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Design of smart nanomedicines for effective cancer treatment

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ABSTRACT

Nanomedicine is a novel field of study that involves the use of nanomaterials to address challenges and issues that are associated with conventional therapeutics for cancer treatment including, but not limited to, low bioavailability, low water-solubility, narrow therapeutic window, nonspecific distribution, and multiple side effects of the drugs. Multiple strategies have been exploited to reduce the nonspecific distribution, and thus the side effect of the active pharmaceutical ingredients (API), including active and passive targeting strategies and externally controllable release of the therapeutic cargo. Site-specific release of the drug prevents it from impacting healthy cells, thereby significantly reducing side effects. API release triggers can be either externally applied, as in ultrasound-mediated activation, or induced by the tumor. To rationally design such nanomedicines, a thorough understanding of the differences between the tumor microenvironment versus that of healthy tissues must be paired with extensive knowledge of stimuli-responsive biomaterials. Herein, we describe the characteristics that differentiate tumor tissues from normal tissues. Then, we introduce smart materials that are commonly used for the development of smart nanomedicines to be triggered by stimuli such as changes in pH, temperature, and enzymatic activity. The most recent advances and their impact on the field of cancer therapy are further discussed.

1. Introduction

The Medical Standing Committee of European Science Foundation defines nanomedicine as: "the science and technology of diagnosing, treating, and preventing disease and traumatic injury, of relieving pain, and of preserving and improving human health, using molecular tools and molecular knowledge of the human body" (Webster, 2006). Nanomedicine takes advantage of nanotechnology in the medical field for imaging and diagnosis purposes as well as delivery of the drugs and other therapeutic agents using nanocarriers in the size range of 1–1000 nm. Cancer therapy has extensively benefited from nanomedicine recently. In this review, we elaborate on the field and introduce criteria for the rational design of nanomedicine for achieving the best therapeutic results.

2. Nanomedicine design

Generally, four elements are required for the design of any object: Function, characteristics, materials, and process. The first step for the design is the clear determination of its main function. Crucial properties of the object are then specified according to the defined function. The desired properties closely depend on the materials from which the object is constructed and the process through which the aimed object is fabricated (Ashby and D. cebon, 1993). Herein, we are focusing on the design of an efficient nanomedicine for the function of cancer therapy, and, its designing considerations will be thoroughly elaborated.

2.1. Materials

Fig. 1 summarizes the most important materials that are being utilized for the fabrication of nanomedicines in clinical and preclinical applications. These materials are categorized into three main classes:

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Inorganic materials, organic materials, and biological materials. The most common examples of inorganic materials are metal-based nanostructures such as gold nanoparticles and nanorods, silver nanostructures, and iron oxide nanoparticles. These materials have gained high attention for photo-enabled therapies, as well as in imaging and diagnosis applications due to their unique optical properties (Huang et al., 2006; Zhang et al., 2014; Xiao et al., 2017; Borghei et al., 2017; Liang et al., 2018; Wang et al., 2017; Enochs et al., 1999; Moore et al., 2000; Deh et al., 2020). Other examples include mesoporous silica-based nanoparticles, carbon-based nanomaterials and quantum dots (Pang et al., 2018; Zayed et al., 2019; Bao et al., 2018; Li et al., 2011; Manzano and Vallet-Regí, 2020; Chen et al., 2019). However, inorganic nanomaterials are associated with a few challenges that limit their application. First, unless further modified, the drug payload must be bound onto the surface of metallic nanoparticles when used as drug carriers. Thus, they cannot stealth and protect the drug from degradation or prevent its impact on untargeted cells. Their potential toxicity also raises serious safety concerns (Chen et al., 2018; Singh and Kim, 2013; Li et al., 2014). Organic materials including natural and synthetic polymers that have been introduced as suitable materials for nanomedicines are mostly biodegradable and biocompatible. Proteins such as human serum albumin (HSA), lipids, and polysaccharides such as chitosan are the most important examples of natural polymers that can form functional nanosystems like nanoparticles and liposomes. These materials usually induce low toxicity and low immunogenicity when introduced to the human body. Synthetic biodegradable polymers are another member of this family. This group consists of a wide range of materials including synthetic polypeptides such as poly(L-lysine), and other biodegradable polymers and copolymers including but not limited to poly(lactic acid), poly(lactic-*co*-glycolic acid), and polycaprolactone. These polymers can be processed to form nanocarriers with controllable properties and encapsulate a variety of drugs. Enhancement of the loading capacity, stability, and release profile from these materials can be improved by facile modification procedures and/or combination with other organic/inorganic materials. The third novel class of materials that are gaining interest in nanomedicine are biologic materials that are obtained directly from a biological source or are biomimietic, i.e. synthesized to mimic biologically originated nanostructures. Extracellular vesicles (EV), including microvesicles (<1 μm) and exosomes, are natural nanocarriers for transporting proteins and lipids in the body. Highly efficient cell uptake and low immunogenicity as well as targeting properties make EV and EV-inspired nanomaterials a great candidate for drug delivery (Elsharkasy et al., 2020; Vader et al., 2016; Ye et al., 2020; Yong et al., 2020). EVs can also be chemically modified to enhance their targeting ability and blood circulation time (Liang et al., 2021; Adriano et al., 2021). Examples of EV-inspired nanomaterials are mimetic nanovesicles derived from plasma membranes that demonstrated improved cell uptake (Martinelli et al., 2020) and exosome-based nanostructures (Ye et al., 2020; Liang et al., 2021; Adriano et al., 2021).

Virosomes are bioinspired nanomaterials that are liposome-like structures that contain special glycoproteins which allow enhanced fusion with the target cell (Kumar et al., 2021; Singh et al., 2017). Bacterial minicells, bacteria-originated vesicles, have been exploited as an alternative for liposomes for cancer treatment (American Cancer

