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A REVIEW OF TARGETTED DRUG DELIVERY SYSTEMS – A NEW ERA OF DRUG CARRIERS IN CANCER THERAPY

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Abstract:

Nanotechnology has been extensively studied and exploited for cancer treatment as nanoparticles can play a significant role as a drug delivery system. Compared to conventional drugs, nanoparticle-based drug delivery has specific advantages, such as improved stability and biocompatibility, enhanced permeability and retention effect, and precise targeting.nanoparticle-based drug delivery systems have been shown to play a role in overcoming cancer-related drug resistance.Several drug-delivery systems have been reported on and often successfully applied in cancer therapyTherapeutic monoclonal antibody (TMA) based therapies for cancer have advanced significantly over the past two decades both in their molecular sophistication and clinical efficacy. In view of the recognized importance of targeted drug delivery strategies for cancer therapy, we discuss the advantages of alternative drug carriers and where these should be applied, focusing on peptide-drug conjugates (PDCs) .

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INTRODUCTION:

Over the pastt 30 years, the number of successful cancer treatments has significantly increased, predominantly driven by our improved understanding of carcinogenesis processes, cell biology, and the tumor microenvironment (1).Finding new and innovative treatments for cancer is a major problem across the world (Siegel et al., 2020). With an increase in the number of methods that can treat cancer and the concept of an individualized treatment, the therapeutic efficacy of some malignant tumors has greatly improved. Chemotherapy is a conventional and widely used cancer treatment method.(2) While chemotherapy works through a number of different mechanisms, its major function includes indiscriminately killing vigorously growing cells, including tumor and normal cells, which causes some serious side effects including bone marrow suppression, hair loss, and gastrointestinal reactions (3)

Advantages of targeted drug delivery

- Improved efficacy: By specifically targeting the affected cells or tissues, the drug can be delivered directly to the site of action, increasing its effectiveness while minimizing side effects on healthy cells..
- Reduced side effects: Targeted delivery allows for the precise control of drug concentration at the target site, reducing the likelihood of harmful effects on other parts of the body.
- Reduced dosage: Targeted drug delivery allows for a lower dose of the drug to be administered while still achieving the desired therapeutic effect. This can help minimize potential side effects and reduce costs associated with drug therapy..
- Enhanced patient compliance: Targeted drug delivery systems often require fewer administrations or less frequent dosing, which can improve patient compliance and ensure that medication is taken as prescribed.
- Improved pharmacokinetics: Targeted drug delivery can result in improved pharmacokinetics, such as increased absorption, distribution, metabolism, and excretion (ADME). This can lead to more predictable drug levels and reduced variability in response to treatment
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- Reduced off-target effects: Targeted drug delivery can minimize off-target effects by reducing exposure to healthy tissues and organs. This can help reduce side effects and improve overall tolerability..
- Customization: Targeted drug delivery allows for customization of drug delivery based on individual patient needs, such as age, weight, disease stage, or genetic factors. This can help optimize treatment plans and improve outcomes..
- Expansion of drug classes: Targeted delivery systems can expand the pool of drugs that can be safely and effectively administered, potentially enabling the development of novel therapies for previously untreatable conditions.
- Reduced side effects: TDD can reduce the side effects on healthy tissues and cells.
- Lower dosage: TDD can reduce the dosage of a drug while still achieving the desired therapeutic effect.
- Improved drug absorption: TDD can improve how well the drug is absorbed from the target site.
- Simplified administration: TDD can make the drug administration protocol simpler.
- Enhanced therapeutic effect: TDD can enhance the therapeutic effect of the drug on tumor cells and tissues.
- Reduced peak and valley plasma concentration: TDD can result in a more consistent drug concentration in the plasm.

Disadvantages of targeted drug delivery

Knowing as much as you can about the various side effects of targeted therapy and what to expect may help you feel more in control and at ease during treatment. Below, find a few main overarching side effects of targeted therapy.

Fatigue: You may experience tiredness or utter exhaustion during cancer treatment, and cancer fatigue feels very different from the fatigue you may have from your normal routine. It’s important to remember the level of fatigue differs between each person, so no two patients have the same experience.

Some ways to manage fatigue include:

- Take time for both relaxation and being active. Work on finding an even balance between time to relax and rest vs. time for light movement and activity (such as a walk around the neighborhood or working in the garden).
- Follow a healthy diet. Make water your drink of choice, and make sure your diet is a mix of protein, carbohydrates, fat, vitamins and minerals to help keep your energy levels up.
- Meet with a mental health expert. Speak with a counselor or psychologist to help you cope with the stress from symptoms and the

difficult thoughts and emotions you may be experiencing during cancer treatments.

Skin irritation: Targeted therapy may cause dry skin, a rash or nail problems. You may also experience sensitivity to light, itching or hand-foot syndrome.

Some ways to manage skin irritation include:

- Avoid the sun. Sunshine may cause further irritation, so try to cover your skin and use a sunscreen with a minimum of SPF 30.
- Use dressings. Your health-care provider may recommend specific creams or ointments for skin swelling or dryness. In more severe cases, your doctor may give you a prescription for antihistamines or steroids.

Fever and chills: Your body temperature may spike during or after targeted therapy treatmen.

Some ways to manage fever and chills include:

- Cool down. Run a cloth under cold water, then place it on top of your forehead.
- Prevent excess heat. Avoid wrapping your body in blankets, as it may raise your temperature even higher

Nausea and vomiting: Targeted therapy may make you vomit, or you may feel queasy or lightheaded.

Some ways to manage nausea and vomiting include:

- Change your diet and the size of your meals. Eating bland foods such as toast or crackers and drinking clear liquids may help. Instead of eating larger meals less often, sample smaller meals more frequently.
- Try to relax. Focus on mindful exercises, which may include practices such as meditation, acupressure or acupuncture

Hair loss (alopecia): Some targeted treatments may cause your hair to thin or fall out. You may lose hair not only on your head (including eyebrows and eyelashes), but also on your arms and legs and in your pubic area.

Some ways to manage hair loss include:

- Try cooling caps. Worn before, during and after treatments, cooling caps may reduce risk of hair loss, but some patients find them to be uncomfortable and cause headaches.
- Cover your head. Some people choose to get wigs or wear scarves. A wig may be covered by your insurance provider, so be sure to ask your care team. Tender Loving Care, a program run by the American Cancer Society, helps provide wigs, hats and scarves as well.

Common approaches of targeted drug delivery

Targeted drug delivery is the ability of the drug to accumulate in the target tissue delivery or organ selectively and quantitatively, independent of the site and methods of administrations. The aim of targeted drug delivery is to obtain high local concentrations of drug in the target area without any side effects in normal tissues, together with low systemic exposure .Targeting may have spatial and temporal properties which deliver the right amount of drug to the right place (double-targeting) Consequently, targeted drug delivery presents many advantages, the most important of which are

(1).simplification of administration protocols;

(2) drastic reduction in the cost of therapy and drug quantity required to achieve a therapeutic effect; and

(3) sharp increase in drug concentration in the required sites without negative effects on nontarget areas.

