorylation (de Sousa Cavalcante and Monteiro, 2014). To optimize gemcitabine therapeutic performance, several forms of NC have been investigated, integrating nanotechnological formulations and gemcitabine as monotherapy or in

combination with other anticancer drugs. For example, incorporation of gemcitabine with curcumin results in 4.5-fold increase in (half-life) $T_{1/2}$ and 2.5-fold increase in AUC compared to gemcitabine solution alone. A prolonged $T_{1/2}$ is crucial for more effective targeted drug delivery, with a minimum requirement of 6 h (Paroha et al., 2021; Xu et al., 2021).

Liposomal gemcitabine, incorporating PEG as a phospholipid component, demonstrated improved characteristics including prolonged half-life in circulation, reduced clearance, improved stability, prolonged concentration within the therapeutic range in target tissues, and improved drug uptake in tumour cells (Habib and Singh, 2021). The accuracy of delivery was further improved with addition of antibodies, folic acid, hyaluronic acid and peptides as ligands for binding to tumour cell receptors (Tang et al., 2019; Xu et al., 2021; Xu et al., 2016). Niosomal gemcitabine, especially in aerosolized form and in combination with cisplatin, has shown very good effectiveness on lung cancer cell lines with low toxicity for cell lines of healthy lung tissue (IC_{50} value 280 and 46 μ g/mL depending on cell line) compared to traditional administration where toxicity is much higher (IC_{50} value < 1.56 μ g/mL), thus demonstrating the potential for therapeutic use in this treatment modality (Mohamad Saimi et al., 2021).

4.3. Doxorubicin as nanomolecular therapeutics

The use of polypeptide NC (PEG-Phis60/Pasp) to deliver antineoplastic drug doxorubicin (DOX) and vascular inhibitor CA4 to tumours demonstrating resistance to conventional therapy has proven to be effective (91.8% inhibition of tumour growth, compared to 8.3% inhibition for free DOX and 60.8% for free CA4). This system is designed to release CA4 in tumour tissue to temporarily "normalize" tumour vasculature, thereby indirectly regulating tumour microenvironment in a way that promotes the uptake of DOX into tumour cells, and therefore its antineoplastic action (Dong et al., 2015). Investigations were conducted to determine the effectiveness of MIL-101 NPs (MIL-101(Fe) metal-organic frameworks) as a DOX delivery system for the treatment of B16-F1 melanoma metastases and early and late-stage metastatic lung cancer. The results demonstrated 11-fold reduction in pulmonary melanoma nodes during early stages of metastasis. Furthermore, in the case of late-stage metastatic lung cancer, a 4.3-fold decrease in pulmonary melanoma nodes was observed, offering promising prospects for targeted treatment of metastatic lung cancer at various stages of

progression. Median survival rates were prolonged up to 36 days for ND doxorubicin delivery compared to 28 and 27 days for PBS and classical DOX administration, respectively (Zelepukin et al., 2022). A similar was achieved by structuring PLGA-lecithin-PEG DOX delivery system together with indocyanine green. The synergistic effects of phototherapeutic and chemotherapeutic interventions on tumour cells *in vitro* were demonstrated resulting in apoptosis in DOX-resistant tumour cell lines (Zheng et al., 2013).

4.4. mRNA as nanomolecular therapeutics

Recently, possibilities provided in oncology treatment by preparations with gene-level action have also been explored, activating beneficial or, more often, silencing those in charge of tumour cell proliferation (Karmacharya et al., 2022). The messenger RNA (mRNA) holds promise as a resource in cancer treatment, but extracellular and endosomal deterioration continues to be a challenge. Lipid mRNA NPs increase the stability of mRNA. The A260 absorbance measurements

revealed consistent mRNA concentrations in various lipid mRNA formulations, within the range of 33.3 to 48.3 ng/ μ L (Billingsley et al., 2020). Following a 30 μ g injection of lipid mRNA that encodes human antibody, peak antibody levels in the serum were observed 24 h after the injection, followed by a gradual decline until day 11 post-injection (Van Hoecke and Roose, 2019). They also facilitate entry into cells, ensure exit from endosome and reach intracellular compartment in which the targeted process takes place. As in the case of previously discussed drugs, precision of delivery to target tissues can be further increased by conjugating tissue-specific ligands to their surface (Karmacharya et al., 2022). Strengthened in this way, mRNA can be effectively introduced into mitotic and non-mitotic cells and transfer the information for protein synthesis without translocation into cell nucleus (Jahanafrooz et al., 2020). Since these proteins are mostly antigens, they can provoke an immune reaction of the organism against tumour tissue cells, so these drugs can be also viewed as oncological vaccines. mRNA preparations provoke a greater degree of immunological response and take precedence over DNA preparations because they do not require integration

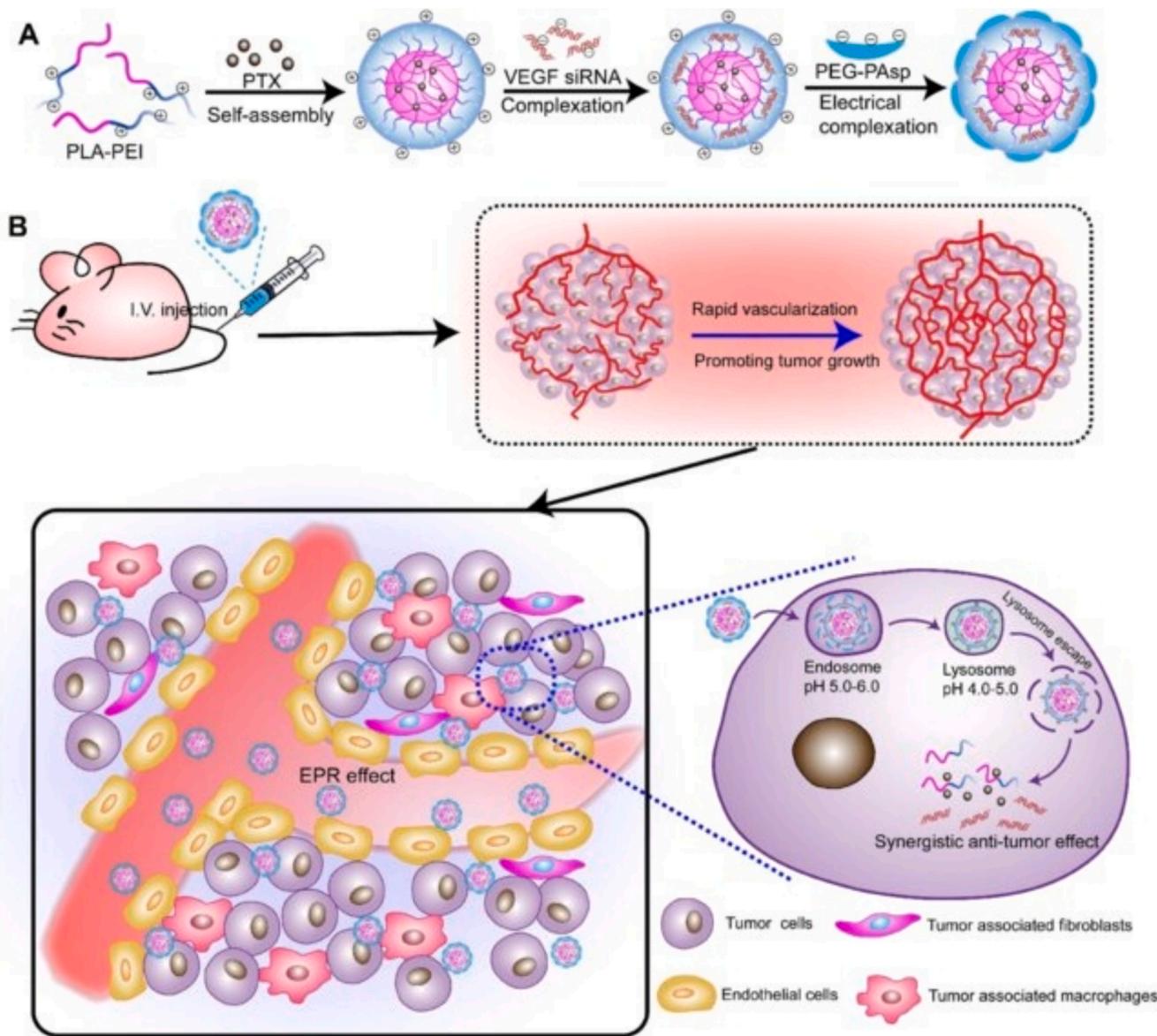


Fig. 6. (A) Formation of nanoparticles carrying PTX and siRNA and (B) The principle of improving delivery of PTX and siRNA loaded NC to target tissues with the help of smart NP. NC can accumulate in cancer tissues due to degradation of vascular endothelial structure and bind to receptors on tumour cells. EPR; enhanced permeability and retention effect. Adopted with permissions from (Jin et al., 2021).

into genome of the cell, there is no risk of insertional mutations (Sahin et al., 2014). When it comes to innovative therapeutic and preventative vaccinations, monoclonal prostheses for CAR T-cell therapy, and immunomodulatory medications containing protein and other types of biomolecules, mRNA has demonstrated superiority (Billingsley et al., 2020; Van Hoecke and Roose, 2019).

The combination of cisplatin and small interference RNA (siRNA) on LNP platform was also investigated. siRNA are fragments of RNA chain of 19–21 dual-sequence nucleotides that can target and at level of mRNA, temporarily silence the activity of certain genes. A combination of cisplatin and siRNA focused on the sequence of genes whose expression is crucial for progression of cisplatin-resistant prostate cancers showed inhibition of gene expression (up to 87%) after first dose for up to 3 days, and inhibition of tumour growth with continuation of the treatment, allowing animals to survive for the entire 50-day study (Xu et al., 2013). Another study looked at using NP platform to treat breast cancer in mice by mixing PTX with small interfering RNA (siRNA) that targets the vascular endothelial growth factor (VEGF) gene (Fig. 6). Survival rates for cells treated were $77.26\% \pm 1.23\%$, $42.66\% \pm 0.62\%$ and $31.55\% \pm 0.69\%$ for siRNA NP, PTX NP and siRNA-PTX combination NP respectively. Indicating a strong antiproliferative effect of combination delivery (Jin et al., 2021).

5. Advanced solutions for viral disease therapeutics

5.1. Viral pathogenesis mechanisms and treatment challenges

Infectious diseases and viral infections in particular have a significant global impact on mortality (Chakravarty and Vora, 2021; Pradhan et al., 2021b). Lower respiratory tract infections, with viruses responsible for 80% of cases, contribute significantly to a mortality rate of 3 million annually (Al-Halifa et al., 2019). Particularly in the light of emergence of drug resistance, novel strategies for treating viral infections are required. Biological nanoparticles with a diameter of 1–100 nm are called viruses. They attach to the cell membrane and then enter the cell through phagocytosis, macropinocytosis, or endocytosis mediated by clathrin or caveolin. Successful entry of the virus into the cell usually leads to a change in the activity of proteolytic enzymes that is manifested by conformational changes in certain proteins that serve to discourage the immune response, which provides time for the installation of the viral genome in the genome of the invaded cell. Subsequently, using the transcription and translation mechanisms of the invaded cell, the synthesis of viral proteins and viral capsid occurs followed by the release of emerging viruses and the spread of the infection to the other cells (Fig. 7) (Pradhan et al., 2021b). The method of cell entry, the conditions in which the implantation of the genome occurs in the host genome, as well as the conditions for transcription of viral structural and nonstructural proteins, and the replication and reconstitution of the virus, can vary significantly from virus to virus but always have same net result; release of viruses from the cell (Chakravarty and Vora, 2021).