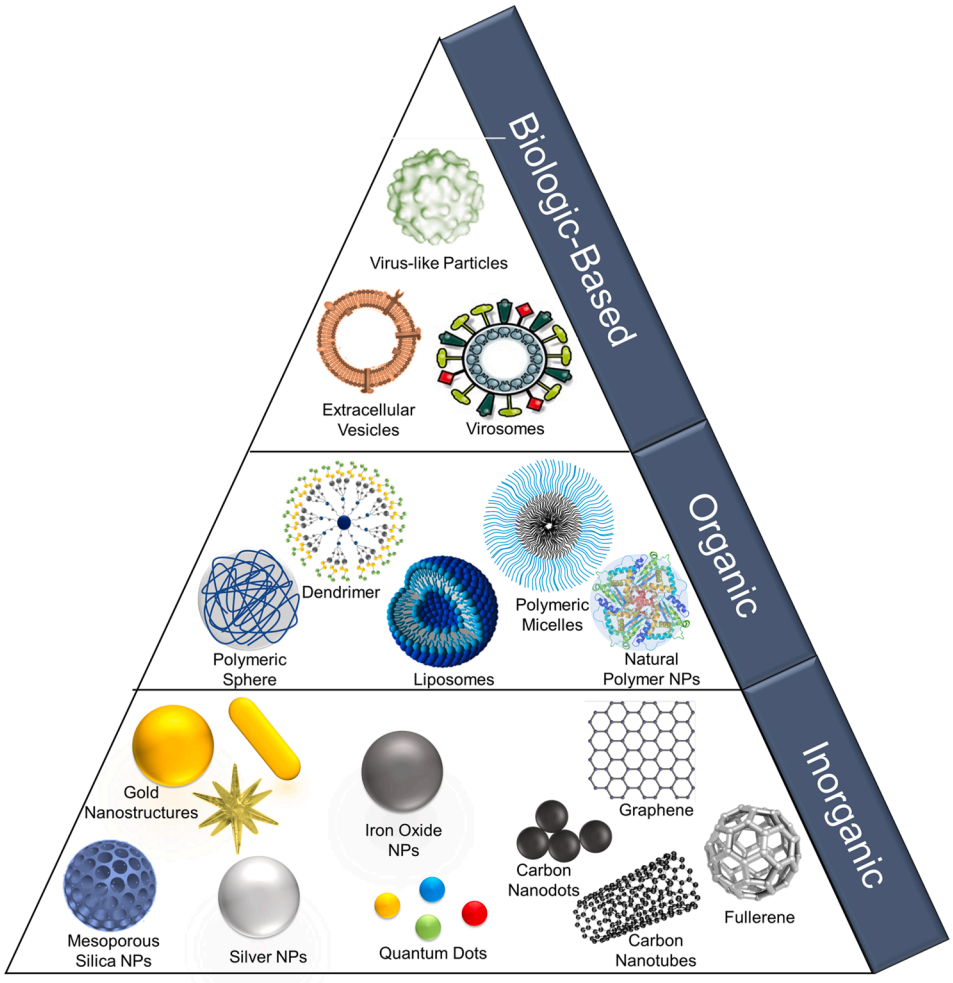

Fig. 1. Common materials in nanomedicine. (NP: Nanoparticle).

Society, 2020). They can efficiently encapsulate a wide variety of therapeutic payloads with different properties such as intrinsic charge and hydrophobicity. Virus-like particles (VLP) are also extensively utilized for cancer drug delivery (Hill et al., 2018; Finbloom et al., 2018; Ding et al., 2018). Efficient cell internalization and biocompatibility are considered as their main advantage. VLPs have unique structures that allow them to induce desired immunogenic responses to assist cancer immunotherapy, yet not be infectious.

2.2. Properties

The physicochemical properties of nanomedicines determine their biodistribution and pharmacokinetics. The most important properties of nanoparticles and their effect on their function are discussed in this section.

2.2.1. Particle size

The most important feature of nanoparticles that dictates their pattern of distribution in the body as well as internalization into the cells is their size. In cancer nanomedicine, the desirable diameter of nanoparticles ranges from 10 nm to 100 nm (Davis et al., 2010).

Cell internalization of nanoparticles with different sizes has been investigated in several studies (Davis et al., 2010; Gratton et al., 2008; Rejman et al., 2004; Wu et al., 2019; Andar et al., 2014; Bannunah et al., 2014). According to these studies, a small diameter allows facile cell uptake. However, bigger particles (as large as 5 μm) are yet capable of entering the cells through a different pathway of endocytosis (Kou et al., 2013). Nanoparticles also can be targeted into the tumor site by proper size design through passive targeting. Briefly, in passive targeting, nanoparticles that are smaller than 200 nm can penetrate the tumor area, taking advantage of the disorganized angiogenic vasculature of the tumor in which, in contrast to normal vessels, epithelial cells are not well aligned and provide wide fenestrations (enhanced permeation) (Rizvi and Saleh, 2018). Furthermore, due to the lack of lymphatic drainage, the particle's retention time in the tumor increases compared to healthy tissues (enhanced retention). The combination of these effects is known as the enhanced permeability and retention (EPR) effect (Rizvi and Saleh, 2018; Hirsjarvi et al., 2011). Fig. 2 illustrates the EPR effect.

2.2.2. Particle surface charge

Nanoparticle surface charge is another important feature that affects both cell internalization and nanoparticle biodistribution due to the electrostatic interaction of the particles with biological molecules, including serum proteins. The surface charge of the nanoparticles can be determined by the zeta potential of the colloidal system that contains nanoparticles (Wang et al., 2011). Zeta potential is the potential difference between the background medium and the fluid on the surface of the nanoparticle. Both positive and negative particles can enter the cells, although through different mechanisms and thus at different rates. Positively charged nanoparticles are more suitable for cell uptake. However, they enter nonspecific cells at a higher rate compared to the nanoparticles with a negative surface charge, which leads to unintended side effects, reduction of effective available dosage for cancer cells, and shorter circulation time. The surface charge also affects the loading capacity of nanoparticles depending on the charge of the payload drug (Wang et al., 2011; Honary and Zahir, 2013; Honary and Zahir, 2013). Therefore, it must be carefully considered for designing nanomedicines.

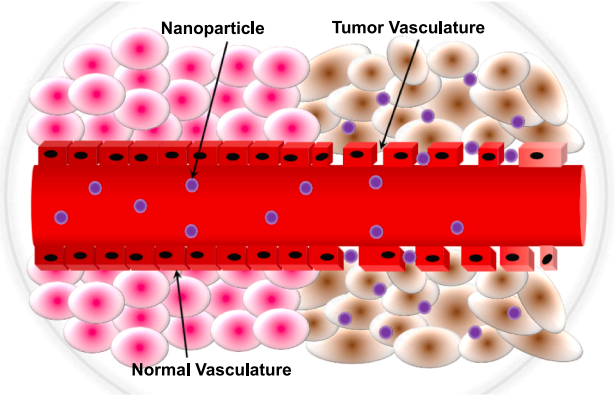

Fig. 2. Passive targeting by enhanced permeability and retention effect.

2.2.3. Particle surface chemistry

The surface chemistry of nanoparticles and their modification allows their active targeting to the tumor site. In active targeting, particles are typically functionalized by targeting ligands such as a small molecule like folic acid or a macromolecule like an antibody, which has a great affinity to highly expressed receptors on cancer cells (Byrne et al., 2008). The affinity that this ligand provides the targeted nanoparticle results in a more significant accumulation of these particles at tumor sites than other tissues (Hirsjarvi et al., 2011; Kouchakzadeh et al., 2017). Surface modification is also a strategy to boost the nanoparticle's characteristics. For example, PEGylation of nanoparticles, or the coating of nanoparticles with poly(ethylene glycol) (PEG), is a common method to protect them from rapid clearance from the body. A PEG layer on the surface of nanoparticles prevents serum protein absorption and allows them to evade phagocytosis (Huang et al., 2005).

2.2.4. Barriers for various therapies

Administered nanoparticles face several barriers in the body which must be taken into consideration for proper design. Nanoparticles can be cleared and removed from the body by two main pathways: the reticuloendothelial system (RES) and renal filtration. Macrophages, monocytes, and dendritic cells (DCs) that are present in the liver, spleen, blood, lymph nodes, and lungs (parts of RES) engulf the nanoparticles that are covered by serum proteins (particles that have undergone 'opsonization') as foreign objects (von Roemeling et al., 2017). Small nanoparticles (<6 nm) are filtered by kidney nephrons in the renal ultrafiltration system (von Roemeling et al., 2017; Cheng et al., 2017). In addition to the nanoparticle's size, nanoparticle surface charge and morphology are also important for renal removal. Positively charged nanoparticles can pass through the negative glomerular basement membrane even with a size greater than 6 nm (Choi et al., 2007). Moreover, nanorods with greater than 100 nm in length and an average diameter of 1 nm can also be removed by renal filtration due to their unique orientation which is dictated by the blood flow (Jiang et al., 2020; Ruggiero et al., 2010). Therefore, nanoparticles must size over 6 nm in all dimensions to ensure premature escape through renal filtration.