Approaches of drug targeting:

Passive drug targeting

In the human body, some molecules (i.e., hormones, growth-factors) have a natural tendency to target their receptors (sites of action) by the action of physicochemical and pathophysiological factors. This process is called “passive targeting,” and can also be applied to drugs (Garnett, 2001). In fact, passive drug targeting can benefit from the presence of (1) physicochemical modifications under diseased conditions, like internal stimuli (pH, temperature, etc.) (X. Zhang et al., 2010), and (2) modified physiologies, such as structural changes (i.e., leaky vasculature) in the microenvironment of inflammatory tissues (4)

Passive drug targeting (or enhanced permeation and retention (EPR) effect–mediated targeting) is based on the longevity of the pharmaceutical carrier in the blood and its accumulation in pathological sites with compromised vasculature (Torchilin, 2010). For example, drugs can penetrate the tumor vasculature through its leaky endothelium and, in this way, accumulate in several solid tumors. This is called the enhanced permeation and retention (EPR) effect (Hirsjärvi et al., 2011; Nakamura et al., 2016). The EPR effect is specifically responsible for passive drug targeting in cancer tissues (5)

Active drug targeting

Unlike passive targeting, which is a nonspecific strategy, active drug targeting is a specific approach that involves interactions between specific biological pairs/systems, such as ligand-receptor, antigen-antibody, and enzyme-substrate. In active targeting, therapeutics can be also transported specifically to relevant cells through stimuli responsive nanocarriers (temperature, ultrasound, magnetic field) (6) Active targeting strategy is based on the anchoring (attachment) of active agents or ligands to the surface of drug delivery system (DDS), which is selectively and specifically recognized by the target in concern. (7)

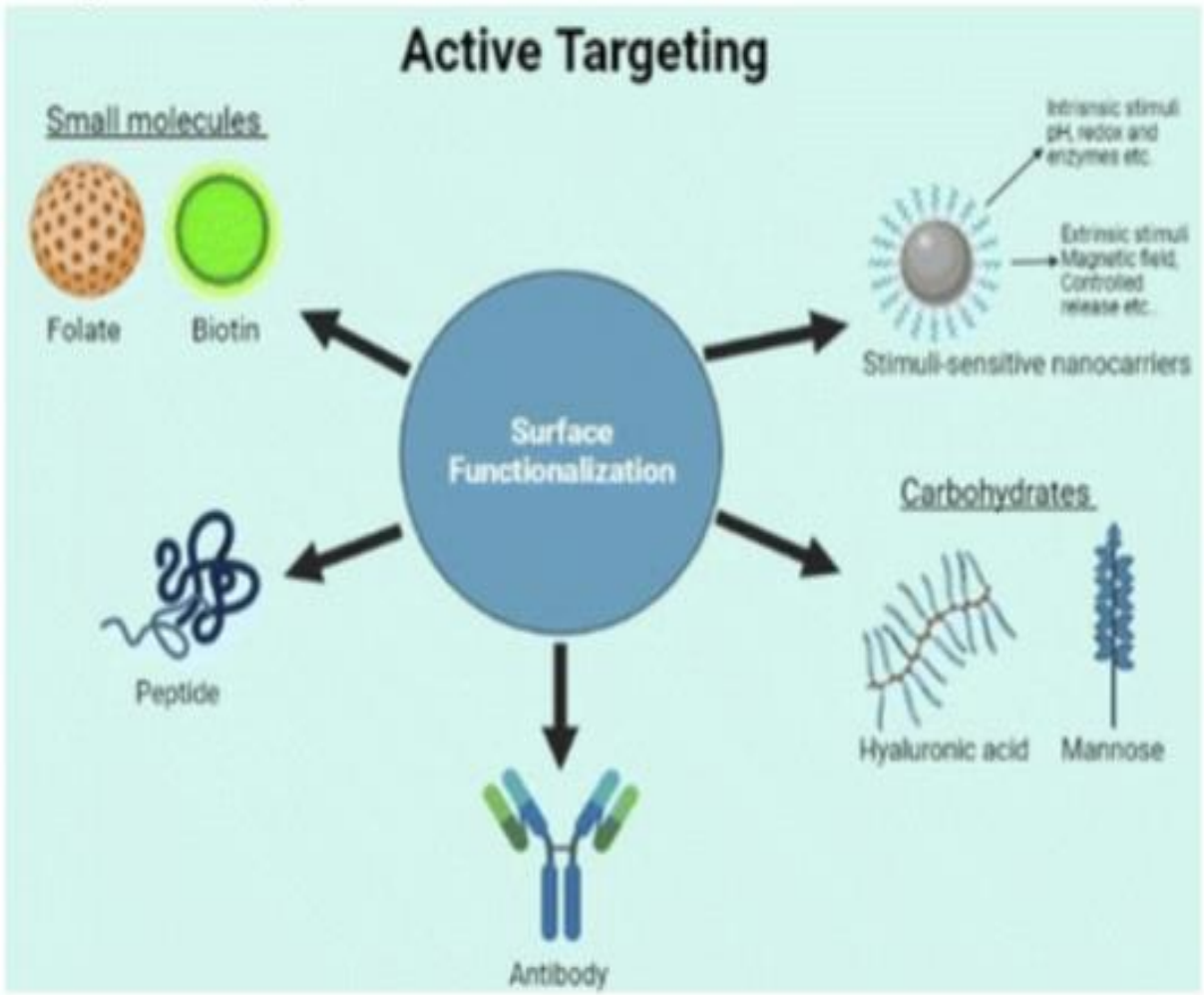

Figure1:Active targeting

Physical, Chemical, and Biological Targeting

Physical targeting describes systems that localize agents to target areas because of their size, composition, or other characteristics that are not specifically designed toward a biological receptor. Chemical targeting involves the localization of agents to targeted areas through the use of site-specific prodrugs. Site specificity is due to higher drug concerns at the site. Agents can also be directed to areas through the use of enzymatic or chemical reactions that lead to the targeting of a vehicle or the controlled release or action of the agent. Biological targeting allows localized agents to target areas through the use of antibodies (Abs), peptides, proteins, or other biomolecules that have affinity with receptors, sites, or other biological targets in a specific manner. Gene expression can also be localized to target areas through the use of cells, tissue, or other specific promoters in vector systems. (8) .Involves formulation of drug using particulate delivery-physical localization-differential release of drug

First-, Second-, Third-, and Fourth-Order targeting

Three (or four) distinct orders of targeting can be used to further categorise drug targeting. The drug-carrier system's distribution to the target site's capillary bed is restricted in first-order targeting. The term "second-order targeting" describes the deliberate administration of medications to particular cell types, such tumour cells. Drugs that target macromolecules like DNA and proteins are sometimes designated as having fourth-order targeting, whereas third-order targeting denotes a special focus on intracellular locations.

Inverse, Dual, Double, and Combination targeting

Inverse targeting is the process of inhibiting the reticuloendothelial system's normal action using a

blank colloidal carrier in order to minimise passive drug absorption. This will cause the system to become saturated with defence mechanism suppression. By delivering a carrier molecule with a distinct therapeutic action, dual targeting increases the drug's (synergistic) therapeutic impact. Double targeting combines temporal and spatial approaches, i.e., temporal delivery at a regulated pace and spatial placement to certain places. Combination targeting is a targeted delivery method that offers a direct path to a target by using carriers, polymers, and homing devices with molecular specificity.