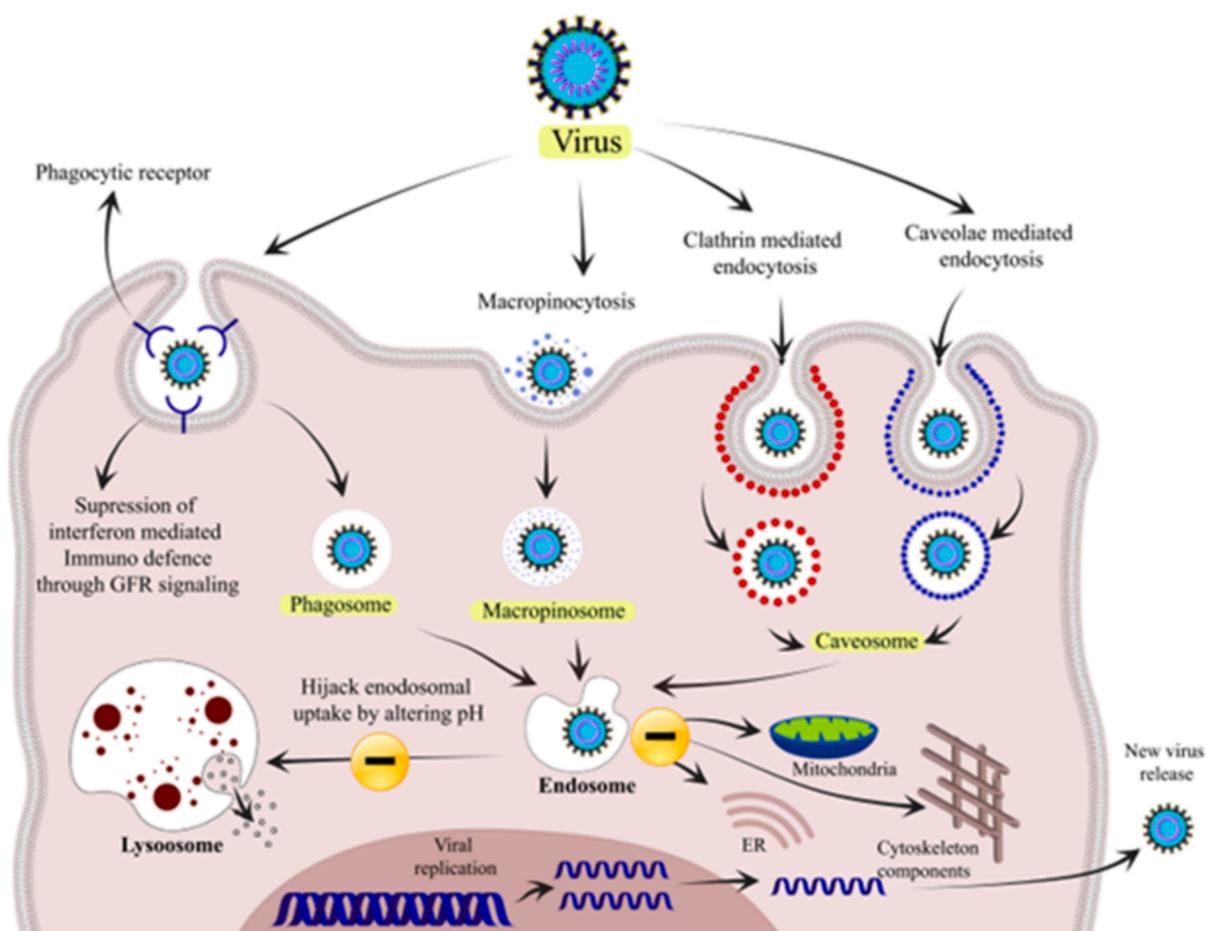


Fig. 7. Entering the cell and replicating the virus through different molecular pathways including caveolae, clathrin, micropinocytosis and phagocytosis mechanism followed by creation of endosome and exit of virus from it. Subsequently, by transcription and translation mechanisms of the cell, the synthesis of viral proteins and viral capsid occurs followed by the release of emerging viruses. Adopted with permission from (Pradhan et al., 2021b).

The development of viral infection depends on the balance between the rate of viral replication and clearance resulting from the host's immune reaction. In most cases, the immune response stops the progress of the infection, so they mainly have a subclinical course. This course of infection is of great importance for the biology of the virus because it allows the better spread of the virus in the population through asymptomatic carriers. However, in certain circumstances, a viral infection overcomes or avoids the defence reaction leading to the accession of the symptomatology (Hie et al., 2021; Pradhan et al., 2021a). Up until recently, individuals with weakened immune systems frequently presented with more severe clinical manifestations. These patients were treated with standard antiviral medications, such as remdesivir, oseltamivir, zalcitabine, stavudine, abacavir, nelfinavir, ritonavir, efavirenz, and others. However, the effectiveness of conventional antiviral drugs faces multiple challenges. These include their physical-chemical properties and short half-life, with examples like nelfinavir (3.5–5 h), abacavir (0.8–1.5 h) and stavudine (1.3–1.4 h). Additionally, poor water solubility (e.g. 8.85, 1.2 and 2.25 µg/L for efavirenz, ritonavir and acyclovir, respectively) hinders efficient absorption in the intestines, leading to insufficient concentration in target tissues. Also, alterations of surface viral proteins due to mutations cause the development of resistance (Pradhan et al., 2021b). For instance, the development of viral resistance to amantadine induced the center for disease control of the United States of America to withdraw the recommendation for the treatment of influenza type A. Similarly, the efficacy of other antiviral drugs is reduced due to the development of resistance that can vary depending on the drug. After 5 years of therapy, in the case of HBV the observed drug resistance rates are approximately 1, 20, 29 and 70% for entecavir, telbivudine, adefovir, and lamivudine respectively (Strasfeld

and Chou, 2010).

5.2. Nanotechnology in viral disease therapeutics

The disadvantages of traditional drug administration in viral diseases are already known. Recently, remdesivir, an RNA polymerase inhibitor for COVID-19 treatment, has been associated with 2–11% incidence of liver dysfunction, indicated by elevated levels of alanine aminotransferase and aspartate aminotransferase. Additionally, short half-life drugs like nelfinavir (3.5–5 h), abacavir (0.8–1.5 h) and stavudine (1.3–1.4 h) require frequent dosing. Another class of antiviral therapeutics, including, efavirenz, ritonavir and acyclovir exhibits poor aqueous solubility at pH 6.8, specifically 8.85, 1.2 and 2.25 µg/L, respectively. This limitation restricts their systemic absorption from the intestines, causing decreased drug bioavailability (Pradhan et al., 2021b). Nanotechnological solutions could improve the solubility and reduction of drug toxicity, increase efficacy and selectivity, and its antiviral activity (Chakravarty and Vora, 2021). For this purpose, various types of NM including lipid, polymer, lipid-polymer, carbon, inorganic and others are used (Pradhan et al., 2021b). The benefits of lipid NC are similar to ones observed with antitumor drugs such as biodegradability, biocompatibility, inertia, non-toxicity, non-immune, availability and price (Puri et al., 2009). In addition, they are also characterized by small dimensions, a large area, a high capacity for transporting medicines, and the ability to interact and control the release of drugs, which is why they increase their bioavailability, improve pharmacokinetics, reduce toxicity and allow for high concentrations of the drug even in otherwise inaccessible or poorly accessible locations. As seen in Table 3, a number of nanomedicines for the treatment of viral infections have received

Table 3

Clinically approved nanomedicines for the treatment of viral infections along with nanomedicines currently under evaluation (Singh et al., 2017).

Name	Nanomedicine description	Mechanism of action	Viruses	Approval year/ development stage
A virosomal vaccine to prevent hepatitis A infection	An inactivated vaccine based on virosome (liposome)	Mimics the natural process to act	HAV	1999
Peginterferon alfa-2a SPL7013	PEGylation of interferon alfa-2b Dendrimer	PEGylation Dendrimer based on lysine with naphthalene disulfonate acid surface groups	HBV, HCV HIV, HSV	2002 Clinical trial (NCT00740584)
Peginterferon alfa-2b Influvac® Plus	PEGylation of interferon alfa-2b Virosome vaccine	PEGylation Containing influenza surface proteins neuraminidase and hemagglutinin	HCV Influenza	2001 2005
Sirnaomics polymer nano system STP702	Short interfering RNA(SiRNA) therapeutic	Gene silencing	H5N1 and H1N1 influenza	Preclinical evaluation
STP 909	Short interfering RNA (SiRNA) therapeutic	Gene silencing	HPV	Preclinical evaluation
Vaccine for HIV/AIDS	Therapeutic vaccine	Synthetic plasmid DNA immunogen expressing 15 antigens, inducing significant expansions of the HIV-specific precursor/memory T cell pool.	HIV	Clinical trial (NCT00270205)
MK-1439	Solid drug nanoparticle formulation	Non-nucleoside reverse transcriptase inhibitor	HIV	Clinical trial (NCT02549040)
ARB-001467 TKM-HBV	Wet lipid nanoparticle	Lipid particles containing three RNAi therapeutics that target three sites on the HBV genome Administered to healthy adults	HBV	Clinical trial (NCT02631096)
Epstein-Barr virus (EBV) gp350-ferritin nanoparticle vaccine	-		-	-
Respiratory syncytial virus (RSV) vaccine	2 different lipid nanoparticles (LNPs)	Evaluate the safety and immunogenicity of RSV vaccine candidate in adult participants	RSV	Clinical trial (NCT05639894)
Human study of TLC-ART 101 (ACTU 2001)	-	Time course and pharmacokinetics (PK) of a single dose of the drug substances of TLC-ART 101 (lopinavir, ritonavir, and tenofovir)	-	-
Safety and immunogenicity of HDT-301 targeting A SARS-CoV-2	-	-	-	-
COVID-19 vaccine and influenza combination vaccine (CIC)	SARS CoV 2 rS nanoparticle and trivalent hemagglutinin nanoparticle influenza combination vaccine	Evaluate the safety and immunogenicity of a CIC vaccine	SARS-CoV-2 and influenza	Clinical trial (NCT06291857)
Safety, and immunogenicity of the RNA MCTI CIMATEC HDT vaccine	Self-replicating nanoparticle carrier replicon RNA carrier (repRNA) vaccine	Investigational product MCTI C HDT will be administered in one of the two doses evaluated (5 µg and 10 µg)	COVID 19	Clinical trial (NCT05542693)

approval or are presently being researched. Due to their dimensions, shape, functionality and surface properties, NC can contribute to the preservation of antigens and their prolonged presentation to the immune system, thereby enhancing and expanding the immunity caused by the vaccine (Al-Halifa et al., 2019).

In the last decade, numerous platforms have been developed to stimulate cellular and humoral immunity against various viral infections based on phospholipid, polymer, inorganic and protein nanosystems (Chakravarty and Vora, 2021). For example, gelatine liposomes stuffed with stavudine in infected HIV enabled linear release of drug for 12 h and showed better control of viremia and greater therapeutic precision (Nayak et al., 2017). The incorporation of efavirenz in glycerol monostearate, Tween 80 particles increases its solubility and effectiveness in HIV-infected patients. In these patients, 2.03-fold ($p<0.01$) increase in the accumulation of lopinavir in lymphatic tissue is also observed when embedded in stearic NPs compared to traditional administration (McDonald et al., 2014; Ravi and Vats, 2017). Another application of nanomedicine (Stearic acid-g-chitosan oligosaccharide micelles) caused an increase in the uptake of lamivudine into cells (65.64% uptake, compared to 4.02% uptake with free lamivudine) and inhibition of the prominence of hepatitis B viral antigens and DNA replication (Li et al., 2010). Polymeric cellulose-acetate-butyrate nanocapsules provide an increase in the effectiveness of nevirapine in the treatment of HIV infection through increase in delivery to macrophages (with release efficiency from $39.87\pm4.50\%$ to $74.55\pm3.24\%$) that are targeted cells of antiretroviral drugs because they are the main reservoirs for HIV dissemination (Varshosaz et al., 2018). With low micromolar EC₅₀, polymeric NPs containing four antiretroviral medications (nevirapine, raltegravir, lamivudine, and zidovudine) efficiently blocked over 90% of HIV-1 infection in CEM T cells. Additionally, when tested on mononuclear blood, these NPs significantly inhibited HIV-1 replication with EC₅₀ of 14 μM (Ogunwuyi et al., 2016). Similar improvements have been shown for zidovudine integrated into SPN polybutylcyanoacrylate (Kuo and Chung, 2012).