The blood–brain barrier (BBB) is another barrier that prevents harmful molecules and materials, including pharmaceutical agents, to reach the tumors in the central nervous system (CNS). The BBB allows penetration of a limited selection of substances such as nutrients, proteins, lipids, ions, and immune cells. Especial designs of nanoparticles are demonstrated to permeate through the BBB. To this aim, nanoparticle surface must be functionalized by suitable ligands such as transferrin and lipoproteins that allow the particles to enter the endothelial cells. Internalization can also be carried out by a physical attachment of the nanoparticles to the plasma proteins that are able to penetrate BBB (Ulbrich et al., 2009). Nanoparticle surface can be modified by surfactants such as polysorbate 80 (Tween® 80) to enhance selective protein adsorption (Ambruosi et al., 2006). Positively charged nanoparticles demonstrate higher rates of penetration; however, they impair the BBB which may result in neurotoxicity. Anionic nanoparticles, on the other hand, can still diffuse across the BBB and potentially cause less damage. Nanoparticles can also be made of or coated with the nutrients that can pass through the BBB (Zensi et al., 2010). Also, the optimum size of nanoparticles that are targeted to CNS

is determined to be in the range of 20 nm to 70 nm (Shilo et al., 2015).

2.3. Manufacturing methods

The main methods of preparing polymeric nanoparticles and liposomes, which are being widely used in cancer nanomedicine and drug delivery, are introduced in this section.

2.3.1. Emulsion-based techniques

Initially, an emulsion, or dispersion of droplets of one liquid in another, is formed to prepare nanoparticles with this method. The emulsion is usually prepared by mixing and homogenizing two immiscible phases, one of which contains the carrier polymer (typically the organic phase). The two phases may contain stabilizers to allow the formation of stable spherical droplets and therefore particles. Homogenization is typically carried out using a high-pressure homogenizer or an ultrasound sonicator. The emulsion contains nanodroplets containing the polymer solution in its solvent. In the next step, the solvent is removed by evaporation or diffusion (or a combination of both) to form solid polymeric nanoparticles. To encapsulate hydrophobic drugs or other therapeutic agents, the drug should be dissolved in the phase in which the polymer exist (Kızılbey, 2019; Cui et al., 2010). To encapsulate hydrophilic drugs, however, a double emulsion technique is required. In double-emulsion procedure, first, a water-in-oil emulsion will be formed. The first aqueous phase contains the drug and stabilizers while the oil phase is the polymer solution (Ali et al., 2019).

Homogenization makes a plurality of stable droplets of the drug solution in the polymer solution matrix. The resulting water-in-oil emulsion is then mixed with the second outer aqueous phase and homogenized. The rest of the process is similar to the single emulsion method (Zambaux et al., 1998). Fig. 3 shows schematics of the double-emulsion process. The characteristics of the polymer, solvents, and stabilizers, as well as their concentration and the method and intensity of homogenization used are important factors that control nanoparticles' properties such as size in this method (Paulo and Santos, 2018).

2.3.2. Nanoprecipitation

In contrast to emulsion-based methods, in nanoprecipitation the organic and aqueous phases must be miscible in one another. The addition of the organic phase, which contains the polymer, to the aqueous phase, which may contain a stabilizer, will form polymeric nanoparticles as a result of the diffusion of the polymer's solvent into the aqueous phase in which the polymer is not soluble. The most critical factor to make identical nanoparticles with this method is proper and fast mixing of both phases (Pustulka et al., 2013). Therefore, the organic phase is added dropwise to the aqueous phase which is under constant stirring in small-scale manufacturing. Several manufacturing platforms are also introduced for allowing efficient mixings such as impinging jet reactors, rotor–stator mixers, and fiber fluidic reactors (Baldyga et al., 1995; Bourne and Studer, 1992; Demyanovich and Bourne, 1989; D'Addio and Prud'homme, 2011; Betancourt et al., 2019; Heshmati Aghda et al., 2020). Our group has employed nanoprecipitation to formulate several types of nanomedicine encapsulating amphiphilic and

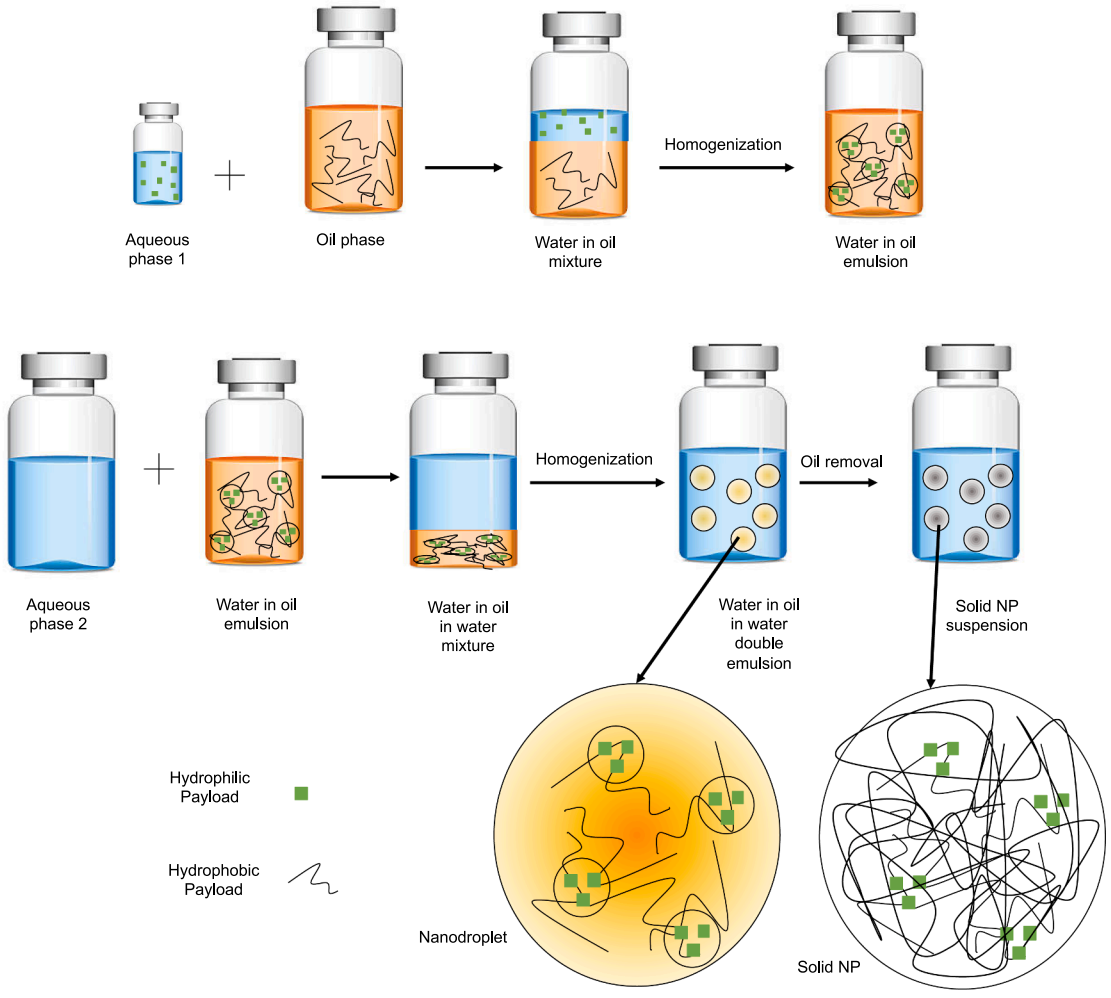

Fig. 3. Schematic of double-emulsion process resulting in the formation of solid nanoparticles (Solid NP).

hydrophobic agents such as indocyanine green (ICG), doxorubicin (Dox), aza-BODIPY, and rhodamine 6G within hydrophobic or amphiphilic block copolymer nanoparticles (Heshmati Aghda et al., 2020; Yildiz et al., 2018; Aghda et al., 2020; Hamon et al., 2016; Weigum et al., 2016; Betancourt et al., 2007).