Delivery vehicles

There are different types of drug delivery vehicles, such as polymeric micelles, liposomes, lipoprotein-based drug carriers, nano-particle drug carriers, dendrimers, etc. An ideal drug delivery vehicle must be non-toxic, biocompatible, non-immunogenic, biodegradable,[5] and must avoid recognition by the host's defense mechanisms(9)

Cell Surface Peptides provide one way to introduce drug delivery into a target cell.(10) This method is accomplished by the peptide binding to a target cells surface receptors, in a way that bypasses immune defenses that would otherwise compromise a slower delivery, without causing harm to the host. In particular, peptides, such as intercellular adhesion molecule-1, have shown a great deal of binding ability in a target cell. This method has shown a degree of efficacy in treating both autoimmune diseases as well as forms of cancer as a result of this binding affinity.[11] Peptide mediated delivery is also of promise due to the low cost of creating the peptides as well as the simplicity of their structure.

Nanoparticle drug delivery

Nanoparticle drug delivery systems are engineered technologies that use nanoparticles for the targeted delivery and controlled release of therapeutic agents. The modern form of a drug delivery system should minimize side-effects and reduce both dosage and dosage frequency. Recently, nanoparticles have aroused attention due to their potential application for effective drug delivery.[12]The National Institute of Biomedical Imaging and Bioengineering has issued the following prospects for future research in nanoparticle drug delivery systems:

1. crossing the blood-brain barrier (BBB) in brain diseases and disorders;
2. enhancing targeted intracellular delivery to ensure the treatments reach the correct structures inside cells;
3. combining diagnosis and treatment.[13]

Advantages of nanoparticles

- Stability: Nanoparticles can have a long shelf life.
- Capacity: Nanoparticles can carry many drug molecules.
- Routes of administration: Nanoparticles can be administered orally, inhaled, or intravenously.
- Innovations in Computing and Electronics
- Improved Accessibility to Diagnostic Tools
- Advanced Energy Production

Disadvantages of nanoparticles

- Toxicity: Nanoparticles can be toxic to humans and plants. They can catalyze harmful reactions inside the body, or bind to toxic substances because of their large surface area to volume ratio.
- Inhalation: Inhaled nanoparticles can cause lung inflammation and heart problems.
- : Nanoparticles can damage cells by disrupting homeostasis, generating reactive oxygen species (ROS), and inducing programmed cell death.
- Agglomeration: Nanoparticles tend to agglomerate.
- Health Concerns.
- Safety Issues
- High Costs
- Poorly Understood Long-term Effects
- Negative Environmental Impact

Classification of nanomaterials

The key elements of nanotechnology are the nanomaterials. Nanomaterials are defined as materials where at least one of their dimensions is in the nanoscale, i.e. smaller than 100 nm [22]. Based on their dimensionalities, nanomaterials are placed into four different classes, summarized in Fig. 1(14)

(1) Zero-dimensional nanomaterials (0-D): the nanomaterials in this class have all their three dimensions in the nanoscale range. Examples are quantum dots, fullerenes, and nanoparticles.

(2) One-dimensional nanomaterials (1-D): the nanomaterials in this class have one dimension outside the nanoscale. Examples are nanotubes, nanofibers, nanorods, nanowires, and nanohorns.

(3) Two-dimensional nanomaterials (2-D): the nanomaterials in this class have two dimensions outside the nanoscale.

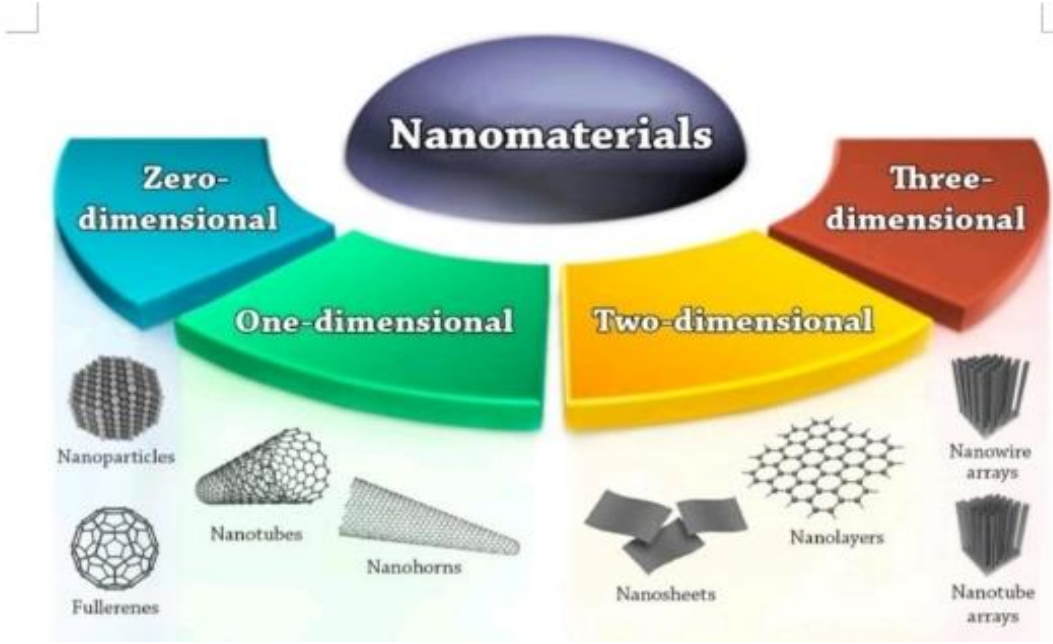

Figure2:Clasiffication of nanometerials

(4)Examples are nanosheets, nanofilms, and nanolayers.
Three-dimensional nanomaterials (3-D) or bulk nanomaterials: in this class the materials are not confined to the nanoscale in any dimension. This class contains bulk powders, dispersions of nanoparticles, arrays of nanowires and nanotubes, etc.

Nanoparticles (NPs)
The International Organization for Standardization (ISO) defines nanoparticles as nano-objects with all external dimensions in the nanoscale, where the lengths of the longest and the shortest axes of the nano-object do not differ significantly. If the dimensions differ significantly (typically by more than three times), terms such as nanofibers or nanoplates maybe preferred to the term NPsFootnote2.
NPs can be of different shapes, sizes, and structures. They can be spherical, cylindrical, conical, tubular, hollow core, spiral, etc., or irregular [15].
The NPs used in medical treatment usually have specific sizes, shapes, and surface characteristics as these three aspects have a major influence on the efficiency of the nano-drug delivery and thus control therapeutic efficacy (16).NPs with a diameter range of 10 to 100 nm are generally considered suitable for cancer therapy, as they can effectively deliver drugs and achieve enhanced permeability and retention (EPR) effect. (17).