Conjugates of nanopolymers and antiviral drugs consist of an active substance that is bound to a polymer covalently to increase plasma stability and delivery to target tissues, thereby increasing efficiency and reducing toxicity (Parveen et al., 2019). In addition, some polymers themselves have an antiviral effect, so they act synergistically with the active substance, as is the case of conjugation of interferon α 2A with PEG in the treatment of hepatitis B virus infection. The therapeutic effect is observed to be directly correlated with the duration of the treatment. Prolonged therapy leads to a significant increase in HBsAg clearance, with values 33.3% at 24 weeks post-treatment compared to 10.5% for standard therapy. Furthermore, at 48 weeks post-treatment, the values were 35.7% in the prolonged therapy group versus 10.5% in the standard therapy group ($p<0.05$ for both) (Chen et al., 2014). Similarly, since they bind to hyaluronic acid and NA on a viral envelope, sowing acid-based nanopolymers have the ability to potentially prevent the entry of viruses. Antiviral medications are also delivered to target tissues utilizing polymers, which range from natural, hydrophilic polymers to synthetic, hydrophobic ones. Polyethylene oxide polypropylene micelles provide implanted antiretroviral drugs such as efavirenz, darunavir or indinavir protection against decomposition, increase their solubility and even improve taste, which is important in pediatric formulations (Li et al., 2015).

5.2.1. Nanotechnology in vaccines

In the case of viral diseases, prevention is still the primary way to protect the population, and one of the most effective methods of prevention is vaccination (Pronin et al., 2021). According to the WHO, vaccines are available for more than 20 infectious diseases, most of which are caused by viruses (WHO, 2022.). Since the COVID-19 pandemic scientific community's focus has been on finding ways to protect the population from infection with the SARS-CoV-2 virus. It consists of a sheath wrapping a single-stranded RNA, which has, like

mRNA, the capability to immediately translate into viral proteins. Viral RNA is translated into a polypeptide that splits into structural and non-structural proteins necessary for the physiology of the virus. Spike-protein (200 nm long) is one of the unstructured proteins and crucial for the entry of virus into the cell as its S1 subunit binds to angiotensin-converting enzyme 2 (ACE2) receptors, and S2 subunit, between 1160 and 1450 amino acids, facilitates the fusion of the virus with the cell membrane (Choudhury and Mukherjee, 2020; Kakavandi et al., 2023; Lei et al., 2021; Pal et al., 2020; Xu et al., 2020).

With the emergence and spread of COVID-19, all forces of the scientific community were directed toward finding an effective vaccine. Among the different solutions, Pfizer/BioNTech and Moderna mRNA COVID-19 vaccines (mRNA-COVID) demonstrated the best relationship between efficiency (95% and 94.5%) and safety. Notably, Moderna exhibited a slightly higher incidence of side effects than Pfizer/BioNTech, including headaches (4.5% vs. 2%) and fatigue (9.7% vs. 3.8%), respectively (Lim et al., 2022). These two vaccines had two basic important advantages: (1) mRNA base – a single-stranded nucleotide sequence is quickly translated into a protein (antigen) in the cytoplasm without the need to enter the cell nucleus, and then broken down, often in just a few minutes avoiding prolonged protein expression and associated undesirable effects; on the other hand, the protein (antigen) is capable of provoking an immune reaction which will protect against infection over a long time (Khurana et al., 2021; Lim et al., 2022); (2) The protection for the unstable mRNA to be delivered to target cells, to enter the cytoplasm and to be used for translation is provided by lipid nanoparticles (LNP) (Buschmann et al., 2021b; Elia et al., 2021). These LNP nanocarriers for mRNA-COVID are the results of decades of scientific and clinical efforts to improve NC for mRNA. Fig. 8. shows the key developments of mRNA and NPs over a certain period (Hou et al., 2021; Qin et al., 2022).

For almost a decade, fragments of the RNA chain of 19–21 nucleotides in double sequence have been used to target and temporarily silence the activity of certain genes at the mRNA level, and therefore the synthesis of corresponding proteins. They enter the cell with the help of cation lipids in the form of liposomes or LNPs or with the help of polymeric NC (Sato et al., 2019). A schematic representation of mRNA structure and its transport through extracellular and intracellular barriers is shown in Fig. 9. For the transfer to targeted sites, a small number (1–10) of copies of mRNA are tied to the centre of the NC core (Buschmann et al., 2021a; Cheng and Lee, 2016). The structure characteristics that make a certain NM suitable for the delivery of RNA load is the multiple insatiability of its functional groups, which is important for the destabilization of intracellular membranes. Lipid NC for RNA delivery should also have a tertiary amine group that can be ionized to help in the initial fusion of lipid nanoparticles with the cell membrane. Fusogenic phospholipids and PEG are usually added to the formulations to improve delivery to the cell and reduce the immune reaction to the drug by keeping it from macrophages and cholesterol to increase the stability of the nanoparticle (Cullis and Hope, 2017; Leung et al., 2014). A two-layer distearoyl-phosphatidyl-choline surrounds the nucleus forming the inner eye around which a PEG is applied to form an outer sheath. Cholesterol is added to fill the rifts to reduce the interaction between LNP and proteins and to improve fusion with the cell membrane. Additional molecules of ionizing lipids with or without charge can be distributed over the entire LNP (Buschmann et al., 2021a).

5.3. Nanotechnology in severe viral infections

Since one drug can rarely entirely cure a viral infection, the use of lipid-polymer NC capable of delivering a combination of drugs with different pharmacokinetic properties has also recently been investigated for the delivery of antiviral drugs. The treatment of severe clinical presentations of COVID-19 continues to be a major challenge. The immune response to SARS-CoV-2 viral infection is mediated by interferons. Interferons' insufficient induction can delay or inhibit the immune

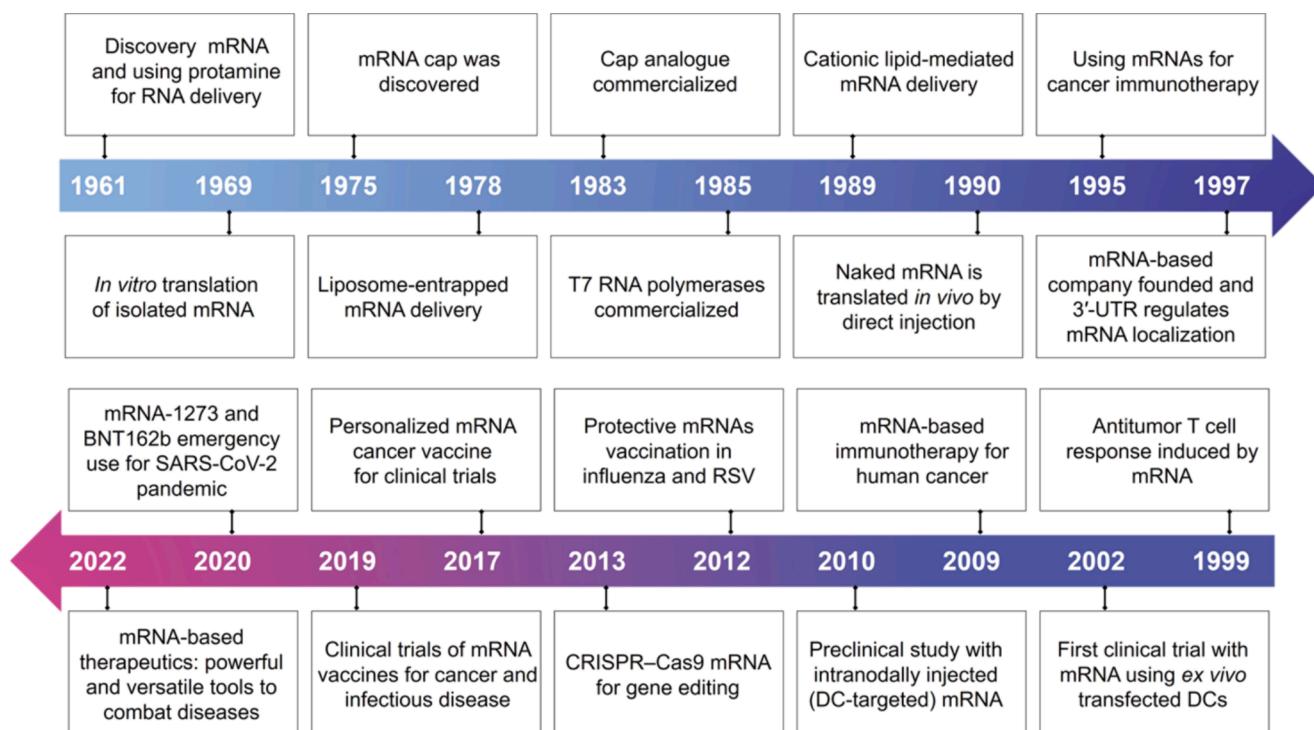


Fig. 8. Chronology of mRNA and its nano-carriers development.
Adopted from with permission (Qin et al., 2022).

response, allowing additional time to replicate the virus. Such a concentration of the virus can provoke an excessive immune response in which cytokines play a key role to a level that culminates in the emergence of a cytokine storm that then further worsens the clinical presentation of COVID-19 Fig. 10. (Yang et al., 2021). When paired with CRP (>97 mg/L), elevated levels of IL-6 (>80 pg/mL) showed good specificity and sensitivity for respiratory failure prediction (AUC 0.97 and 0.86, respectively) (Herold et al., 2020). Cytokines operate through transmembrane receptors gathered around one or more Janus-kinases (JAK) that are completely inactive without cytokine binding, and when activated they mediate the effects of cytokines and exacerbate the immune response (Tang et al., 2020).

Early on in COVID-19, several medications have demonstrated beneficial clinical effects. These include convalescent plasma transfusions, antiviral medications (lopinavir, ritonavir, favipiravir), interferon, azithromycin, angiotensin-converting enzyme inhibitors (captopril, enalapril), antimarial medications (hydroxy-chloroquine and chloroquine), and many more. However, most of them lack the effectiveness in containing or preventing a cytokine storm that can develop in the late stages of COVID-19 (Tang et al., 2020; Zou et al., 2021). Numerous immunomodulators and anti-inflammatory medications have been tried for this purpose, such as corticosteroids, IL-6 (interleukin-6) and IL-1 antagonists (interleukin-1), TNF- α (tumour necrosis factor inhibitors α), and JAK inhibitors. However, some studies have shown that JAK inhibitors may be able to control pathological reactions to COVID-19 by lowering the risk of COVID-19-related mortality. Overall, however, an acceptable level of effectiveness has not been achieved (Iovino et al., 2021; Lariccia et al., 2020; Levy et al., 2022; Patoulas et al., 2021; Soy et al., 2020). This might be because there are several inflammatory pathways in which multiple molecules participate and cytokine interactions are complex; therefore, blocking one or more of these routes does not ensure that the cytokine storm would not arise (Zoulikha et al., 2022).