To encapsulate the hydrophobic or amphiphilic drugs, they must be added to the organic phase prior to mixing. However, this method is not suitable for encapsulating hydrophilic drugs since they prefer to stay in the outer aqueous phase rather than inside the hydrophobic polymer unless the drug and polymer can bind together through electrostatic or other intermolecular interactions (Tao et al., 2019). Fig. 4 shows a scheme of this method.

2.3.3. Spray drying

In this method, a mixture of polymer and the drug are fed to a spray drier as Fig. 5 illustrates. The mixture is sprayed into a drying chamber in the form of nanosized droplets. The solvent is then be evaporated, and the nanoparticles are collected at the spray dryer output. Variation of operational parameters such as spray nozzle size and pressure can control nanoparticle size (Okuyama et al., 2006; Wong and John, 2016). Due to the processing of nanoparticles at high temperatures, this method may not be applicable for encapsulation of heat-sensitive drugs. To address this challenge, the process can be modified to operate at a lower temperature depending on the solvents that are utilized (Lee et al., 2011). The evaporation can even be substituted by sublimation in a modified spray freeze-drying method (Ali and Lamprecht, 2014).

2.3.4. Desolvation

In this method, the ionic strength of the polymeric solution (mostly hydrophilic polymers such as proteins and polysaccharides) is changed by changing the charge, polarity, ionic strength or pH of the homogeneous dispersion by addition of a desolvating agent like ethanol or concentrated organic salt solution in the protein or charged polymer solution (Fathi et al., 2018; Jain et al., 2018; Heshmati Aghda et al., 2021). Further, the formed nanoparticles are hardened by the addition of the cross-linking agent. Fig. 6 shows this process in a scheme. Size of the nanoparticles can be controlled through this process by adjusting multiple variables such as the concentration, ionic strength, and pH of the aqueous solution, nonsolvent identity and addition rate (Galisteo-González and Molina-Bolívar, 2014).

2.3.5. Liposome preparation

Liposomes are bilayer lipid nanostructures that can co-encapsulate both hydrophilic and hydrophobic drugs. Their versatility to carry

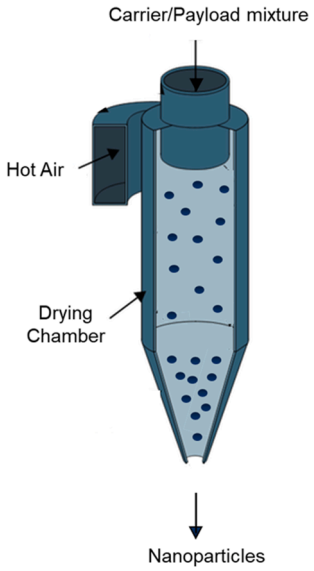

Fig. 5. Schematic of spray drying process.

cargo with varying properties and biocompatibility make them an attractive nanomedicine for clinical applications. Extrusion is the most common method for manufacturing liposomes. In this method, thin layers of a mixture of lipid and the hydrophobic drug are deposited on the surface of the vessel by slowly rotating the vessel and evaporating the organic solvent. Then, the layers are swollen by adding an aqueous phase and agitation. The resulting mixture is then extruded with high-pressure nitrogen gas through filters with selected pore sizes to make liposomes. Ultrasound sonication is also a common alternative for extrusion (Wagner and Vorauer-Uhl, 2011; Zhang, 2017; Maja et al., 2020; Sforzi et al., 2020). Fig. 7 shows this process.

3. Application of nanomedicine in cancer therapy and diagnosis

As previously mentioned, the last element of the design of a nanomedicine is its function. Nanomedicines have been readily investigated for the development of diagnostic and therapeutic strategies for cancer detection and treatment. Cancer is a known disease that is characterized by the uncontrolled growth and spread of abnormal cells. It can result in death if this uncontrollable spread is not stopped. Cancer is the second most common cause of mortality after heart disease in the U.S.

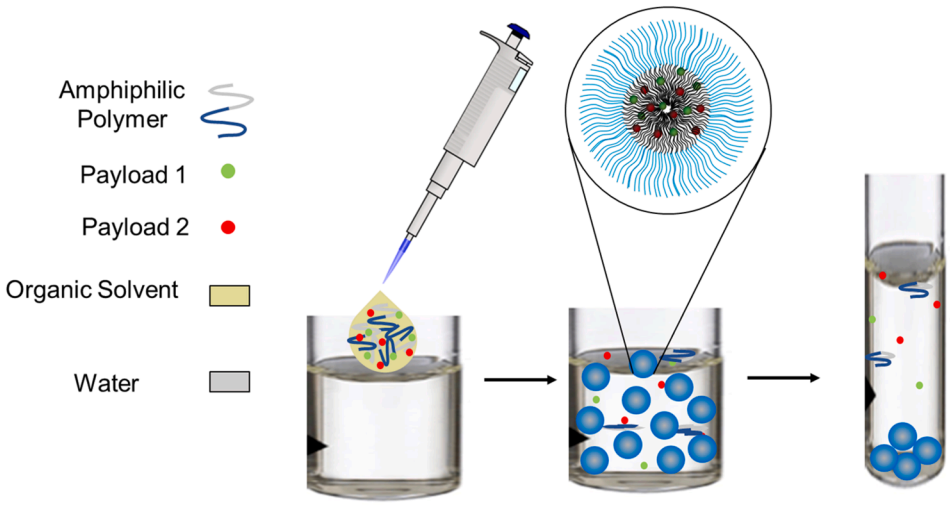

Fig. 4. Schematic of nanoprecipitation process utilizing a solution of an amphiphilic polymer dissolved in a water-miscible organic solvent, followed by centrifugation for nanoparticle recovery.

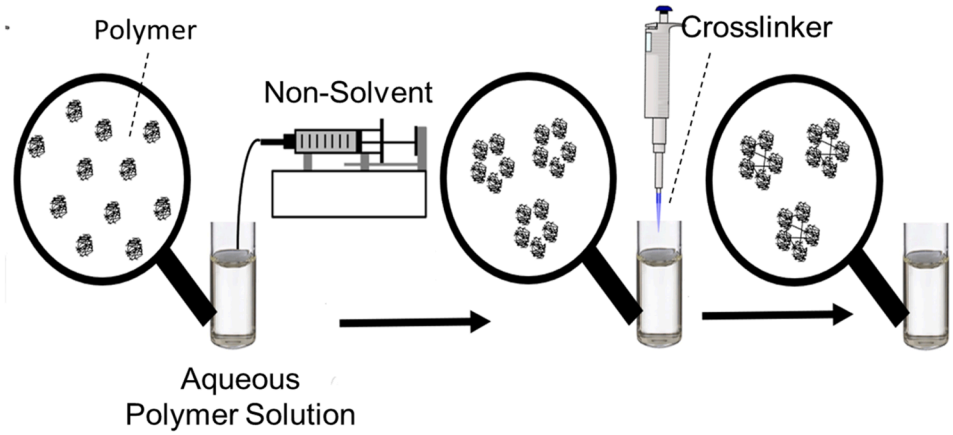

Fig. 6. Schematic of desolvation process.