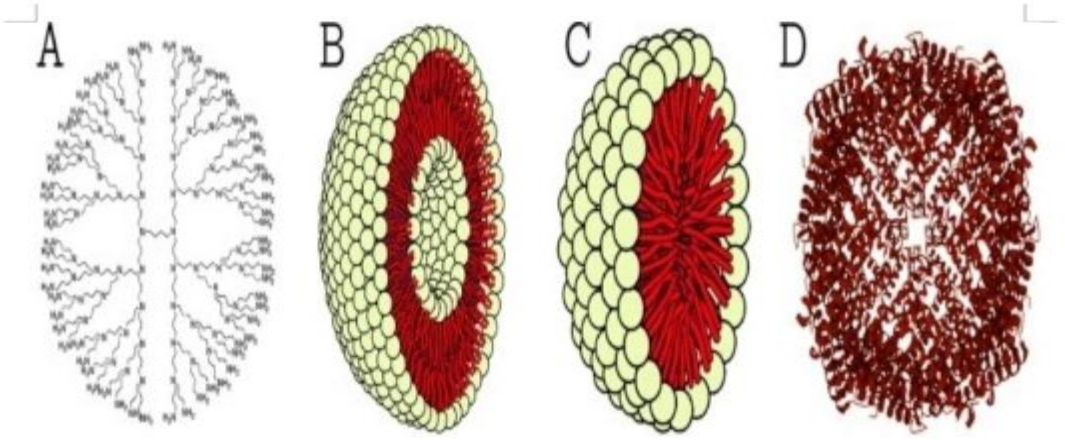

Figure 3. Different types of nanoparticles (NPs) for cancer therapy.

NPs applied to drug delivery systems include organic NPs, inorganic NPs and hybrid NPs. The organic NPs contain liposome-based NPs, polymer-based NPs and dendrimers. Among polymer-based NPs, polymeric NPs and polymeric micelles are common. The inorganic NPs consist of gold NPs (Au NPs), carbon nanotubes, silica NPs, magnetic NPs, and quantum dots. Hybrid NPs combine the advantages of different NPs, including lipid-polymer hybrid NPs, organic-inorganic hybrid NPs, and cell membrane-coated NPs.

Organic NPs

Organic NPs have been widely explored for decades and contain many types of materials. Liposome, the first nano-scale drug approved for clinical application(18) The hydrophobic core enables the insoluble anticancer drugs to be absorbed and delivered smoothly, while the hydrophilic segment increases stability, thus reducing the uptake of the drug by the reticuloendothelial system and prolonging their time period in circulation(19)

Inorganic NPso

Inorganic NPs have the advantages of a higher surface area to volume ratio. They have a wide and easily modified surface conjugation chemistry and facile preparation, although this usually occurs at the expense of poorer biocompatibility and biodegradability (20)

Hybrid NPs

As both organic and inorganic NPs have their own advantages and disadvantages, combining the two in a single hybrid drug delivery system endows the multifunctional carrier with better biological properties that can enhance treatment efficacy as well as reduce drug resistance (21)

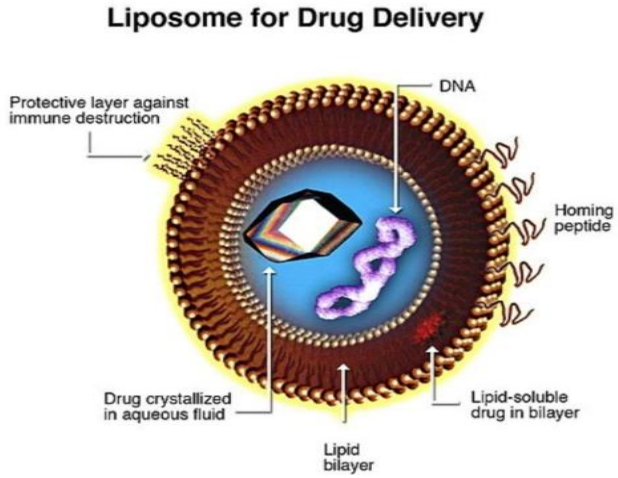

Figure 4: liposomes for drug delivery

Liposomes

Liposomes are composite structures made of phospholipids and may contains Though liposomes can vary in size from low micrometer range to tens of micrometers, unilamellar liposomes, as pictured here, are typically in the lower size range, with various targeting ligands attached to their surface, allowing for their surface-attachment and accumulation in pathological areas for treatment of disease.[22]The most common vehicle currently used for targeted drug delivery is the liposome.[23]Liposomes are non-toxic, non-hemolytic, and non-immunogenic even upon repeated injections;they are biocompatible and biodegradable and can be designed to avoid clearance mechanisms (reticuloendothelial system (RES), renal clearance, chemical or enzymatic inactivation, etc.)(24)Lipid-based, ligand-coated nanocarriers can store their payload in the hydrophobic shell or the hydrophilic interior depending on the nature of the drug/contrast agent being carried.[25]The only problem to using liposomes in vivo is their immediate uptake and clearance by the RES system and their relatively low stability in vitro. To combat this, polyethylene glycol (PEG) can be added to the surface of the liposomes. Increasing the mole percent of PEG on the surface of the liposomes by 4-10% significantly increased circulation time in vivo from 200 to 1000 minutes.[26]PEGylation of the liposomal nanocarrier elongates the half-life of the construct while maintaining the passive targeting mechanism that is commonly conferred to lipid-based nanocarriers.[27] When used as a delivery system, the ability to induce instability in the construct is commonly exploited allowing the selective release of the encapsulated therapeutic agent in close proximity to the target tissue/cell in vivo. This nanocarrier system is commonly used in anti-cancer treatments as the acidity of the tumour mass caused by an over-reliance on glycolysis triggers drug release.(28)Additional endogenous trigger pathways have been explored through the exploitation of inner and outer tumor environments, such as reactive oxygen species, glutathione, enzymes, hypoxia, and adenosine-5'- triphosphate (ATP), all of which are generally highly present in and around tumors.[29] External triggers are also used, such as light, low frequency ultrasound (LFUS), electrical fields, and magneticfields.[30] In specific, LFUS has demonstrated high efficacy in the controlled trigger of various drugs in mice, such as cisplatin and calcein.[31].

Micelles and dendrimers

Another type of drug delivery vehicle used is polymeric micelles. They are prepared from certain amphiphilic co-polymers consisting of both hydrophilic and hydrophobic monomer units.[32]They can be used to carry drugs that have poor solubility. This method offers little in the terms of size control or function malleability. Techniques that utilize reactive polymers along with a

hydrophobic additive to produce a larger micelle that create a range of sizes have been developed.[33) Dendrimers are also polymer-based delivery vehicles. They have a core that branches out in regular intervals to form a small, spherical, and very dense nanocarrier.(34)

Biodegradable particles

Biodegradable particles bearing ligands to P-selectin, endothelial selectin (E-selectin) and ICAM-1 have been found to adhere to inflamed endothelium.(35)Therefore, the use of biodegradable particles can also be used for cardiac tissue.