However, many of these medicines may also have limited effectiveness due to poor bioavailability, instability and adverse biodistribution resulting in a considerable number of undesirable effects. Thus,

researchers are focused on finding a system that will deliver these drugs to target sites more effectively. In addition, these systems may be trained to respond to stimuli of inflammation factors or to bind to specific inflammatory markers to selectively release active substances transported (Zoulikha et al., 2022). In addition, nanotechnology tools can be used to deliver drugs to the respiratory system that would prevent the interaction of S-protein viruses and ACE2 receptors and thus prevent infection of a larger number of cells. Due to their low specific weight and dimensions, NMs are ideal for inhalation and penetration to the terminal parts of the respiratory system. In addition, nanotechnological solutions can help develop the concept of “designed nano immunity” that would entail the modification of immune response in the direction of its stimulation or suppression, which could also be applied to COVID-19 in terms of advancing the vaccine or treating cytokine storm (Weiss et al., 2020).

6. Conclusion

In pharmaceutical industry, NPs-based delivery methods are a spectacular revolution that has found many uses across a wide range of areas. Today's nanotechnological solutions offer more accurate delivery and more control over the release of active substance at the point of action, compared to earlier ones that just protected the active material in the target tissue. This reduces toxic effects and associated adverse effects while enabling a reduction in the dose of active pause required to produce a therapeutic benefit. Furthermore, surviving patients have greater levels of long-term safety. The trend in nanomedicine research groups is undoubtedly the application of various types of nanoparticles for the delivery of specific drugs to damaged cells, such as cancer/tumour cells, or the delivery of gene therapy, monoclonal antibodies, orphan drugs for rare diseases, and vaccines, without interfering with the physiology of normal nearby tissues. Notably, this approach has shown promising results, with an observed increased survival rate of up to 40% after 60 days in a melanoma mouse model. In addition, novel NC also allows combining multiple active substances as well as treatment methods, which allows, until recently unthinkable, therapeutic approaches. With

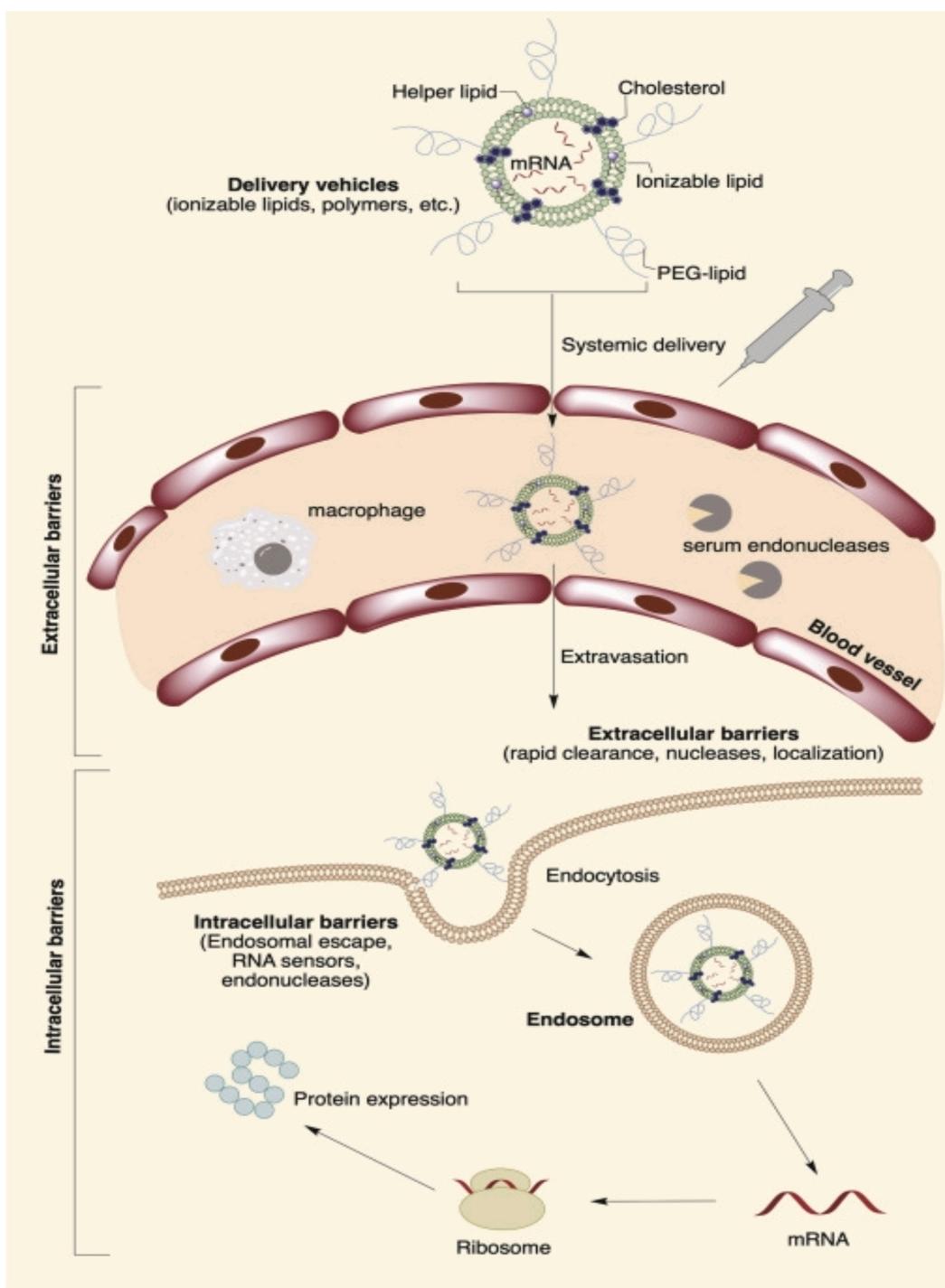


Fig. 9. Mrna nanocarrier structure and its transport through extracellular and intracellular barriers. adopted with permission from (Kowalski et al., 2019).

this method, the inhibition of tumour growth has increased significantly, up to 78%, as opposed to 44% or 46% in the case of monotherapy. The pharmaceutical industry's future lies in the areas where nanotechnological solutions can be applied to improve therapeutic outcomes and deliver medicines. This is evident from the volume and quality of recent research as well as the scientific community's focus on this field. However, bridging the gap in translation between findings from animal studies and their applicability to humans is crucial for facilitating the drug approval process. Further investigations in this field are important to comprehensively address and overcome these translational difficulties.

CRediT authorship contribution statement

Emina Karahmet Sher: Writing – review & editing, Writing – original draft, Supervision, Data curation, Conceptualization. **Mirna Alebić:** Writing – original draft, Software, Resources, Investigation. **Marijana Marković Boras:** Writing – review & editing, Writing – original draft, Visualization, Formal analysis. **Emina Boškailo:** Validation, Software, Resources, Project administration. **Esma Karahmet Farhat:** Formal analysis, Data curation, Conceptualization. **Alma Karahmet:** Project administration, Methodology, Investigation. **Bojan Pavlović:** Visualization, Software, Project administration. **Farooq Sher:** Writing – review & editing, Visualization, Supervision, Funding

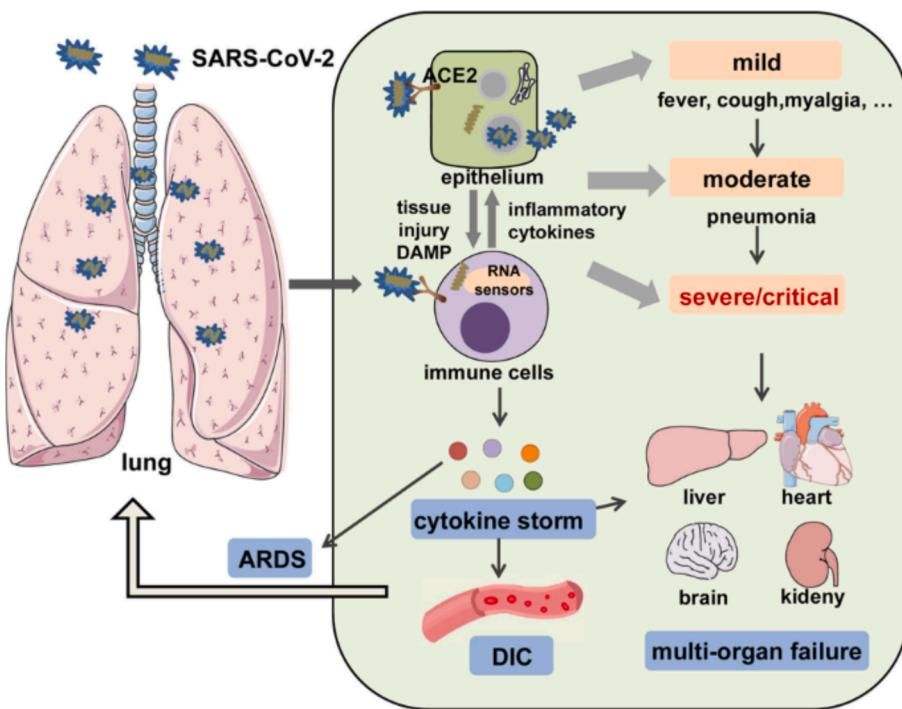


Fig. 10. Hyper-inflammatories reaction in the severe form of COVID-19 presented in the form of cytokine storm and increased inflammatory interleukins which leads to failure in the brain, lungs, heart, liver, kidney or colon. DIC disseminated intravascular coagulation, ARDS acute respiratory distress syndrome, DAMP danger-associated molecular pattern. Adopted with permission from (Yang et al., 2021).

acquisition, Conceptualization, Methodology. **Lana Lekić:** Methodology, Investigation, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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References