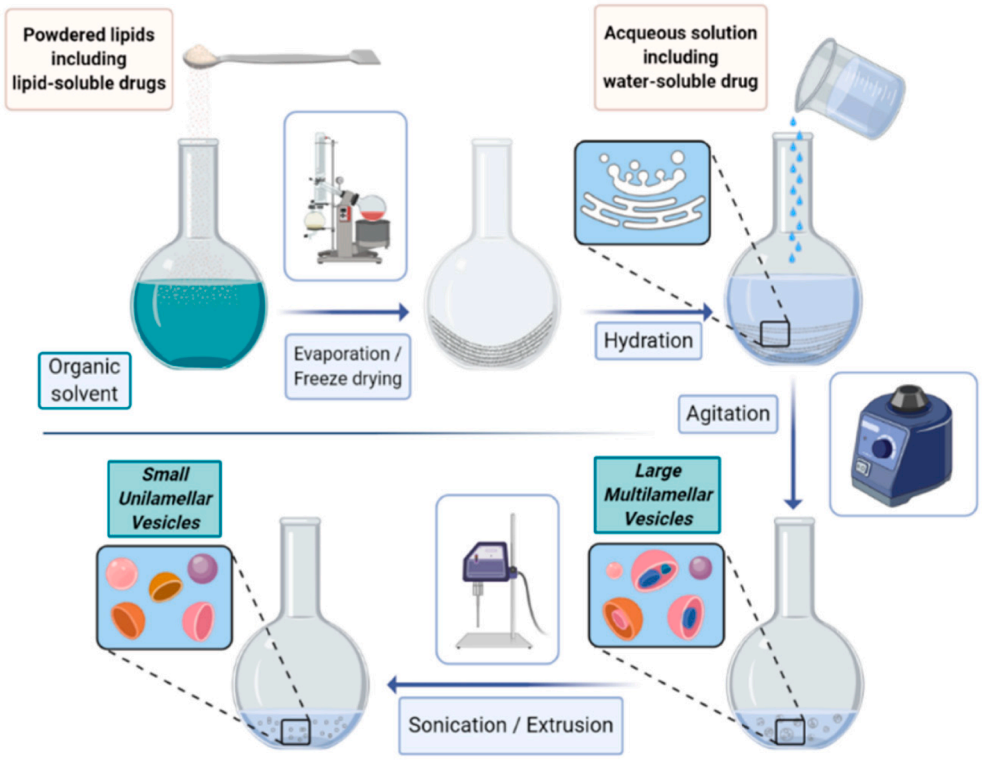

Fig. 7. Schematic of the process of conventional liposome preparation. Image reprinted with permission from Sforzi *et al.* (2020) (Sforzi et al., 2020).

According to the American Cancer Society (ACS), almost 1.9 million new cancer cases were expected to be diagnosed in 2021 in the U.S. (Figures, 2020). It is estimated that cancer will cause 608,570 deaths in this country, which means that about 1,660 patients will lose their battle against cancer per day (Figures, 2020).

The financial costs of cancer are also high for both the patient and society. The Agency for Healthcare Research and Quality estimates that cancer-related direct medical costs, i.e. all health care expenditures, in the U.S. in 2015 were $80.2 billion (Figures, 2020). Indirect cost (for example, the inability of the patient to work and earn) added, this disease leaves an enormous negative impact on the economy (Figures, 2020).

Several cancer treatment methods, including surgery, chemotherapy, radiotherapy, and hyperthermia have been developed and are selected based on the type and stage of cancer. Despite the high degree of success that many of these treatments have been able to achieve, most of them are associated with multiple side effects. For instance, many cancer therapies can cause adverse cardiovascular events (Minami et al., 2010).

Nanomedicine can step in to address challenges, enhance treatments and introduce new strategies to fight cancer. Understanding the unique features of the tumors harnessing them is important for a rational design of smart effective nanomedicine.

3.1. *Smart nanomedicines for cancer therapy*

Stimuli-responsive drug carriers have been extensively used for the delivery and site-specific release of therapeutic agents into tumors. These drug carriers are designed such that the payload is not released and therefore does not affect neighboring cells unless it is triggered by a stimulus. Therefore, these nanocarriers can be pre-programmed to release the drug at specific regions, thus minimizing undesired side

effects and toxicity. These delivery systems are categorized into two major classes based on the type of stimuli to which they are designed to respond: External and internal stimuli-responsive nanomaterials (Das et al., 2020). External stimuli such as magnetic fields, laser beams, and ultrasound waves must be applied externally by the administrator. For instance, Yao *et al.* fabricated near-infrared (NIR)-light responsive poly (*N*-isopropylacrylamide) (PNIPAAM) nanogels containing 5-fluorouracil (5-FU) and ICG, as chemotherapeutic and photothermal agents, respectively. By irradiating the nanoparticles at the tumor site, ICG heats the polymer and leads to deformation of the thermosensitive PNIPAAM nanogel and consequent release of 5-FU. However, since the nanogel that exists at healthy tissues is not irradiated, meaning that it is not triggered, 5-FU will not release and cause toxicity at nontarget sites. External stimuli-responsive materials are usually utilized for imaging, diagnostic and therapeutic purposes (Yao et al., 2021), and will be further discussed in later sections.

3.1.1. *pH-Responsive nanomedicines*

The tumor extracellular environment has lower pH compared to normal tissues. This is a result of the high glycolysis rate of cancer cells which results in overproduction and secretion of lactic acid. In addition, the lack of lymphatic drainage in tumors causes the lactate product to remain in the tumor microenvironment and decrease local pH to around 6.5 to 6.8 (Feng et al., 2018). Another reason for the acidic pH of the tumor is overexpressed carbonic anhydrase that produces an excessive amount of carbonic acid (H_2CO_3) (Feng et al., 2018). Nanomedicine takes advantage of this pH difference between normal and tumor tissues to generate a tumor-specific response by utilizing a wide range of materials that exhibit different characteristics in different pH due to their chemical structure. For instance, pH-responsive micelles can be made of polymers with carboxyl or amine pendent groups that can protonate/deprotonate at different pH and lead to swelling or dissociation of the nanoparticles and therefore drug release. The surface of nanoparticles can also be functionalized by protonatable materials such as 2,3-dimethylmaleic amide (DMMA) that changes the surface charge of the nanoparticles at the tumor site and enhances cell internalization of nanoparticles. DMMA can also be used as a linker to bind the drug to the nanoparticles and release it in the tumor area when cleaved by the acidic pH (Hajebi et al., 2019).

Liao *et al.* developed pH-responsive nanoparticles for enhanced release of Dox in the tumor. In this work, they linked Dox to the carrier, hyaluronic acid, using hydrazone linkages which can be cleaved in an acidic environment and release the drug. Nanoparticles can selectively enter the cancer cells upon CD44 receptor-mediated capture of hyaluronic acid (Liao et al., 2018).

3.1.2. *Reactive oxygen species (ROS)-responsive nanomedicine*

Reactive oxygen species (ROS) such as singlet oxygen, hydrogen peroxide, and radicals of hydroxyl are overproduced in the tumor due to the unique metabolism and respiratory dynamics of cancer cells (Pelicano et al., 2004).

Several materials with different chemical structures can react with ROS which makes them good candidates as a smart drug carrier for targeted tumor drug delivery. Fig. 8 summarizes the key functional groups and chemical structures of ROS-responsive materials that have been used for cancer nanomedicine. When the materials undergo a chemical reaction with ROS, a critical material characteristic such as solubility changes, which leads to dissociation or swelling of the nanocarrier and therefore drug release. Dissociation can also occur due to the cleavage of a bond either within the polymer backbone or between the drug and the polymer (Liang and Liu, 2016). To boost the performance of this type of nanomedicine, it can be combined with an external stimuli-responsive agent, known as photosensitizer (PS), that can produce a higher level of ROS in response to an external stimulus such as NIR light. When a PS is used, excess ROS produced upon photoactivation invades cancer cells and, together with the therapeutic effect of the released drug from ROS-responsive nanocarrier, reduces the size of the tumor. This treatment modality is called photodynamic therapy (PDT). Ren *et al.* developed a photo/ROS responsive thin film for tumor drug delivery (Ren et al., 2013). This drug delivery system consists of anionic poly(styrene sulfonate) (PSS) layers and diselenide cationic copolymer (PDSe) layers that form a uniform structure via electrostatic interactions. PDSe layers contain a diselenide group that undergoes a reaction with singlet oxygen when exposed to light. This reaction leads to diselenide cleavage and dissociation of the drug carrier which, in turn, causes the drug release (Ren et al., 2013).