Microalgae-based delivery

There are biocompatible microalgae hybrid microrobots for active drug-delivery in the lungs and the gastrointestinal tract. The microrobots proved effective in tests with mice. In the two studies, "Fluorescent dye or cell membrane–coated nanoparticle functionalized algae motors were further embedded inside a pH-sensitive capsule" and "antibiotic-loaded neutrophil membrane-coated polymeric nanoparticles [were attached] to natural microalgae(36)

Artificial DNA nanostructures

The success of DNA nanotechnology in constructing artificially designed nanostructures out of nucleic acids such as DNA, combined with the demonstration of systems for DNA computing, has led to speculation that artificial nucleic acid nanodevices can be used to target drug delivery based upon directly sensing its environment. These methods make use of DNA solely as a structural material and a chemical, and do not make use of its biological role as the carrier of genetic information. Nucleic acid logic circuits that could potentially be used as the core of a system that releases a drug only in response to a stimulus such as a specific mRNA have been demonstrated.[37] In addition, a DNA "box" with a controllable lid has been synthesized using the DNA origami method. This structure could encapsulate a drug in its closed state, and open to release it only in response to a desired stimulus.

Types of Targeted Drug-Delivery Systems

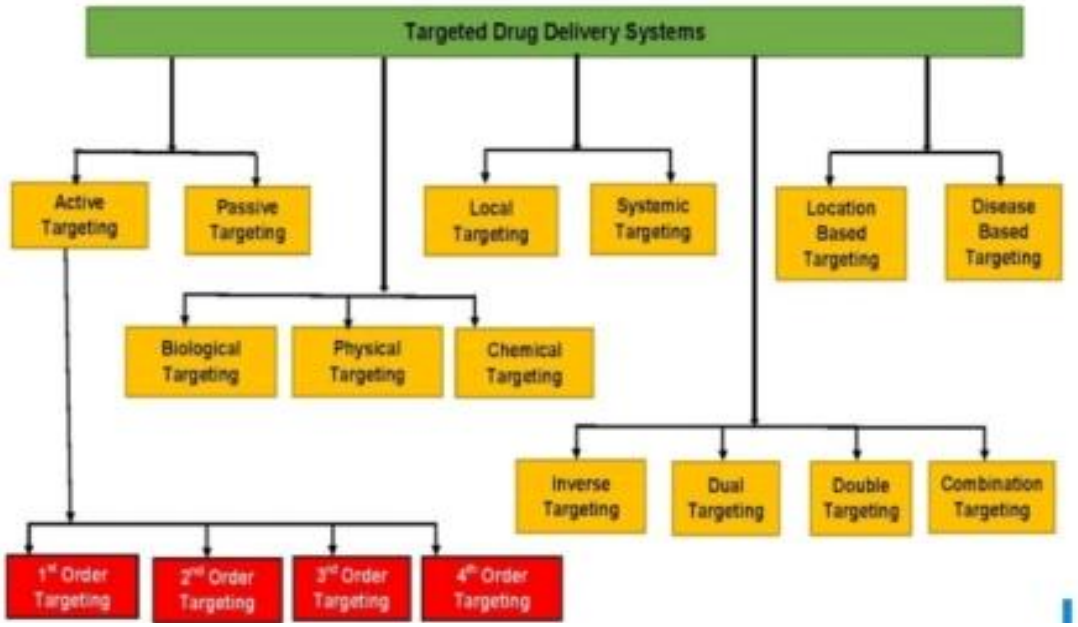

Figure5: type of targeted drug delivery

Bringing a new drug to the market can cost between 1 and 2 billion US Dollars over the span of 10–15 years [38] As of 2023, there have been 15 liposomal drug products approved by the FDA, and their indications include a wide range of applications including cancer treatments, vaccines, infections, and pain management [30].Liposomes are self-assembled (phospho)lipid-based drug vesicles that form a bilayer (uni-lamellar) and/or a concentric series of multiple bilayers (multilamellar) enclosing a central aqueous compartment [31]The field of liposomology was launched by the British scientist Alec Bangham and colleagues at Babraham Cambridge in the mid-1960s [32]Liposomes are the most explored nanocarriers used in targeted drug delivery systems. Liposomes are spherical lipid vesicles (usually 50–500 nm in diameter particle size) composed of one or more lipid bilayers, as a result of emulsifying natural or synthetic lipids in an aqueous medium (33)liposomes are considered promising to be used

effectively as drug delivery systems. Several liposomal-based drug delivery systems have been approved by Food and Drug Administration (FDA) for disease treatment in the market (34) Liposomes are primarily created from phospholipids such as soybean phosphatidylcholine [35]

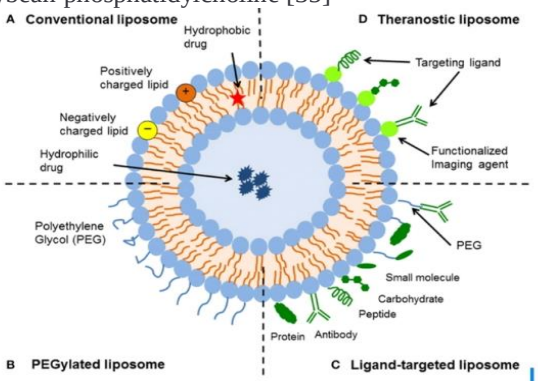

Figure 6:liposomes

Advantages of liposomes

Liposomes offer several advantages in delivering genes to cells.

> Liposomes can complex both with negatively and positively charged molecules.

> Liposomes offer a degree of protection to the DNA from degradative processes.

> Liposomes can carry large pieces of DNA, possibly as big as a chromosome.

> Liposomes can be targeted to specific cells or tissues.

Disadvantages of liposomes

> Production cost is high.

> Leakage and fusion of encapsulated drug / molecules.

> Sometimes phospholipid undergoes oxidation and hydrolysis-like reactions.

> Short half-life.

> Low solubility.

> Fewer stables.

Liposomes types

Based on their compositions and applications, liposmes can be classified into conventional liposomes [36]

1.Conventional liposomes

These liposomes were synthesized from natural or synthetic phospholipids with or without cholesterol as a liposomes first generation [37].Wu et al hat revealed that liposomal membrane rigidity decreased with the addition of cholesterol into a liposomes composed of hydrogenated soybean phospholipids (HSPC) and DSPE-PEG2000. Moreover, liposomes with some rigidity showed excellent tumor penetration and enhanced anti-tumor activity [38]. As a result, stealth stable liposomes were invented to increase blood circulation and enhanced in vivo liposomes stability (39)

2. Charged liposomes

Oleic acid and N-[1(2,3-dioleoyloxy) propyl]-N,N,N-trimethylam-monium chloride (DOTAP) are usually used to prepare anionic and cationic liposomes, respectively. Charged liposomes showed higher liposomal stability during the storage, as charged particles repel each other and reduce aggregation abilities. Cationic liposomes are used in gene therapy due to their ability to successfully encapsulate nucleic acids by electrostatic attractions [40]..Cationic liposomes can cross the BBB by receptor-mediated transcytosis [41]

3.Stealth stabilized liposomes

These second-generation liposomes are characterized by surface decoration with synthetic polymers, glycoproteins, polysaccharides, or specific receptors ligands to achieve narrowed distribution, and accumulation at the intended site [42]Stealth stabilized liposomes showed longer circulation time, leading to a better target accumulation than conventional liposomal drugs [43].