- Abedi-Gaballu, F., Dehghan, G., Ghaffari, M., Yekta, R., Abbaspour-Ravasjani, S., Baradaran, B., Dolatabadi, J.E.N., Hamblin, M.R., 2018. PAMAM dendrimers as efficient drug and gene delivery nanosystems for cancer therapy. *Appl. Mater. Today* 12, 177–190.
- Aldea, M., Orillard, E., Mansi, L., Marabelle, A., Scotte, F., Lambotte, O., Michot, J.-M., 2020. How to manage patients with corticosteroids in oncology in the era of immunotherapy? *Eur. J. Cancer* 141, 239–251.
- Alghamdi, M.A., Fallica, A.N., Virzì, N., Kesharwani, P., Pittalà, V., Greish, K.J.J.o.p.m., 2022. The promise of nanotechnology in personalized medicine. *J. Personal. Med.* 12, 673.
- Al-Halifa, S., Gauthier, L., Arpin, D., Bourgault, S., Archambault, D., 2019. Nanoparticle-based vaccines against respiratory viruses. *Front. Immunol.* 10, 22.
- Al-Nemrawi, N.K., AbuAlSamen, M.M., Alzoubi, K.H., 2020. Awareness about nanotechnology and its applications in drug industry among pharmacy students. *Curr. Pharm. Teach. Learn.* 12, 274–280.
- Ambekar, R.S., Choudhary, M., Kandasubramanian, B., 2020. Recent advances in dendrimer-based nanoplatform for cancer treatment: A review. *Eur. Polym. J.* 126, 109546.
- Anversa Dimer, F., de Souza Carvalho-Wodarz, C., Goes, A., Cirnski, K., Herrmann, J., Schmitt, V., Pätzold, L., Abed, N., De Rossi, C., Bischoff, M., Couvreur, P., Müller, R., Lehr, C.M., 2020. PLGA nanocapsules improve the delivery of clarithromycin to kill intracellular *Staphylococcus aureus* and *Mycobacterium abscessus*. *Nanomedicine* 24, 102125.
- Araújo, R.V.d., Santos, S.d.S., Igne Ferreira, E., Giarolla, J., 2018. New advances in general biomedical applications of PAMAM dendrimers. *Molecules* 23, 2849.
- Avci, P., Gupta, A., Sadashivam, M., Vecchio, D., Pam, Z., Pam, N., Hamblin, M.R., 2013. Low-level laser (light) therapy (LLLT) in skin: stimulating, healing, restoring. *Seminars in cutaneous medicine and surgery*. NIH Public Access, p. 41.
- Baig, N., Kammakakam, I., Falath, W., 2021. Nanomaterials: A review of synthesis methods, properties, recent progress, and challenges. *Materials Advances* 2, 1821–1871.
- Battogtokh, G., Joo, Y., Abuzar, S.M., Park, H., Hwang, S.-J., 2022. Gelatin coating for the improvement of stability and cell uptake of hydrophobic drug-containing liposomes. *Molecules* 27, 1041.
- Bayda, S., Adeel, M., Tuccinardi, T., Cordani, M., Rizzolio, F., 2019. The History of Nanoscience and Nanotechnology: From Chemical-Physical Applications to Nanomedicine. *Molecules* 25.
- Billingsley, M.M., Singh, N., Ravikumar, P., Zhang, R., June, C.H., Mitchell, M.J., 2020. Ionizable Lipid Nanoparticle-Mediated mRNA Delivery for Human CAR T Cell Engineering. *Nano Lett.* 20, 1578–1589.
- Bishop Bryan, A., Berry, M., 2024. Novel Compositions and Methods for Ribosomal Synthesis of Nucleobase Amino Acid Polymers and Their Conversion Into Nucleic Acids. Nucleostream Inc, US.
- Buschmann, M.D., Carrasco, M.J., Alishetty, S., Paige, M., Alameh, M.G., Weissman, D., 2021b. Nanomaterial Delivery Systems for mRNA Vaccines. *Vaccines* 9, 65.
- Buschmann, M.D., Carrasco, M.J., Alishetty, S., Paige, M., Alameh, M.G., Weissman, D., 2021a. Nanomaterial Delivery Systems for mRNA Vaccines. *Vaccines* (Basel) 9.
- Caddeo, C., Pucci, L., Gabriele, M., Carbone, C., Fernández-Busquets, X., Valenti, D., Pons, R., Vassallo, A., Fadda, A.M., Manconi, M., 2018. Stability, biocompatibility and antioxidant activity of PEG-modified liposomes containing resveratrol. *Int. J. Pharm.* 538, 40–47.
- Chakravarty, M., Vora, A., 2021. Nanotechnology-based antiviral therapeutics. *Drug Deliv. Transl. Res.* 11, 748–787.
- Chang, E., Bu, J., Ding, L., Lou, J.W., Valic, M.S., Cheng, M., Rosilio, V., Chen, J., Zheng, G., 2021. Porphyrin-lipid stabilized paclitaxel nanoemulsion for combined photodynamic therapy and chemotherapy. *J. Nanobiotechnol.* 19, 1–15.
- Chatterjee, S., Mahmood, S., Hilles, A.R., Thomas, S., Roy, S., Provažník, V., Romero, E. L., Ghosal, K.J.I.j.o.b.m., 2023. Cationic starch: a functionalized polysaccharide-based polymer for advancement of drug delivery and health care system-A review. *Int. J. Biol. Macromol.* 125757.
- Chauhan, A.S., 2018. Dendrimers for drug delivery. *Molecules* 23, 938.
- Chen, X., Chen, X., Chen, W., Ma, X., Huang, J., Chen, R., 2014. Extended peginterferon alfa-2a (Pegasys) therapy in Chinese patients with HBeAg-negative chronic hepatitis B. *J. Med. Virol.* 86, 1705–1713.
- Chen, C., Hu, H., Qiao, M., Zhao, X., Wang, Y., Chen, K., Guo, X., Chen, D., 2015. Tumor-targeting and pH-sensitive lipoprotein-mimic nanocarrier for targeted intracellular delivery of paclitaxel. *Int. J. Pharm.* 480, 116–127.

- Chen, Z., Li, J., Norton, A., Wang, S., Xia, Z., 2024. Anti-Igfbp7 Constructs and Uses Thereof. Dynamicure Biotechnology Llc, US.
- Cheng, X., Lee, R.J., 2016. The role of helper lipids in lipid nanoparticles (LNPs) designed for oligonucleotide delivery. *Adv. Drug Deliv. Rev.* 99, 129–137.
- Chikuma, K., Arima, K., Asaba, Y., Kubota, R., Asayama, S., Sato, K., Kawakami, H., 2020. The potential of lipid-polymer nanoparticles as epigenetic and ROS control approaches for COPD. *Free Radic. Res.* 54, 829–840.
- Chou, P.-L., Huang, Y.-P., Cheng, M.-H., Rau, K.-M., Fang, Y.-P., 2020. Improvement of paclitaxel-associated adverse reactions (ADRs) via the use of nano-based drug delivery systems: A systematic review and network meta-analysis. *Int. J. Nanomed.* 1731–1743.
- Choudhury, A., Mukherjee, S., 2020. In silico studies on the comparative characterization of the interactions of SARS-CoV-2 spike glycoprotein with ACE-2 receptor homologs and human TLRs. *J. Med. Virol.* 92, 2105–2113.
- Christoforidis, J.B., Chang, S., Jiang, A., Wang, J., Cebulla, C.M., 2012. Intravertebral devices for the treatment of vitreous inflammation. *Mediators of inflammation* 2012.
- Conroy, T., Hammel, P., Hebbal, M., Ben Abdelghani, M., Wei, A.C., Raoul, J.-L., Choné, L., Francois, E., Artru, P., Biagi, J.J., 2018. FOLFIRINOX or gemcitabine as adjuvant therapy for pancreatic cancer. *N. Engl. J. Med.* 379, 2395–2406.
- Cryer, A.M., Thorley, A.J., 2019. Nanotechnology in the diagnosis and treatment of lung cancer. *Pharmacol. Ther.* 198, 189–205.
- Cullis, P.R., Hope, M.J., 2017. Lipid nanoparticle systems for enabling gene therapies. *Mol. Ther.* 25, 1467–1475.
- Das, B., Patra, S., Jampilek, J., Králová, K., Bakirhan, N., Uslu, B., Ozkan, S., Alfredo, N., Rodríguez-Hernández, J., Bernstein, A., 2017. Nanostructures for Antimicrobial Therapy: Nanostructures in Therapeutic Medicine Series. Elsevier: Amsterdam, The Netherland.
- Dave, V., Tak, K., Sohgaura, A., Gupta, A., Sadhu, V., Reddy, K.R., 2019. Lipid-polymer hybrid nanoparticles: synthesis strategies and biomedical applications. *J. Microbiol. Methods* 160, 130–142.
- Davis Mark, E., Wyent Emily, A., 2024. Nanoparticles for crossing the blood brain barrier and methods of treatment using the same. California Inst of Technn, US.
- de Sousa Cavalcante, L., Monteiro, G., 2014. Gemcitabine: metabolism and molecular mechanisms of action, sensitivity and chemoresistance in pancreatic cancer. *Eur. J. Pharmacol.* 741, 8–16.
- Deng, S., Gigliobianco, M.R., Censi, R., Di Martino, P., 2020. Polymeric Nanocapsules as Nanotechnological Alternative for Drug Delivery System: Current Status, Challenges and Opportunities. *Nanomaterials* 10, 847.
- Dong, Y., Yang, J., Liu, H., Wang, T., Tang, S., Zhang, J., Zhang, X., 2015. Site-specific drug-releasing polypeptide nanocarriers based on dual-pH response for enhanced therapeutic efficacy against drug-resistant tumors. *Theranostics* 5, 890.
- Drittanti, L., Vega Juan, P., Pruvost, J., Vega, M., 2024. Extracellular Vesicles From Microalgae, Their Preparation, and Uses. Ags M Sas, Univ Nantes, US, Ags Therapeutics Sas.
- Duan, Y., Dhar, A., Patel, C., Khimani, M., Neogi, S., Sharma, P., Kumar, N.S., Vekariya, R.L., 2020a. A brief review on solid lipid nanoparticles: Part and parcel of contemporary drug delivery systems. *RSC Adv.* 10, 26777–26791.
- Duan, Y., Dhar, A., Patel, C., Khimani, M., Neogi, S., Sharma, P., Siva Kumar, N., Vekariya, R.L., 2020b. A brief review on solid lipid nanoparticles: part and parcel of contemporary drug delivery systems. *RSC Adv.* 10, 26777–26791.
- Džidić-Krivić, A., Kusturica, J., Sher, E.K., Selak, N., Osmancević, N., Karahmet Farhat, E., Sher, F., 2023. Effects of intestinal flora on pharmacokinetics and pharmacodynamics of drugs. *Drug Metab. Rev.* 1–14.