3.1.3. *Enzyme-responsive nanomedicines*

Due to the imbalanced level of growth factors, cytokines, and other factors that regulate enzyme expression in the tumor, some enzymes,

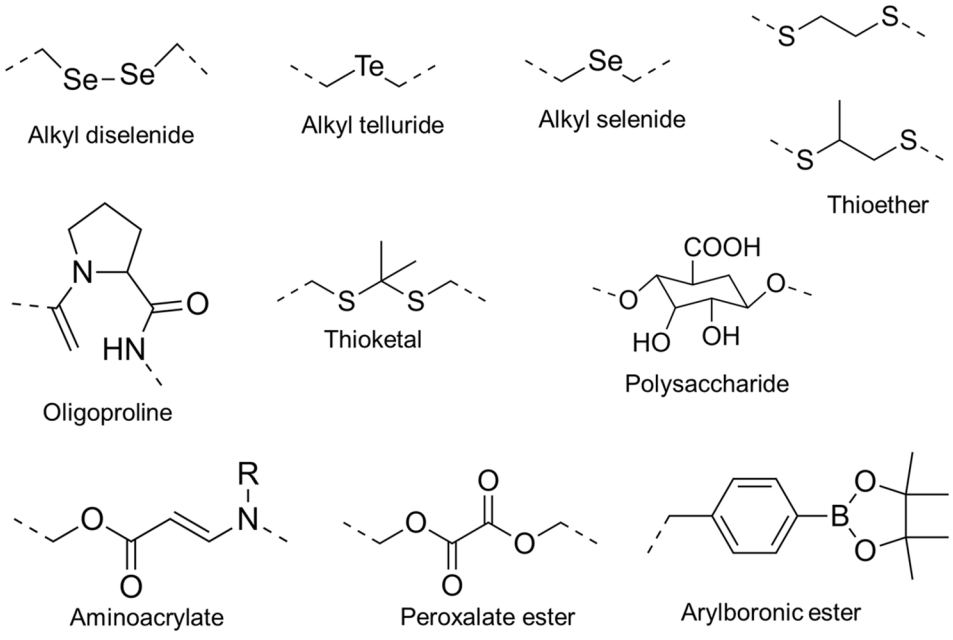

Fig. 8. Chemical structures of frequently used ROS-responsive materials in cancer nanomedicine.

such as hyaluronidase (HAase) and matrix metalloproteinases (MMPs), are over expressed in the tumor (Mura et al., 2013). Enzyme-responsive nanomedicine is designed as a targeting strategy for tumor drug delivery by taking advantage of the higher level of these enzymes in the tumor compared to the normal tissue (Jin et al., 2019). The main function of HAase in the tumor is hydrolyzing hyaluronic acid (which allows the tumor to grow and metastasize). Therefore, hyaluronic acid-containing nanomedicines disintegrate in presence of a high level of HAase and release their therapeutic cargo (Choi et al., 2011; Zhang et al., 2013). A similar strategy can be followed for designing MMP-responsive nanoparticles. MMP is a protease that cleaves a specific sequence of peptides. When the substrate peptide is included in the structure of the nanoparticle, it will be degraded in the tumor and exhibit faster drug release kinetics. For example, Jiang *et al.* induced over expression of MMP9 in the tumor and used an MMP9-activated NP that increased the release of the therapeutic load up to 3.7 folds (Jiang et al., 2019). . Our group designed an enzymatically activated nanoprobe for imaging cancer. The nanoprobe was composed of a blend of poly(lactic-acid)-*b*-poly(ethylene glycol) (PLA-mPEG) and poly(lactic-co-glycolic acid)-b-poly(L-lysine) (PLGA-PLL) block copolymers where lysine moieties were covalently bonded to a fluorescent dye, AlexaFluor-750 (AF750). The fluorescence is quenched due to the proximity of the dye molecules in the nanoparticle structure. However, in presence of a protease enzyme, the PLL block is cleaved and the dye is released from the nanoparticles regaining its fluorescence intensity for imaging (Özel et al., 2015).

3.1.4. Glutathione (GSH)-responsive nanomedicines

The concentration of glutathione (GSH) within the cancer cells and tumor microenvironment is greater than the healthy sites. GSH is a tripeptide, γGlu-Cys-Gly, that functions as an antioxidant by undergoing reversible redox reactions with ROS. Two strategies can be followed for smart nanomedicine design based on this property of the tumor. First, a nanomaterial can be introduced to the tumor to consume the extra amount of GSH. This then leaves a high level of ROS which can be harnessed by a ROS-responsive nanoparticle such as that was explained in section 3.1.2 (Ruan et al., 2019). Second, a nanocarrier that undergoes a chemical reaction with GSH can degrade and thereby release its cargo. Generally, the carriers that have a disulfide bond in their chemical structure can be cleaved by GSH and disintegrate. The drug will release by a similar mechanism if it is linked to the carrier's surface through an S-S bond (Xie et al., 2020). Shen *et al.* prepared such a system using poly(ethylene glycol)-*b*-poly(camptothecin) (mPEG-*b*-PCPT) copolymer to carry Dox and release it within tumors (Shen et al., 2019).

3.1.5. Cancer metabolism inspired nanomedicine

Several nanomedicines have been designed and developed to target cancer's unique metabolic pathways to eradicate the tumor. Three main metabolic pathways that have been mostly targeted by cancer nanomedicine are mitochondrial oxidative phosphorylation (OXPHOS), glycolysis, and autophagy (Yang and Shi, 2020).

OXPHOS is an aerobic respiration pathway through which energy sources such as carbohydrates react with oxygen and produce adenosine triphosphate (ATP), the energy source for the cells. Tumors consume a high level of oxygen through aerobic respiration due to the high energy demand of the cancer cells and create a hypoxic environment. Several strategies have been designed to take advantage of this feature. First, nanoparticles have been designed that release their therapeutic payload as the response to hypoxia. Ahmad *et al.* used this strategy by introducing a hypoxia-responsive moiety, nitro imidazole derivative, in their Dox-loaded polymeric NPs (Ahmad et al., 2016). Another possibility is to use a nanomedicine to consume the little oxygen available in the hypoxic tumor microenvironment to suffocate the tumor. Zhang *et al.* used this strategy by introducing Mg_2Si nanoparticles to the tumor which consumes the oxygen upon a chemical reaction that leads to the production of SiO_2 aggregates at the tumor site (Zhang et al., 2017). These aggregates can block the vasculature fenestration of the tumor that delivers nutrients to the cancer cells and lead to tumor starvation in addition to suffocation. Oxygen consumption can also be inhibited by interfering with the OXPHOS pathway (Zhang et al., 2017). Yu *et al.* developed a smart nanomedicine that produces nitric oxide at the tumor site that competes with oxygen in the OXPHOS pathway (Yu et al., 2019). In another study, Chen *et al.* designed a nanosystem to prevent uptake of lactate as an energy source by the cancer cells. As mentioned earlier, the lactate level in the tumor is higher than in the normal tissues. The strategy of preventing oxygen consumption can favor the effectiveness of photodynamic therapy when used as an adjuvant therapy by providing more oxygen, which is required for ROS production, and diminishing hypoxia (Chen et al., 2018).