4. Actively-targeted liposomes

liposomes represent third-generation liposomes. Liposomes' active targeting increases the selectivity of liposome interaction with diseased cells and triggers receptor-mediated endocytosis of the liposome and its payload into the desired cellular target (44)

5. Stimuli-responsive liposomes

Stimuli-responsive liposomes are smart liposomal systems that display rapid release of their drug payload upon physicochemical or biochemical stimuli, such as pH, temperature, redox potentials, enzymes concentrations, ultrasound, electric or magnetic fields [45]

6. Bubble liposomes Bubble liposomes

Bubble liposomes (gas-encapsulated liposomes) are expected to create new applications in the field of gene delivery and drug delivery systems [46]

Biophysical properties of liposomes for drug delivery

Liposome size

The size of liposomes is very important for drug delivery.(47)In comparison, penetration through regular healthy vasculature is limited to 1–2 nm.69M(48) To achieve a long blood-circulation time, charge neutral zwitterionic PC liposomes are the most frequently used to reduce protein binding(49)Since nucleic acids are negatively charged, they can be condensed by cationic lipids facilitating cellular uptake. Cationic lipids are in general toxic to cells and are rapidly cleared from circulation.(50)The structure of lipid tails strongly influences the Tc of lipids, and controls their mechanical strength, lateral diffusion and

permeability. The membrane permeability is the largest at Tc because of the coexistence and interconversion of the two phases, creating leaky phase boundaries (51),Tumor targeting by manipulating membrane fluidity was demonstrated in a recent work, with fluid liposomes preferentially targeting the tumor cells and gel-phase liposomes targeting the healthy cells.(52)

Another related factor that can be manipulated to facilitate drug delivery is lipid membrane rigidity or mechanical properties (53)

Liposome fusion

Lipid membrane fusion is critical in many biological processes, but it does not happen spontaneously.(54) In comparison with cellular uptake via endocytosis, the membrane fusion strategy delivers drug into the cytosol directly, avoiding lysosomal degradation.(55)

Liposomes in Clinical Applications

1.Liposomes for Cancer Therapy

Compared with traditional drug delivery systems, liposomes exhibit better biological properties, including high biocompatibility, low toxicity, easy surface modification, high targeting, encapsulation of various drugs, and protection from degradation. Given these merits, several liposomal drug products have been successfully approved and used in clinics over recent decades (Table 4). Among these, Doxil (Doxorubicin HCl liposome injection) was the first liposomal product approved by the FDA in 1995 [15]. In fact, the progress of nanoliposomes has promoted the treatment of cancer(56)In clinical trials, ThermoDox® has been combined with radiofrequency ablation to treat hepatocellular carcinoma. However, the OPTIMA trial did not achieve the endpoints, though this did not mean that ThermoDox® was not feasible. Early clinical data of ThermoDox® has demonstrated feasibility, safety and activity [57].developed a liposome-based, light-triggered efficient sequential delivery method for multimodal chemotherapy, antiangiogenic and anti-myeloid-derived suppressor cell therapy in melanoma. This delivery strategy demonstrates the effectiveness of cancer multimodal therapy targeting multiple targets at different spatial locations in the TME [58]

2.Liposomes for Vaccines

Due to their adaptability and excellent biocompatibility, liposomes can be utilized as adjuvants in vaccines. It has been demonstrated that the encapsulation of peptide antigens or viral membrane proteins into liposomes results in humoral and cell-mediated immune responses, as well as strong and long-lasting immunity against the pathogen [59]. Liposomes were initially described as immunological adjuvants by Gregoriadis and Allison in 1974

Niosomes

The concept of targeted drug delivery is designed for attempting to concentrate the drug in the tissues of interest while reducing the relative concentration of the medication in the remaining tissues. As a result, drug is localised on the targeted site. Hence, surrounding tissues are not affected by the drug. In addition, loss of drug does not happen due to localisation of drug, leading to get maximum efficacy of the medication. Different carriers have been used for targeting of drug, such as immunoglobulin, serum proteins, synthetic polymers, liposome, microspheres, erythrocytes and niosomes.[60]Noisome made of alpha , omega-hexadecyl-bis-(1-aza-18-crown-6) (Bola-surfactant)-Span 80-cholesterol (2:3:1 molar ratio) is named as Bola-Surfactant containing noisome.[61] .As with liposomes, the properties of niosomes depend on the composition of the bilayer as well as method of their production. It is reported that the intercalation of cholesterol in the bilayers decreases the entrapment volume during formulation, and thus entrapment efficiency.[62]Niosomes have been used for studying the nature of the immune response provoked by antigens.[63]

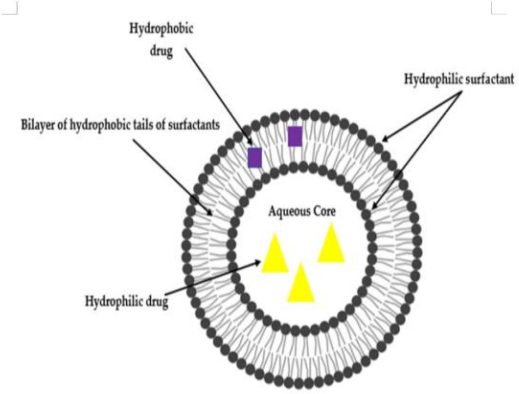

Figure7:components of niosomes

Components of niosomes

The niosome composition is a determinative factor in the fabrication, pharmacokinetic behavior, and application of drug-loaded niosomes. In general, a niosome comprises non-ionic surfactants, lipids such as cholesterol, charge-inducing agents, and hydration medium, which are relatively biocompatible and nontoxic(64)

1. Non-ionic surfactants

Non-ionic surface-active molecules are the fundamental elements in the preparation of niosomes. They are amphiphilic molecules with a polar head and a non-polar tail. These uncharged surfactants are more stable and less toxic than anionic, cationic, and

amphoteric surfactants. These non-ionic surface-active agents, wetting agents, and emulsifiers have diverse capabilities including inhibiting p-glycoprotein, causing less hemolysis and irritation to cellular surfaces, enhancing permeability, and improving solubility (65) HLB (hydrophilic-lipophilic balance), CPP (critical packing parameter), and gel liquid transition are important factors of entrapment efficiency (EE) (66) Surfactants with gel transfer temperatures below 10 °C can cause oxidation when combined with iodides, mercury salts, salicylates, sulfonamides, and tannins, phenolic substances (67)

2. Cholesterol

Cholesterol is not an essential additive in the formulation of niosomes, however, it can drastically affect the properties of niosomes if applied. It is common for niosomes to be formulated using cholesterol, for example in a 1:1 M ratio with a non-ionic surfactant (68) Cholesterol can affect membrane permeability and stiffness, drug trapping efficiency, rehydration of dried niosomes, stability, storage condition, and toxicity (69)By influencing the fluidity of chains within bilayers, it increases the transition temperature of vesicles, thereby improving their stability(70)

3. Charge-inducing molecules

Charge-inducing molecules are used to stabilize the niosomes by electrostatic repulsion and help to prevent their fusion (71) Dicetylphosphate (negatively charged), phosphatidic acid (negatively charged), and stearyl amine (positively charged) are among the charge-inducing molecules (72)

4. Hydration medium

In addition to the components mentioned earlier, the fabrication of niosomes necessitates the use of a synthesis medium known as a hydration medium. Hydration is a crucial step in the production of niosomes, and phosphate buffer is commonly employed due to its ability to facilitate both niosome synthesis and drug loading (73) It has been evident that longer hydration times result in reduced niosome size, higher entrapment efficiency, and greater stability, and more acidic media tend to lead to increased drug release (74)

CLASSIFICATION OF NIOSOMES

The various types of niosomes are described below

1. Multi lamellar vesicles
2. Large unilamellar vesicles
3. Small unilamellar vesicles (SUV)

Multilamellar vesicles (MLV)

It consists of a number of bilayers surrounding the aqueouslipid compartment separately. The approximate size of thosevesicles is 0.5-10µm diameter. Multilamellar vesicles arethe foremost widely used niosomes. It is type of vesicles arehighly suitable as drug carrier for lipophilic compounds

Large unilamellar vesicles (LUV

(LUV)Niosomes of this sort have a high aqueous/lipid com-partment ratio, in order that larger volumes of bio-activematerials are often entrapped with a really economical useof membrane lipids.