- Ebata, T., Hirano, S., Konishi, M., Uesaka, K., Tsuchiya, Y., Ohtsuka, M., Kaneoka, Y., Yamamoto, M., Ambo, Y., Shimizu, Y., 2018. Randomized clinical trial of adjuvant gemcitabine chemotherapy versus observation in resected bile duct cancer. *Journal of British Surgery* 105, 192–202.
- Elia, U., Ramishetti, S., Rosenfeld, R., Dammes, N., Bar-Haim, E., Naidu, G.S., Makdasi, E., Yahalom-Ronen, Y., Tamir, H., Paran, N., Cohen, O., Peer, D., 2021. Design of SARS-CoV-2 hFc-conjugated receptor-binding domain mRNA vaccine delivered via lipid nanoparticles. *ACS Nano* 15, 9627–9637.
- Foulkes, R., Man, E., Thind, J., Yeung, S., Joy, A., Hoskins, C., 2020. The regulation of nanomaterials and nanomedicines for clinical application: Current and future perspectives. *Biomater. Sci.* 8, 4653–4664.
- Gasiunas, G., Ladha, A., Presnyak, V., Jayaraman, M., 2024. Gene Editing Components, Systems, and Methods of Use. Renegade Therapeutics M. Inc, US.
- Ghezzi, M., Pescina, S., Padula, C., Santi, P., Del Favero, E., Cantù, L., Nicolì, S., 2021. Polymeric micelles in drug delivery: An insight of the techniques for their characterization and assessment in biorelevant conditions. *J. Control. Release* 332, 312–336.
- Ghosal, K., Chatterjee, S., Thomas, S., Roy, P.J.A.P., 2022. A detailed review on synthesis, functionalization, application, challenges, and current status of magnetic nanoparticles in the field of drug delivery and gene delivery system. *AAPS PharmSciTech* 24, 25.
- Ghosh, B., Biswas, S., 2021. Polymeric micelles in cancer therapy: State of the art. *J. Control. Release* 332, 127–147.
- Goyal, A.K., Rath, G., Faujdar, C., Malik, B., 2019. Application and perspective of pH-responsive nano drug delivery systems, Applications of Targeted Nano Drugs and Delivery Systems. Elsevier 15–33.
- Gu, M., Yin, F., Qin, Y., Tian, Y., Xiu, X., Shen, H., Zhu, J., 2022. Synergistic antitumor efficacy of PD-1-conjugated PTX- and QSZ-loaded nanoliposomes against multidrug-resistant liver cancers. *Drug Deliv. Transl. Res.* 12, 2550–2560.
- Guo, P., Binzel, D., Blanco Carcache, P., Li, X.I.N., Xu, C., 2024. Targeted Delivery of Drug Molecules With Drug Ligands Conjugated to Rna Nanoparticle Motion Elements. Ohio State Innovation Foundation, US.
- Guo, P., Huang, J., Moses, Marsha A., 2024. Intercellular Adhesion Molecule 1 (Icam1) Antibody Drug Conjugate and Uses Thereof. Childrens Medical Center, US.
- Gutierrez-Romero, L., Díez, P., Montes-Bayón, M., 2024. Bioanalytical strategies to evaluate cisplatin nanodelivery systems: From synthesis to incorporation in individual cells and biological response. *J. Pharm. Biomed. Anal.* 237, 115760.
- Habib, S., Singh, M., 2021. Recent advances in lipid-based nanosystems for gemcitabine and gemcitabine-combination therapy. *Nanomaterials* 11, 597.
- Halwani, A.A., 2022. Development of Pharmaceutical Nanomedicines: From the Bench to the Market. *Pharmaceutics* 14.
- Han, S., Lee, M., Chang, H., Nam, M., Park, H.-O., Kwak, Y.-S., Ha, H.-J., Kim, D., Hwang, S.-O., Hoe, K.-L., 2013. Construction of the first compendium of chemical-genetic profiles in the fission yeast *Schizosaccharomyces pombe* and comparative compendium approach. *Biochem. Biophys. Res. Commun.* 436, 613–618.
- Harris, J.M., Martin, N.E., Modi, M., 2001. Pegylation: a novel process for modifying pharmacokinetics. *Clin. Pharmacokinet.* 40, 539–551.
- Herold, T., Jurinovic, V., Arnreich, C., Lipworth, B.J., Hellmuth, J.C., von Bergwelt-Baildon, M., Klein, M., Weinberger, T., 2020. Elevated levels of IL-6 and CRP predict the need for mechanical ventilation in COVID-19. *J. Allergy Clin. Immunol.* 146, 128–136.e124.
- Hie, B., Zhong, E.D., Berger, B., Bryson, B., 2021. Learning the language of viral evolution and escape. *Science* 371, 284–288.
- Hou, X., Zaks, T., Langer, R., Dong, Y., 2021. Lipid nanoparticles for mRNA delivery. *Nat. Rev. Mater.* 6, 1078–1094.
- Iovino, L., Thur, L.A., Gnajtic, S., Chapuis, A., Milano, F., Hill, J.A., 2021. Shared inflammatory pathways and therapeutic strategies in COVID-19 and cancer immunotherapy. *J. Immunother. Cancer* 9.
- Jahanafrooz, Z., Baradaran, B., Mosafer, J., Hashemzaei, M., Rezaei, T., Mokhtarzadeh, A., Hamblin, M.R., 2020. Comparison of DNA and mRNA vaccines against cancer. *Drug Discov. Today* 25, 552–560.
- Jeevanandam, J., Barhoum, A., Chan, Y.S., Dufresne, A., Danquah, M.K., 2018. Review on nanoparticles and nanostructured materials: history, sources, toxicity and regulations. *Beilstein J. Nanotechnol.* 9, 1050–1074.
- Jiang, Y., Jiang, Y., Li, M., Yu, Q., 2023. Will nanomedicine become a good solution for the cardiotoxicity of chemotherapy drugs? *Front. Pharmacol.* 14, 1143361.
- Jin, M., Hou, Y., Quan, X., Chen, L., Gao, Z., Huang, W., 2021. Smart Polymeric Nanoparticles with pH-Responsive and PEG-Detachable Properties (II): Co-Delivery of Paclitaxel and VEGF siRNA for Synergistic Breast Cancer Therapy in Mice. *Int. J. Nanomed.* 16, 5479–5494.
- Kakavandi, S., Zare, I., VaezJalali, M., Dadashi, M., Azarian, M., Akbari, A., Ramezani Farani, M., Zalpoor, H., Hajikhani, B., 2023. Structural and non-structural proteins in SARS-CoV-2: potential aspects to COVID-19 treatment or prevention of progression of related diseases. *Cell Commun. Signal* 21, 110.
- Karmacharya, P., Patil, B.R., Kim, J.O., 2022. Recent advancements in lipid-mRNA nanoparticles as a treatment option for cancer immunotherapy. *J. Pharm. Investigig.* 52, 415–426.
- Khaled, A., Zhai, L.E.I., McKinstry, K.A.I., Nierenberg, D., 2024. Coronal Protein-Coated Nanoparticles and Uses Thereof. Univ Central Florida Res Found Inc, US.
- Khalid, A.D., Ur-Rehman, N., Tariq, G.H., Ullah, S., Buzdar, S.A., Iqbal, S.S., Sher, E.K., Alsaiari, N.S., Hickman, G.J., Sher, F., 2023. Functional bioinspired nanocomposites for anticancer activity with generation of reactive oxygen species. *Chemosphere* 310, 136885.
- Khurana, A., Allawadhi, P., Khurana, I., Allawadhi, S., Weiskirchen, R., Banothu, A.K., Chhabra, D., Joshi, K., Bharani, K., 2021. Role of nanotechnology behind the success of mRNA vaccines for COVID-19. *Nano Today* 38, 101142.
- Kotta, S., Aldawsari, H.M., Badr-Eldin, S.M., Nair, A.B., Yt, K.J.P., 2022. Progress in polymeric micelles for drug delivery applications. 14, 1636.
- King Michael, R., Zhang, Z., 2024. Engineered Liposomes for Neutralization of Sars-CoV-2 and Other Enveloped Viruses. Univ Vanderbilt, US.
- Kowalski, P.S., Rudra, A., Miao, L., Anderson, D.G., 2019. Delivering the Messenger: Advances in Technologies for Therapeutic mRNA Delivery. *Mol. Ther.* 27, 710–728.
- Kuhn, C., Shapiro, G., 2024. Cell Therapy Compositions and Methods for Modulating Tgf-B Signaling. Takeda Pharmaceuticals Co, US.
- Kuo, Y.C., Chung, C.Y., 2012. Transcytosis of CRM197-grafted polybutylcyanoacrylate nanoparticles for delivering zidovudine across human brain-microvascular endothelial cells. *Colloids Surf. B Biointerfaces* 91, 242–249.
- Lariccia, V., Magi, S., Serfilippi, T., Toujani, M., Gratteri, S., Amoroso, S., 2020. Challenges and Opportunities from Targeting Inflammatory Responses to SARS-CoV-2 Infection: A Narrative Review. *J. Clin. Med.* 9, 4021.
- Lei, Y., Zhang, J., Schiavon, C.R., He, M., Chen, L., Shen, H., Zhang, Y., Yin, Q., Cho, Y., Andrade, L., 2021. SARS-CoV-2 spike protein impairs endothelial function via downregulation of ACE 2. *Circ. Res.* 128, 1323–1326.
- Leung, A.K., Tam, Y.Y., Cullis, P.R., 2014. Lipid nanoparticles for short interfering RNA delivery. *Adv. Genet.* 88, 71–110.
- Levy, G., Guglielmelli, P., Langmuir, P., Constantinescu, S.N., 2022. JAK inhibitors and COVID-19. *J. Immunother. Cancer* 10.
- Levy, R., Haabetz Ole Audun, W., Sallets, A., Blake Timothy, R., Wender, P., Waymouth, Robert M., et al., 2024. A Three Component Vaccine for Covid-19. Univ Leland Stanford Junior, US.
- Li, Q., Du, Y.Z., Yuan, H., Zhang, X.G., Miao, J., Cui, F.D., Hu, F.Q., 2010. Synthesis of lamivudine stearate and antiviral activity of stearic acid-g-chitosan oligosaccharide polymeric micelles delivery system. *Eur. J. Pharm. Sci.* 41, 498–507.
- Li, M., Wang, C., Di, Z., Li, H., Zhang, J., Xue, W., Zhao, M., Zhang, K., Zhao, Y., Li, L., 2019. Engineering multifunctional DNA hybrid nanospheres through coordination-driven self-assembly. *Angew. Chem. Int. Ed.* 58, 1350–1354.
- Li, J., Yu, F., Chen, Y., Oupický, D., 2015. Polymeric drugs: Advances in the development of pharmacologically active polymers. *J. Control. Release* 219, 369–382.