Glycolysis is another metabolic pathway that provides energy for the cells. Although this pathway produces less ATP than OXPHOS does, it uses the same amount of glucose (2 vs 28 mol of ATP/1 mol glucose) and is a faster pathway (100-folds faster), which makes it favorable for the tumor to supply its high energy needs. In this anaerobic pathway, glucose is converted to pyruvate and then to lactate (Yang and Shi, 2020). If the main reactant, i.e. glucose, is consumed by a therapeutic nanomedicine such as glucose oxidase-loaded nanoparticles or gold nanoparticles with the same catalytic function as glucose oxidase, the glycolytic reaction ceases. Interfering glucose uptake by the cells using therapeutic nanoparticles has the same effect. For example, Huo *et al.* encapsulated glucose oxidase and iron oxide NPs in porous dendritic silica NPs. Glucose oxidase depleted glucose and produced hydrogen peroxide (H_2O_2) which subsequently was converted to hydroxyl radical in presence of iron oxide nanoparticles (Huo et al., 2017).

While interference with the OXPHOS and glycolysis pathways can effectively arrest tumor growth, cancer cells are capable of interchanging their metabolic pathways depending on the situation. Therefore, therapeutic modalities that target both of the main metabolism mechanisms are more effective. Liang *et al.* reported promising results from the study in which they took advantage of this strategy (Liang et al., 2018). Since these pathways are also used by normal cells, the untargeted treatment can cause lethal side effects. The side effects can be avoided by targeted therapy using nanomedicine through the strategies that were introduced in the previous sections.

Autophagy is a process in which the cells degrade the elements in the cytoplasm and consume the released energy from this reaction. The therapies that target tumor metabolism can be improved by inhibition of autophagy since it compensates energy depravation of the cells. Cancer cells also use autophagy to develop resistance against toxic agents including chemotherapeutic drugs. Thus, autophagy inhibition can benefit other treatment modalities as well (White, 2012). For instance, Cui *et al.* used nanodiamonds to inhibit autophagy and subsequently enhance antitumor effect of arsenic trioxide, a chemotherapeutic agent to which solid tumors are demonstrated to resist (Cui et al., 2018).

Table 1 provides examples of smart nanomedicines that have been recently developed.

3.2. Nanomedicine in common and novel treatments of cancer

3.2.1. Nanomedicine in drug delivery

A drug delivery system (DDS) refers to a formulation or device that introduces the therapeutic/diagnostic agent to the body in a safe and effective way (Siepmann and Goepferich, 2001). Many of these formulations include micro/nanoparticles. The mechanism through which DDS increases therapeutic efficacy mostly depends on the drug characteristics. For example, a DDS can improve the drug bioavailability of hydrophobic drugs by encapsulating them in a nanoparticulate carrier that can be easily suspended and circulated in the biological fluids. Instable drugs with low circulation time, such as biomolecular agents like proteins and polynucleotides that undergo rapid enzymatic degradation, can be benefited from a DDS. A suitable DDS can encapsulate/cloak the drug and protect it until it is released in the site of action. Other important examples are the drugs with narrow therapeutic window.

Table 1
Examples of smart or stimuli-responsive nanomedicines.

Stimuli	Nanocarrier	Therapeutic payload	Treatment modality	Tumor type	Reference
pH	mPEG-poly(α-lipoic acid) NPs	Dox and paclitaxel	Chemotherapy	Osteosarcoma	(Li et al., 2020)
pH and Temperature	Mesoporous silica NPs coated with poly(N-isopropyl acrylamide-*co*-methacrylic acid)	Dox	Chemotherapy	Breast cancer (SK-BR-3)	(Zhuang et al., 2021)
pH and Redox	Biodegradable mesoporous silica NPs incorporating calcium and bis (triethoxysilylpropyl) disulfide	Dox	Chemotherapy	Breast cancer (MDA-MB-231)	(He et al., 2021)
pH	PLGA-carboxymethyl chitosan NP	Dox and 5-FU	Chemotherapy	Skin cancer (melanoma)	(Gonsalves et al., 2021)
pH and Enzyme (cathepsin B)	Poly(L-glutamic acid-L-tyrosine) NP	Hematoporphyrin	Sonodynamic therapy leading to ROS generation	Prostate cancer	(Hadi et al., 2021)
pH and Enzyme (Hyaluronidase)	PEG-poly(β-amino ester) (PEG-PBAE) micelles coated with hyaluronic acid	Thioridazine (Thz)	Chemotherapy	Breast cancer	(Li et al., 2021)
pH	Cationic liposome made up of 3ß-[N-(N',N'-dimethylaminoethane)-carbamoyl]cholesterol hydrochloride	Dox	Chemotherapy	osteosarcoma	(Rayamajhi et al., 2020)
pH and Redox	Mesoporous silica NPs coated via disulfide bonds with polyethyleneimine and coupled with citraconic anhydride	Dox	MR imaging and chemotherapy	Breast cancer	(Wan et al., 2020)
pH and ROS	$NaYF_4$:20% Yb^{3+}/3% Er^{3+} upconverting NPs@mesoporous silica NPs	Dox and Ce6	Chemotherapy and PDT	Skin cancer	(Rafique et al., 2020)
pH	dioleoylglycerophosphate-diethylenediamine conjugate (DOP-DEDA) lipid NPs	siRNA	Gene therapy	Breast cancer	(Hirai et al., 2020)
pH and ROS	Dextran-thioketal-paclitaxel prodrug and poly(L-histidine) NPs	Paclitaxel and beta-lapachone	Chemotherapy, ROS and ATP consumption	Colon cancer	(Chang et al., 2020)
Enzyme (MMP-2)	GGPLGLAGGKG peptide conjugated dendrimer	Fluorescein isothiocyanate	Tumor fluorescent imaging	Tumor in lymph nodes	(Nagai et al., 2021)
Enzyme (MMP-2)	Gelatin NP	Dox and ICG	PTT and chemotherapy	Breast cancer	(Chen et al., 2021)
Enzyme (MMP-2) and Redox	Mesoporous silica NPs loaded with Fe_3O_4-Au and methylene blue and coated via disulfide bonds with cleavable peptide to block mesopores	Fe_3O_4-Au, methylene blue and a short D-peptide antagonist of PDL-1 (P^DPPA-1)	MRI and CT imaging-guided photodynamic-immunotherapy	Carcinoma (EMT-6)	(Feng et al., 2021)
Redox	Disulfide-linked oxidized cysteine-phenylalanine NP	Dox	Chemotherapy	Glioma and melanoma (C6 and B16F10)	(Chibh et al., 2020)
Redox	Gold nanoparticles decorated with lonidamine-conjugated albumin	Lonidamine	PTT and chemotherapy	Breast cancer and prostate cancer (MCF 7, MDA MB 231, and DU145)	(Ruttala et al., 2020)
Redox	Hyaluronic acid coated branched polyethyleneimine-SS-cisplatin (HA-BPEI-SS-Pt)	Cisplatin	Chemotherapy	Lung cancer (A549)	(Jia et al., 2020)
Redox	Redox-responsive folic acid (FA) modified PEGylated polycaprolactone nanoparticles (F-TeNP$_{DOX}$) containing ditelluride linkages	Dox	Chemotherapy	Breast cancer (4 T1)	(Pang et al., 2020)
Redox	Iron-copper co-doped polyaniline nanoparticles (Fe-Cu@PANI)	–	Photoacoustic imaging and PTT	Breast cancer (4 T1)	(Wang et al., 2021)
Cancer Glycolysis	Polyacrylamide nanoparticles	Glucose oxidase (GOx)	Tumor starvation	Breast cancer (MCF7)	(Rrustemi et al., 2020)
Cancer Autophagy and Glycolysis	Rattle-structured polydopamine@mesoporous silica nanoparticles	Chloroquine (CQ) and GOx	Tumor starvation, PTT and photoacoustic imaging	Hepatocyte carcinoma	(Shao et al., 2020)
Cancer Glycolysis	Erythrocyte membrane camouflaged metal–organic framework	GOx and gold nanorods	Tumor starvation and PTT	Colon cancer	(Zhu et al., 2021)

Abbreviations. NPs – nanoparticles, PLGA – poly(lactic-co-glycolic acid), PEG – poly(ethylene glycol), mPEG – methoxy-PEG.