Small unilamellar vesicles (SUV)

the approximate size of this vesicle are 10-100 nm andthis types of vesicle is prepared from multilamellar vesiclesby sonication method, Frenchpress extrusion electrostaticstabilization in that the inclusion of diacetyl phosphate in 5-carboxythyuorescein loaded Span based niosomes. (78)

Application of niosomes

1. Delivery of phytochemicals

Natural products have been utilized for their therapeutic effects for centuries. The high cost of developing new drugs has raised research interest in the delivery of plant constituents and natural products as new pharmaceutical agents (77) Natural products, also known as phytochemicals, can be found and extracted from plants, especially vegetables, fruits, and grains. These phytochemicals have amazing medicinal features such as anti-cancer, antioxidant, antimicrobial, and anti-inflammatory activities. However, most of them cannot be administered directly because of some limitations like poor solubility or instability, requiring novel delivery approaches such as encapsulation using niosome nanoparticles (78)formulated niosomal encapsulated curcumin and PTX to explore their synergistic effects against breast tumors. Kumar et al. prepared a gel formulation containing niosomal curcumin encapsulations for transdermal delivery targeting high-efficacy anti-inflammatory and anti-arthritic activities (79)They also investigated different preparation methods for its topical delivery (80)

Monoclonal antibody

Monoclonal antibodies (mAbs) are by far the largest class of therapeutic proteins and a key driver in the biopharmaceutical growth [81].Approximately 70 mAb products have been predicted to be available in market by 2020 for the treatment of various diseases [82]The N-terminal domain of an IgG consists of a variable (V) region with the complementarity-determining region (CDR) that binds to a specific epitope on antigens. Other domains within the IgG make up the constant (C) regions. The structure of an IgG is broadly divided into the Fab (2/3) and Fc regions (1/3). The two identical Fabs each comprise of a light chain that is closely associated by non-covalent interactions with the heavy chain. There is a solvent-accessible interchain disulfide (S-S) between the light chain and heavy chain of the Fab. The heavy

chains are closely associated through non-covalent interactions within the Fc region. The hinge region links the Fabs to the Fc and there are (usually) two solvent accessible disulfides between the heavy chains in the hinge region. There are also intra-molecular disulfides within each constant and variable region of both the heavy and light chains. These disulfides are not solvent-accessible. Many aspects of mAbs, including epitope specificity, immunogenicity, pharmacokinetic and immune-related effector functions, are active areas of research that is focused on the continued evolution of antibodies for therapeutic use (83)

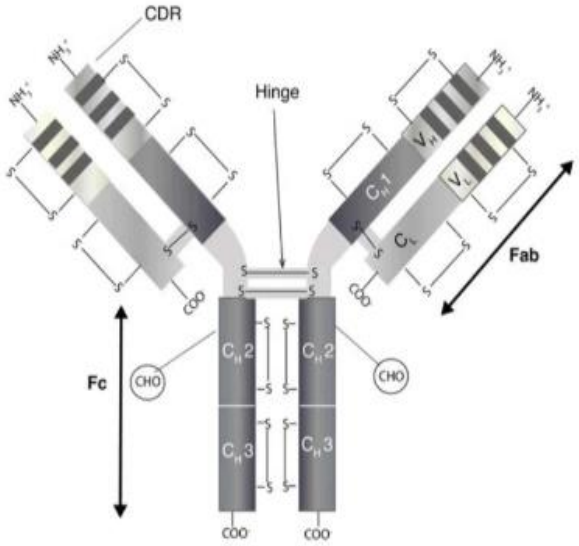

Figure:8 fuction of monoclonal anti body

Function

The five antibody classes (as classified by heavy chain sequence) are IgM, IgD, IgG, IgE, and IgA.[84] .In addition to the oncological application of mAbs, another major area of application is seen in autoimmune conditions including, but not limited to, rheumatoid arthritis (RA), inflammatory bowel disease (IBD), systemic lupus erythematosus (SLE), and spondyloartherites.This is due to the pharmacokinetics, stability, low immunogenicity (especially newer, humanized/human agents), limited toxicity profiles, and accessible producibility of a large number of mAbs to a variety of antigens with relative simplicity. General properties of antibodies include composition with two light and heavy chains, with both light and heavy chains containing variable and constant domains (one variable, one constant, and one variable, three constant domains in light and heavy chains, respectively).[85]. Complementary-determining regions (CDRs) contained within each antigen-binding fragment (Fab) of each respective antibody play an essential role in determining the specificity and affinity with which antibodies bind their target antigens. These highly specific regions are why mAbs can be applied to target precise targets whilst limiting the effects on alternate systems. The Fc region is another region of the antibody that contains constant domains and acts to activate the immune system against the target of mAbs. These functions are mediated by the binding and activation of other Fc receptors expressed on endogenous cells and the complement system, leading to the activation of effector function.[86].Immune-mediated cell destruction is another mechanism by which mAbs have been applied in oncology. This strategy utilized the immune system to target malignant cells and induce destruction through a variety of mechanisms. Examples of such mechanisms include complement-dependent cytotoxicity (CDC), antibody-dependent cell-mediated phagocytosis (ADCP), and antibody-dependent cellular toxicity (ADCC). These mechanisms are triggered when Fc receptors expressed on endogenous cells (natural killer cells, macrophages, etc.) are activated through binding with Fc receptors on mAbs. Finally, vascular disruption is also a potential target for mAbs in oncological applications. Several mechanisms are possible, including toxin administration to vasculature or stromal cells, stromal cell inhibition, and vascular receptor antagonism. One example of an anti-vascular agent is bevacizumab, a humanized mAb that binds directly to vascular endothelial growth factor-A (VEGF-A) and thereby defers vascular growth in tumors.In addition to the oncological application of mAbs, another major area of application is seen in autoimmune conditions including, but not limited to, rheumatoid arthritis (RA), inflammatory bowel disease (IBD), systemic lupus erythematosus (SLE), and spondyloarthropathies. These diseases create an inflammatory environment in the body whereby CD4+ T-cells are exposed to antigens (via antigen-presenting cells (APCs) and B-cells) and activated in an autoimmune fashion(87)

Therapeutic Applications of Antibody

Despite their high sensitivity and reproducibility, conventional diagnostic methods for a microbial infection require cumbersome sample preparation and long readouce(88) .Unique electrical, magnetic, luminescent, and catalytic properties of nanomaterials enable fast, sensitive, and cost-effective diagnosis, as well as rapid determination of the susceptibility and resistance of antibacterial drugs (89).Antibody-conjugated nanoparticles amplify the signals for bioanalysis and enumeration of highly pathogenic bacteria, such as E. coli O157:H7, resulting in highly selective, convenient, and rapid detection of single bacterium within 20 min

(90).Dextrancoated supermagnetic iron oxide.nanoparticles were clustered by Con-A treatment, or equipped with Con A-conjugated nanosensors (Zhao et al., 2004) (91) .A quick method for detecting infections in the urinary tract has also been developed using gold nano-wire arrays in conjunction with a linker arm attached to specific E. coli antibodies (de la Escosura-Muñiz and Merkoçi, 2011).(92)The broad absorption spectra of quantum dots (QDs) can be exploited to simultaneously excite QDs emitting different colors using a single wavelength (2002)(93).