- Liang, Y., Liu, J., Liu, T., Yang, X., 2017. Anti-c-Met antibody bioconjugated with hollow gold nanospheres as a novel nanomaterial for targeted radiation ablation of human cervical cancer cell. *Oncol. Lett.* 14, 2254–2260.
- Liao, J., Jia, Y., Wu, Y., Shi, K., Yang, D., Li, P., Qian, Z., 2020. Physical-, chemical-, and biological-responsive nanomedicine for cancer therapy. *Wiley Interdiscip. Rev. Nanomed. Nanobiotechnol.* 12, e1581.
- Lim, S.A., Cox, A., Tung, M., Chung, E.J., 2022. Clinical progress of nanomedicine-based RNA therapies. *Bioact. Mater.* 12, 203–213.
- Liu, L., Hu, F., Wang, H., Wu, X., Eltahan, A.S., Stanford, S., Bottini, N., Xiao, H., Bottini, M., Guo, W., 2019. Secreted protein acidic and rich in cysteine mediated biomimetic delivery of methotrexate by albumin-based nanomedicines for rheumatoid arthritis therapy. *ACS Nano* 13, 5036–5048.
- Luo, D., Carter, K.A., Lovell, J.F., 2015. Nanomedical engineering: shaping future nanomedicines. *Wiley Interdiscip. Rev. Nanomed. Nanobiotechnol.* 7, 169–188.
- Majumder, N., G Das, N., Das, S.K., 2020. Polymeric micelles for anticancer drug delivery. *Therap. Deliv.* 11, 613–635.
- Malakar, A., Kamel, S.R., Ray, C., Snow, D.D., Nadagouda, M.N., 2021. Nanomaterials in the environment, human exposure pathway, and health effects: a review. *Sci. Total Environ.* 759, 143470.
- Marcowicz, J., Wołowiec, S., Rode, W., Uram, Ł., 2022. Synthesis and Properties of α -Mangostin and Vadimezan Conjugates with Glucoheptoamidated and Biotinylated 3rd Generation Poly(amideamine) Dendrimer, and Conjugation Effect on Their Anticancer and Anti-Nematode Activities. *Pharmaceutics* 14.
- Mateos-Maroto, A., Fernández-Peña, L., Abelenda-Núñez, I., Ortega, F., Rubio, R.G., Guzmán, E., 2022. Polyelectrolyte multilayered capsules as biomedical tools. *Polymers* 14, 479.
- Mattuzzi, C., Lippi, G., 2019. Current cancer epidemiology. *J. Epidemiol. Global Health* 9, 217.
- McDonald, T.O., Giardiello, M., Martin, P., Siccardi, M., Liptrott, N.J., Smith, D., Roberts, P., Curley, P., Schipani, A., Khoo, S.H., Long, J., Foster, A.J., Rannard, S.P., Owen, A., 2014. Antiretroviral solid drug nanoparticles with enhanced oral bioavailability: production, characterization, and in vitro-in vivo correlation. *Adv. Healthc. Mater.* 3, 400–411.
- Melisi, D., García-Carbonero, R., Macarulla, T., Pezet, D., Deplanque, G., Fuchs, M., Trojan, J., Oettle, H., Kozloff, M., Cleverly, A., 2018. Galunisertib plus gemcitabine vs. gemcitabine for first-line treatment of patients with unresectable pancreatic cancer. *Br. J. Cancer* 119, 1208–1214.
- Mi, P.J.T., 2020. Stimuli-responsive nanocarriers for drug delivery, tumor imaging, therapy and theranostics. 10, 4557.
- Mirkin Chad, A., Teplensky Michelle, H., Evangelopoulos, M., Wang, S., 2024. Targeting Multiple T Cell Types Using Spherical Nucleic Acid Vaccine Architecture. Univ Northwestern, US.
- Mitchell, M.J., Billingsley, M.M., Haley, R.M., Wechsler, M.E., Peppas, N.A., Langer, R., 2021. Engineering precision nanoparticles for drug delivery. *Nat. Rev. Drug Discov.* 20, 101–124.
- Mohamad Saimi, N.I., Salim, N., Ahmad, N., Abdulmalek, E., Abdul Rahman, M.B., 2021. Aerosolized Niosome Formulation Containing Gemcitabine and Cisplatin for Lung Cancer Treatment: Optimization, Characterization and In Vitro Evaluation. *Pharmaceutics* 13.
- Mohamed, M., Abu Lila, A.S., Shimizu, T., Alaaeldin, E., Hussein, A., Sarhan, H.A., Szelenyi, J., Ishida, T., 2019. PEGylated liposomes: immunological responses. *Sci. Technol. Adv. Mater.* 20, 710–724.
- Montana, M., Ducros, C., Verhaeghe, P., Terme, T., Vanelle, P., Rathelot, P., 2011. Albumin-bound paclitaxel: the benefit of this new formulation in the treatment of various cancers. *J. Chemother.* 23, 59–66.
- Moody Rebecca, 2022. Truchan. In: *Topoisomerase Inhibitors*. Nanomedicine Innovation Center LLC, USA.
- Moskowitz Keith, Jorda, R., Zheng, Ying, Sheik Daniel, A., 2024. Platelets loaded with anti-cancer agents. Cellphire Inc, US.
- Mosquera, J., García, I., Liz-Marzán, L.M., 2018. Cellular Uptake of Nanoparticles versus Small Molecules: A Matter of Size. *Acc. Chem. Res.* 51, 2305–2313.
- Mukherjee, A., Waters, A.K., Kalyan, P., Achrol, A.S., Kesari, S., Yenugonda, V.M., 2019. Lipid-polymer hybrid nanoparticles as a next-generation drug delivery platform: State of the art, emerging technologies, and perspectives. *Int. J. Nanomed.* 14, 1937.
- Münster, R., Bak, M., Christensen, E., Kempen, P.J., Larsen, J.B., Kristensen, K., Parhamifar, L., Andresen, T.L., 2022. Mechanisms of selective monocyte targeting by liposomes functionalized with a cationic, arginine-rich lipopeptide. *Acta Biomater.* 144, 96–108.
- Nakhaei, P., Margiana, R., Bokov, D.O., Abdelbasset, W.K., Jadidi Kouhbanani, M.A., Varma, R.S., Marofi, F., Jarahian, M., Beheshtkhoo, N., 2021. Liposomes: structure, biomedical applications, and stability parameters with emphasis on cholesterol. *Front. Bioeng. Biotechnol.* 748.
- Naseri, N., Valizadeh, H., Zakeri-Milani, P., 2015. Solid lipid nanoparticles and nanostructured lipid carriers: structure, preparation and application. *Adv. Pharm. Bull.* 5, 305.
- Nayak, D., Boxi, A., Ashe, S., Thathapudi, N.C., Nayak, B., 2017. Stavudine loaded gelatin liposomes for HIV therapy: Preparation, characterization and in vitro cytotoxic evaluation. *Mater. Sci. Eng. C Mater. Biol. Appl.* 73, 406–416.
- Nepotchatykh, O., Nepotchatykh, E., Nepotchatykh, O., 2024. Zip-in Technology for Antiviral Therapeutic Nanoformulations. Parole Laboratories Inc, US.
- Nieberler, M., Reuning, U., Reichart, F., Notni, J., Wester, H.-J., Schwaiger, M., Weinmüller, M., Räder, A., Steiger, K., Kessler, H., 2017. Exploring the role of RGD recognizing integrins in cancer. *Cancers* 9, 116.
- Niemelä, Erik J., 2024. Virus-Like Particles for Preventing the Spreading and Lowering the Infection Rate of Viruses. Finncure Oy, US.
- Ogochukwu, O.O., Fabiyi, M.B., Aworunse, O.S., Oyewole, O.A., Isibor, P.O., 2024. Nanoparticle Properties and Characterization, Environmental Nanotoxicology: Combating the Minute Contaminants. Springer, pp. 23–40.
- Ogunwuyi, O., Kumari, N., Smith, K.A., Bolshakov, O., Adesina, S., Gugssa, A., Anderson, W.A., Nekhai, S., Akala, E.O., 2016. Antiretroviral drugs-loaded nanoparticles fabricated by dispersion polymerization with potential for HIV/AIDS treatment. *Infect. Dis.: Res. Treatm.* 9. IDRT.S38108.
- Pal, M., Berhanu, G., Desalegn, C., Kandi, V., 2020. Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2): An Update. *Cureus* 12, e7423.
- Paliwal, R., Paliwal, S.R., Kenwat, R., Kurmi, B.D., Sahu, M.K., 2020. Solid lipid nanoparticles: A review on recent perspectives and patents. *Expert Opin. Ther. Pat.* 30, 179–194.
- Pandey, A.J.E.C.L., 2021. Cyclodextrin-based nanoparticles for pharmaceutical applications: A review. *Environ. Chem. Lett.* 19, 4297–4310.
- Park, S.-M., Aalipour, A., Vermesh, O., Yu, J.H., Gambhir, S.S., 2017. Towards clinically translatable in vivo nanodiagnoses. *Nat. Rev. Mater.* 2, 1–20.
- Paroha, S., Verma, J., Dubey, R.D., Dewangan, R.P., Molugulu, N., Bapat, R.A., Sahoo, P. K., Kesharwani, P., 2021. Recent advances and prospects in gemcitabine drug delivery systems. *Int. J. Pharm.* 592, 120043.
- Parveen, S., Arjmand, F., Tabassum, S., 2019. Clinical developments of antitumor polymer therapeutics. *RSC Adv.* 9, 24699–24721.
- Pascual-Pasto, G., Castillo-Ecija, H., Unceta, N., Aschero, R., Resa-Pares, C., Gómez-Caballero, A., Vila-Ubach, M., Muñoz-Aznar, O., Suñol, M., Burgueno, V., 2022. SPARC-mediated long-term retention of nab-paclitaxel in pediatric sarcomas. *J. Control. Release* 342, 81–92.
- Patel, S., Robinson, E., Brown, A., Almarsson, O.R.N., Benenato Kerry, E., Sabnis, S., Sahay, G., Narayana Ashwani, K., 2024. Lipid nanoparticle formulation. Modernatx Inc , Univ Oregon State, US.
- Pathak, C., Vaidya, F.U., Pandey, S.M., 2019. Mechanism for development of nanobased drug delivery system. *Appl. Targeted Nano Drug Delivery Syst.* 35–67.
- Patoulias, D., Doumas, M., Papadopoulos, C., Karagiannis, A., 2021. Janus kinase inhibitors and major COVID-19 outcomes: time to forget the two faces of Janus! A meta-analysis of randomized controlled trials. *Clin. Rheumatol.* 40, 4671–4674.
- Patra, J.K., Das, G., Fracteo, L.F., Campos, E.V.R., Rodriguez-Torres, M.d.P., Acosta-Torres, L.S., Diaz-Torres, L.A., Grillo, R., Swamy, M.K., Sharma, S., Habtemariam, S., Shin, H.-S., 2018. Nano based drug delivery systems: recent developments and future prospects. *J. Nanobiotechnol.* 16, 71.
- Pearson, R., Chakrabarty, A., 2024. Compositions and Methods for Delivering Nucleic Acids to Cells. Univ Maryland, US.
- Peng, J., Chen, J., Xie, F., Bao, W., Xu, H., Wang, H., Xu, Y., Du, Z., 2019. Herceptin-conjugated paclitaxel loaded PCL-PEG worm-like nanocrystal micelles for the combinatorial treatment of HER2-positive breast cancer. *Biomaterials* 222, 119420.
- Pradhan, D., Biswasroy, P., Goyal, A., Ghosh, G., Rath, G., 2021a. Recent Advancement in Nanotechnology-Based Drug Delivery System Against Viral Infections. *AAPS PharmSciTech* 22, 47.
- Pradhan, D., Biswasroy, P., Goyal, A., Ghosh, G., Rath, G., 2021b. Recent advancement in nanotechnology-based drug delivery system against viral infections. *AAPS PharmSciTech* 22, 1–19.
- Pronin, A.V., Narovlyansky, A.N., Sanin, A.V., 2021. New approaches to the prevention and treatment of viral diseases. *Arch. Immunol. Ther. Exp. (Warsz.)* 69, 1–11.
- Puri, A., Loomis, K., Smith, B., Lee, J.H., Yavlovich, A., Heldman, E., Blumenthal, R., 2009. Lipid-based nanoparticles as pharmaceutical drug carriers: from concepts to clinic. *Crit. Rev. Ther. Drug Carrier Syst.* 26, 523–580.
- Qin, S., Tang, X., Chen, Y., Chen, K., Fan, N., Xiao, W., Zheng, Q., Li, G., Teng, Y., Wu, M., Song, X., 2022. mRNA-based therapeutics: powerful and versatile tools to combat diseases. *Signal Transduct. Target. Ther.* 7, 166.
- Qiu, H., Cao, S., Xu, R., 2021. Cancer incidence, mortality, and burden in China: a time-trend analysis and comparison with the United States and United Kingdom based on the global epidemiological data released in 2020. *Cancer Commun.* 41, 1037–1048.
- Rashid, M., Ahmad, Q.Z., 2019. Trends in nanotechnology for practical applications, Applications of targeted nano drugs and delivery systems. Elsevier 297–325.
- Ravi, P.R., Vats, R., 2017. Comparative pharmacokinetic evaluation of lopinavir and lopinavir-loaded solid lipid nanoparticles in hepatic impaired rat model. *J. Pharm. Pharmacol.* 69, 823–833.
- Ravikanti, S., Chitrabhanu, L., 2023. Nanoformulation With Diverse Functional Molecules From Turmeric and Process for Preparation of the Same. ZeroHarm Sciences Private Ltd, EP.
- Rennick, J.J., Johnston, A.P.R., Parton, R.G., 2021. Key principles and methods for studying the endocytosis of biological and nanoparticle therapeutics. *Nat. Nanotechnol.* 16, 266–276.
- Rinoldi, C., Zargarian, S.S., Nakielki, P., Li, X., Liguori, A., Petronella, F., Presutti, D., Wang, Q., Costantini, M., De Sio, L., Gualandi, C., Ding, B., Pierini, F., 2021. Nanotechnology-Assisted RNA Delivery: From Nucleic Acid Therapeutics to COVID-19 Vaccines. *Small Methods* 5, 2100402.
- Sahay, G., Alakhova, D.Y., Kabanov, A.V., 2010. Endocytosis of nanomedicines. *J. Control. Release* 145, 182–195.
- Sahin, U., Karikó, K., Türeci, Ö., 2014. mRNA-based therapeutics—developing a new class of drugs. *Nat. Rev. Drug Discov.* 13, 759–780.
- Sahoo, D., Bandaru, R., Samal, S.K., Naik, R., Kumar, P., Kesharwani, P., Dandela, R., 2021. Oral drug delivery of nanomedicine, Theory and applications of nonparenteral nanomedicines. Elsevier 181–207.
- Saleh, T.A., 2020. Nanomaterials: Classification, properties, and environmental toxicities. *Environ. Technol. Innov.* 20, 101067.
- Sato, Y., Hashiba, K., Sasaki, K., Maeki, M., Tokeshi, M., Harashima, H., 2019. Understanding structure-activity relationships of pH-sensitive cationic lipids