Recent advancements in targeted drug delivery systems for cancer treatment

Several novel advancements in targeted drug delivery systems for cancer treatment include: 1) Immunoliposomes: Immunoliposomes are liposome-based targeted drug delivery systems that incorporate antibodies or other immunological agents to improve specificity for cancer cells. Recent research has focused on developing more stable and efficient immunoliposomes that effectively deliver drugs to tumor cells. 2) RNA-based drug delivery: RNA-based drug delivery systems have emerged as a promising

Prospects of targeted drug delivery systems

The future of targeted drug delivery systems for cancer treatment is promising, with several potential avenues for further development and improvement. Some of the prospects of targeted drug delivery systems include: 1) Precision medicine: Targeted drug delivery systems can play a critical role in precision medicine by enabling the delivery of personalized therapies based on the unique characteristics of individual tumors. 2) Nanorobotics: Nanorobotics is an emerging field that uses nanoscale Integration of targeted drug delivery systems with other cancer therapies

Targeted drug delivery systems can be integrated with other cancer therapies to improve treatment outcomes and reduce side effects. Some examples of how targeted drug delivery systems can be combined with other cancer therapies include: 1) Chemotherapy: Targeted drug delivery systems can deliver chemotherapy drugs directly to tumor cells while minimizing exposure to healthy tissues. This approach can reduce side effects and improve treatment outcomes [13]. 2) Radiation therapy: Targeted drug

Development of personalized, targeted drug delivery systems

Personalized targeted drug delivery systems have the potential to revolutionize cancertreatment by enabling the delivery of highly individualized therapies tailored to the unique characteristics of each patient's tumor. Here are some critical factors that need to be considered for developing personalized, targeted drug delivery systems: 1) Tumor profiling: The first step in creating personalized, targeted drug delivery systems is to perform a comprehensive tumor profiling to identify the

Advancements in nanotechnology and its impact on targeted drug delivery systems

Advancements in nanotechnology have profoundly impacted the development of targeted drug delivery systems. Here are some ways nanotechnology has advanced targeted drug delivery: 1) Improved drug delivery: Nanoparticles can be engineered to target specific cells or tissues and release drugs in a controlled manner, making available drugs delivered directly to the tumor site while minimizing exposure to healthy tissues. 2) Increased drug stability: Nanoparticles can protect drugs from degradation,

Future directions and conclusion

There are several future directions for research and development of targeted drug delivery systems that could significantly improve cancer treatment outcomes. These include 1) Developing more precise targeting strategies for current targeted drug delivery systems has limited their ability to target cancer cells precisely. Further research is needed to identify specific targets and develop more efficient targeting strategies. 2) Integration with other therapies: Combining targeted drug delivery

Application of targeted drug delivery in cancer therapy

Targeted drug delivery can be used to treat many diseases, such as the cardiovascular diseases and diabetes. However, the most important application of targeted drug delivery is to treat cancerous tumors. In doing so, the passive method of targeting tumors takes advantage of the enhanced permeability and retention (EPR) effect. This is a situation specific to tumors that results from rapidly forming blood vessels and poor lymphatic drainage. When the blood vessels form so rapidly, large fenestrae result that are 100 to 600 nanometers in size, which allows enhanced nanoparticle entry. Further, the poor lymphatic drainage means that the large influx of nanoparticles are rarely leaving, thus, the tumor retains more nanoparticles for successful treatment to take place.(102)

The American Heart Association rates cardiovascular disease as the number one cause of death in the United States. Each year 1.5 million myocardial

infarctions (MI), also known as heart attacks, occur in the United States, with 500,000 leading to deaths. The costs related to heart attacks exceed $60 billion per year. Therefore, there is a need to come up with an optimum recovery system. The key to solving this problem lies in the effective use of pharmaceutical drugs that can be targeted directly to the diseased tissue. This technique can help develop many more regenerative techniques to cure various diseases. The development of a number of regenerative strategies in recent years for curing heart disease represents a paradigm shift away from conventional approaches that aim to manage heart disease.Recent developments have shown that there are different endothelial surfaces in tumors, which has led to the concept of endothelial cell adhesion molecule-mediated targeted drug delivery to tumors.

Liposomes can be used as drug delivery for the treatment of tuberculosis. The traditional treatment for TB is skin to chemotherapy which is not overly effective, which may be due to the failure of chemotherapy to make a high enough concentration at the infection site. The liposome delivery system allows for better microphage penetration and better builds a concentration.

Conclusion:

Nanoparticle-based drug delivery systems have shown promise in overcoming limitations in traditional cancer therapies. Researchers have successfully used nanoparticles to deliver chemotherapy drugs directly to cancer cells, reducing side effects on healthy tissues. These advancements can be designed to target specific molecular markers in cancer cells, increasing treatment effectiveness while minimising harm to healthy cells..These advancements have the potential to significantly improve cancer patient outcomes. By specifically targeting cancer cells, drug delivery systems can enhance the efficacy of treatment and potentially reduce the risk of tumour recurence(103) Additionally, the ability to minimise harm to healthy cells can improve patients' quality of life during and after treatment. In addition to nanoparticle-based drug delivery, immunotherapies are of research.These therapies harness the immune system's ability to recognise and destroy cancer cells, potentially treating existing tumours and preventing future cancer recurrence. Immune checkpoint inhibitors, which block proteins that prevent immune cells from attacking cancer cells, allow the immune system to recognise and destroy cancer cells more effectively. Some patients with advanced melanoma have shown remarkable responses, with their tumours shrinking or disappearing completely. These promising results have led to the approval of immune checkpoint inhibitors for the treatment of various types of cancer, including lung, bladder, and kidney cancer .However, it is important to note that not all patients respond equally well to these therapies, and further research is needed to understand why some individuals benefit more than others. However, not all patients experience positive outcomes with immune checkpoint inhibitors. In some cases, the treatment fails to elicit a significant response from the immune system, resulting in minimal or no tumour regression. This highlights the need for further research and a better understanding of factors influencing the effectiveness of immunotherapies in different individuals .it is important to consider that immune checkpoint inhibitors can also lead to immune-related adverse events in some patients. These adverse events can range from mild to severe and may require additional medical intervention. Therefore, it is crucial for healthcare professionals to closely monitor patients undergoing immunotherapy and develop strategies to manage any potential side effects

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