- facilitates the rational identification of promising lipid nanoparticles for delivering siRNAs *in vivo*. *J. Control. Release* 295, 140–152.
- Scioli Montoto, S., Muraca, G., Ruiz, M.E., 2020. Solid lipid nanoparticles for drug delivery: pharmacological and biopharmaceutical aspects. *Front. Mol. Biosci.* 7, 319.
- Senapati, S., Mahanta, A.K., Kumar, S., Maiti, P., 2018. Controlled drug delivery vehicles for cancer treatment and their performance. *Signal Transduct. Target. Ther.* 3, 7.
- Sengupta, P., Das, A., Datta, D., Dewanjee, S., Khanam, J., Ghosal, K.J.R., Polymers, F., 2024. Novel super porous nanosponge-based drug delivery system synthesized from cyclodextrin/polymer for anti-fungal medication. *React. Funct. Polym.* 105830.
- Shah, S., Dhawan, V., Holm, R., Nagarsenker, M.S., Perrie, Y., 2020. Liposomes: Advancements and innovation in the manufacturing process. *Adv. Drug Deliv. Rev.* 154–155, 102–122.
- Shi, Y., 2020. Clinical Translation of Nanomedicine and Biomaterials for Cancer Immunotherapy: Progress and Perspectives. *3*, 1900215.
- Siegel, R.L., Miller, K.D., Wagle, N.S., Jemal, A., 2023. Cancer statistics, 2023. *CA Cancer J. Clin.* 73, 17–48.
- Singh, G., Majeed, A., Singh, R., George, N., Singh, G., Singh, H., Kaur, G., Singh, J.J.R.a., 2023. CuAAC ensembled 1, 2, 3-triazole linked nanogels for targeted drug delivery: A review. *13*, 2912–2936.
- Singh, L., Kruger, H.G., Maguire, G.E.M., Govender, T., Parboosing, R., 2017. The role of nanotechnology in the treatment of viral infections. *Ther. Adv. Infect. Dis* 4, 105–131.
- Sousa de Almeida, M., Susnik, E., Drasler, B., Taladriz-Blanco, P., Petri-Fink, A., Rothen-Rutishauser, B., 2021. Understanding nanoparticle endocytosis to improve targeting strategies in nanomedicine. *Chem. Soc. Rev.* 50, 5397–5434.
- Soy, M., Keser, G., Atagündüz, P., Tabak, F., Atagündüz, I., Kayhan, S., 2020. Cytokine storm in COVID-19: pathogenesis and overview of anti-inflammatory agents used in treatment. *Clin. Rheumatol.* 39, 2085–2094.
- Strasfeld, L., Chou, S., 2010. Antiviral drug resistance: mechanisms and clinical implications. *Infect. Dis. Clin. North Am.* 24, 413–437.
- Sun, L., Liu, H., Ye, Y., Lei, Y., Islam, R., Tan, S., Tong, R., Miao, Y.B., Cai, L., 2023. Smart nanoparticles for cancer therapy. *Signal Transduct. Target. Ther.* 8, 418.
- Surekha, B., Kommana, N.S., Dubey, S.K., Kumar, A.P., Shukla, R., Kesharwani, P., 2021. PAMAM dendrimer as talented multifunctional biomimetic nanocarrier for cancer diagnosis and therapy. *Colloids Surf. B Biointerfaces* 204, 111837.
- Tang, R., Kim, C.S., Solfield, D.J., Rana, S., Mout, R., Velázquez-Delgado, E.M., Chompoosor, A., Jeong, Y., Yan, B., Zhu, Z.-J., 2013. Direct delivery of functional proteins and enzymes to the cytosol using nanoparticle-stabilized nanocapsules. *ACS Nano* 7, 6667–6673.
- Tang, Y., Liu, J., Zhang, D., Xu, Z., Ji, J., Wen, C., 2020. Cytokine Storm in COVID-19: The Current Evidence and Treatment Strategies. *Front. Immunol.* 11, 1708.
- Tang, M., Svirskis, D., Leung, E., Kanamala, M., Wang, H., Wu, Z., 2019. Can intracellular drug delivery using hyaluronic acid functionalised pH-sensitive liposomes overcome gemcitabine resistance in pancreatic cancer? *J. Control. Release* 305, 89–100.
- Tashima, T., 2021. Delivery of orally administered digestible antibodies using nanoparticles. *Int. J. Mol. Sci.* 22, 3349.
- Teede, H.J., Misso, M.L., Costello, M.F., Dokras, A., Laven, J., Moran, L., Piltonen, T., Norman, R.J., 2018. Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome. *Hum. Reprod.* 33, 1602–1618.
- Tenchov, R., Bird, R., Curtze, A.E., Zhou, Q., 2021. Lipid nanoparticles—from liposomes to mRNA vaccine delivery, a landscape of research diversity and advancement. *ACS Nano* 15, 16982–17015.
- Trac, N., Chung Yoo Eun, JI P., 2024. CD70-Targeted micelles enhance HIF2? siRNA delivery and inhibit oncogenic functions in patient-derived clear cell renal carcinoma cells. University of Southern California, US.
- Tripathy, S., Das, M.K., 2013. Dendrimers and their applications as novel drug delivery carriers. *J. Appl. Pharm. Sci.* 3, 142–149.
- Van Hoecke, L., Roose, K., 2019. How mRNA therapeutics are entering the monoclonal antibody field. *J. Transl. Med.* 17, 54.
- Vashist, A., Raymond Andrea, D., Chapagain, P., Nair Madhavan, P., Runowicz, Carolyn D., 2024. Polyols and polyol-based hydrogels with anti-cancer activity. The Florida International Univ Board of Trustees, US.
- Varshosaz, J., Taymouri, S., Jafari, E., Jahanian-Najafabadi, A., Taheri, A., 2018. Formulation and characterization of cellulose acetate butyrate nanoparticles loaded with nevirapine for HIV treatment. *J. Drug Delivery Sci. Technol.* 48, 9–20.
- Vitulò, M., Gnodi, E., Meneveri, R., Barisani, D.J.I.O.M.S., 2022. Interactions between nanoparticles and intestine. *Int. J. Mol. Sci.* 23, 4339.
- Wang, J., Ding, Y., Zhou, W., 2020a. Albumin self-modified liposomes for hepatic fibrosis therapy via SPARC-dependent pathways. *Int. J. Pharm.* 574, 118940.
- Wang, X., Qiu, L., Ouyang, H., Li, T., Han, L., Zhang, X., Xu, W., Chu, K., 2020b. Evaluation of intestinal permeation enhancement with carboxymethyl chitosan-rhein polymeric micelles for oral delivery of paclitaxel. *Int. J. Pharm.* 573, 118840.
- Wang, G., Wang, Z., Li, C., Duan, G., Wang, K., Li, Q., Tao, T., 2018. RGD peptide-modified, paclitaxel prodrug-based, dual-drugs loaded, and redox-sensitive lipid-polymer nanoparticles for the enhanced lung cancer therapy. *Biomed. Pharmacother.* 106, 275–284.
- Weiss, C., Carriere, M., Fusco, L., Capua, I., Regla-Nava, J.A., Pasquali, M., Scott, J.A., Vitale, F., Unal, M.A., Mattevi, C., Bedognetti, D., Merkoçi, A., Tasciotti, E., Yilmazer, A., Gogotsi, Y., Stellacci, F., Delogu, L.G., 2020. Toward nanotechnology-enabled approaches against the COVID-19 Pandemic. *ACS Nano* 14, 6383–6406.
- (WHO), W.H.O., 2022. Vaccine-Preventable Diseases (including pipeline vaccines).
- Wesche, H., Lemon Bryan, D., Austin, Richard J., 2024. B cell maturation antigen binding proteins. Harpoon Therapeutics Inc, US.
- Wu, J., 2021. The enhanced permeability and retention (EPR) effect: The significance of the concept and methods to enhance its application. *J. Personalized Med.* 11, 771.
- Xu, P., 2024. Carrier-Free Curcumin Nanoparticles for EGFR-Positive Cancer Therapy. University of South, Carolina, US.
- Xu, X., Chen, P., Wang, J., Feng, J., Zhou, H., Li, X., Zhong, W., Hao, P., 2020. Evolution of the novel coronavirus from the ongoing Wuhan outbreak and modeling of its spike protein for risk of human transmission. *Sci. China Life Sci.* 63, 457–460.
- Xu, H., Paxton, J.W., Wu, Z., 2016. Development of long-circulating pH-sensitive liposomes to circumvent gemcitabine resistance in pancreatic cancer cells. *Pharm. Res.* 33, 1628–1637.
- Xu, F.E.I., Hao, R., Zhang, W., Wu, S.H.U., 2024. Engineered Immune Cells and Uses Thereof. Nanjing Legend Biotech Co Ltd, US.
- Xu, H., Li, Y., Paxton, J.W., Wu, Z., 2021. Co-delivery using pH-sensitive liposomes to pancreatic cancer cells: the effects of curcumin on cellular concentration and pharmacokinetics of gemcitabine. *Pharm. Res.* 38, 1209–1219.
- Xu, L., Qiu, L., Sheng, Y., Sun, Y., Deng, L., Li, X., Bradley, M., Zhang, R., 2018. Biodegradable pH-responsive hydrogels for controlled dual-drug release. *J. Mater. Chem. B* 6, 510–517.
- Xu, X., Xie, K., Zhang, X.Q., Pridgen, E.M., Park, G.Y., Cui, D.S., Shi, J., Wu, J., Kantoff, P. W., Lippard, S.J., Langer, R., Walker, G.C., Farokhzad, O.C., 2013. Enhancing tumor cell response to chemotherapy through nanoparticle-mediated codelivery of siRNA and cisplatin prodrug. *PNAS* 110, 18638–18643.
- Yang, L., Xie, X., Tu, Z., Fu, J., Xu, D., Zhou, Y., 2021. The signal pathways and treatment of cytokine storm in COVID-19. *Signal Transduct. Target. Ther.* 6, 255.
- Zelepukin, I.V., Griaznova, O.Y., Shevchenko, K.G., Ivanov, A.V., Baidyuk, E.V., Serejnikova, N.B., Volovetskiy, A.B., Deyev, S.M., Zvyagin, A.V., 2022. Flash drug release from nanoparticles accumulated in the targeted blood vessels facilitates the tumour treatment. *Nat. Commun.* 13, 6910.
- Zhang, Y., Chen, L., Hu, G.-Q., Zhang, N., Zhu, X.-D., Yang, K.-Y., Jin, F., Shi, M., Chen, Y.-P., Hu, W.-H., 2019. Gemcitabine and cisplatin induction chemotherapy in nasopharyngeal carcinoma. *N. Engl. J. Med.* 381, 1124–1135.
- Zhang, R.X., Li, J., Zhang, T., Amini, M.A., He, C., Lu, B., Ahmed, T., Lip, H., Rauth, A.M., Wu, X.Y., 2018. Importance of integrating nanotechnology with pharmacology and physiology for innovative drug delivery and therapy – an illustration with firsthand examples. *Acta Pharmacol. Sin.* 39, 825–844.
- Zhang, F., Segel, M., Ladha, A., Walsh, M., Frangieh, C., 2024. Nuclease-Guided Non-Ltr Retrotransposons and Uses Thereof. Broad Inst Inc, Massachusetts Inst Technology, US.
- Zheng, M., Yue, C., Ma, Y., Gong, P., Zhao, P., Zheng, C., Sheng, Z., Zhang, P., Wang, Z., Cai, L., 2013. Single-step assembly of DOX/ICG loaded lipid-polymer nanoparticles for highly effective chemo-photothermal combination therapy. *ACS Nano* 7, 2056–2067.
- Zottel, A., Videtić Paska, A., Jovčevska, I., 2019. Nanotechnology meets oncology: nanomaterials in brain cancer research, diagnosis and therapy. *Materials* 12, 1588.
- Zou, H., Yang, Y., Dai, H., Xiong, Y., Wang, J.Q., Lin, L., Chen, Z.S., 2021. Recent updates in experimental research and clinical evaluation on drugs for COVID-19 treatment. *Front. Pharmacol.* 12, 732403.
- Zoulikha, M., Huang, F., Wu, Z., He, W., 2022. COVID-19 inflammation and implications in drug delivery. *J. Control. Release* 346, 260–274.