Therapeutic window is a range of drug concentration in the plasma which provides effective treatment without causing toxicity. To avoid severe side effects, the drug dosage must be carefully adjusted to remain in the therapeutic window.

DDSs can be employed to improve effectiveness of these drugs by two main strategies: First, localization of the drug in targeted tissues by means of passive and active targeting as explained earlier in nanomedicine design section. In this strategy, the drug can be administered in higher dosage without causing toxicity to non-target tissues. Second, the controlled release of the drugs over a longer period of time can maintain the drug concentration in the therapeutic window without the need for multiple administrations, as Fig. 9 illustrates (Perrie and Rades, 2012). However, microparticles are better candidates than nanoparticles for achieving sustained drug release (Natarajan et al., 2014). Small size of nanoparticles provides a very low diffusion path for the drug to release. Thus, in general, diffusion-based drug release occurs quite fast in nanoparticulate drug delivery systems. Also, smaller quantities of the drug can be loaded into nanoparticles, thereby limiting prolonged release. To date, most of the approved particulate drug delivery systems for sustained drug release are microparticles while nanoparticles are utilized for improved drug solubility and cell uptake, as well as longer blood circulation time most of which the microparticles cannot provide. Several attempts have been made to prevent rapid drug diffusion out of nanoparticles. One strategy is to incorporate the drug within the nanoparticles by means of intermolecular electrostatic and polar interactions that prevent the drug molecule from diffusing out and keep it entrapped within the carrier until the nanoparticle is disintegrated. For example, Natarajan *et al.* demonstrated that intermolecular interactions,

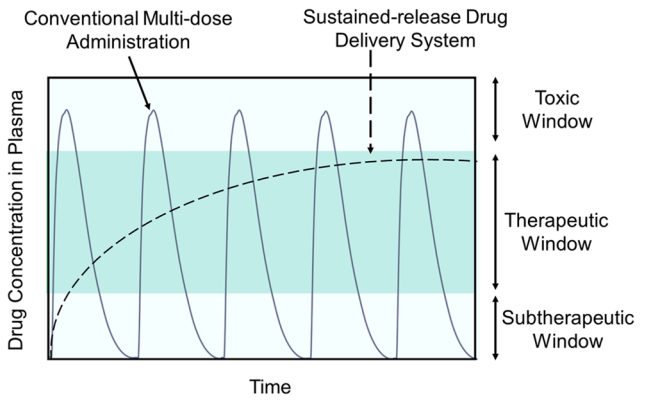

Fig. 9. Profile of drug concentration upon conventional multi-dose administration and sustained-release drug delivery system.

including hydrogen bonding, between latanoprost (the drug) and lipids in nanoliposomes increases release time (Natarajan et al., 2014).

3.2.2. Nanomedicine in Immunotherapy

James P. Allison and Tasuku Honjo won the Nobel Prize of medicine in 2018 for the discovery of cancer therapy by inhibition of negative immune regulation (The Nobel Prize, 2018). Amongst different types of immunotherapy, immune checkpoint (ICP) therapy has gained the most successful outcomes in the treatment of metastatic cancers. The idea behind ICP focuses on interfering with immune checkpoints, which cancer cells use to avoid being recognized by the immune system (Sharma and Allison, 2015). For example, the PD-1 checkpoint protein on T cells is activated when it binds to PD-L1, a protein that is overexpressed on cancer cells. Since PD-1 acts as an "off switch" to prevent the immune system from attacking native tissues, its activation by the cancer cells helps them evade the immune system (Sharma and Allison, 2015). In ICP therapy, antibodies that target PD-1 or PD-L1 can prevent the binding of these proteins, thereby preventing immune system avoidance by the cancer cells (Sharma and Allison, 2015).

While ICP therapy has shown significant promise, low response rate and the potential for high toxicity are the two main drawbacks of this approach (Kourie and Klastersky, 2016). The reason for low response rates is believed to be the non-immunogenic environment of the tumor, which contains numerous factors that help to evade immune system activation and attack (Wu et al., 2015). For instance, upregulation of adhesion molecules like ICAM-1/2, VCAM-1, and CD34 prevents T cells from infiltrating the tumor. Moreover, alteration of tumor cells' major histocompatibility complex (MHC) Class I, tumor antigenic peptide complexes, and antigen presentation biomolecules lead to T-cell recognition evasion. Production and secretion of numerous immunosuppressive factors to the microenvironment like gangliosides is one of the most important means that tumors utilize to downplay T-cell function or induce T-cell apoptosis. Overexpression of anti-apoptotic proteins such as Bcl-2 and Bcl-xL is another mechanism for immune response suppression (Wu et al., 2015) Because of this, a treatment such as combinatorial nanoparticle-mediated photothermal therapy (PTT) and chemotherapy that induces immunogenic cell death to alter the tumor environment and make it ready for ICP therapy is expected to improve patient outcomes.

3.2.2.1. Immunogenic cell death (ICD). A type of cancer cell death that is known to elicit an immune activity against the tumor is known as immunogenic cell death (ICD). ICD activates the dendritic cells, initiates a cascade process, and consequently leads to an antigen-specific T-cell response (Kroemer et al., 2013) The main hallmarks of ICD are the secretion, release, or surface exposure of damage-associated molecular patterns (DAMPs), including adenosine triphosphate (ATP), high mobility group box 1 (HMGB1), heat shock proteins (HSPs), and calreticulin (CRT) (Krysko et al., 2012). Each molecule and its role in involving the immune system are briefly described:

A. Heat Shock Proteins (HSPs).

One of the most critical characteristics of cell death is the presentation or translocation of specific proteins on or to the cell membrane (Gardai et al., 2006). Some of these proteins, such as phosphatidylserine, can initiate the phagocytosis of dying cells by antigen-presenting cells (APCs) (Kharitonenkov et al., 1997). Such signals from the plasma membrane of dying cells are received by a specific set of receptors on APCs that, as a consequence, cause a further immunological response (Tesniere et al., 2008).

Heat-shock proteins (HSPs) are molecular chaperones that are responsible for the correct folding or refolding of proteins when cells are under stress. Typically, they exist intracellularly. However, at least two of these molecules, HSP70 and HSP90, can be translocated to the cell surface and activate the immune system. Overexpression of HSPs in cancerous cells has been demonstrated, which can be the result of stress that is applied to the cells (Tesniere et al., 2008). Although overexpression of HSPs within the cells has a cytoprotective effect and inhibits apoptosis, when they overexpress on the plasma membrane, they have different immunological functionality. HSPs that are located on the membrane of cells can bind to the specific receptors on APCs' surface (Arispe et al., 2004).

It has been shown that HSPs can enhance DC maturation by binding to CD40 and CD86 receptors on the surface of the DCs (Becker et al., 2002; Singh-Jasuja et al., 2000). HSP90 has also been demonstrated to upregulate CD91 on APCs, another factor that can lead to DC maturation (Binder and Srivastava, 2004). Moreover, HSP70 and HSP90 participate in the presentation of tumor-derived peptide antigens on major histocompatibility complex (MHC) class I molecules, which leads to the activation of $CD8^+$ T-cells that kill cancer cells, infected cells, or other damaged cells. HSPs also stimulate the natural killer (NK) cells, which initiate an immune response to the tumor formation (Doody et al., 2004; Schild et al., 1999). Therefore, the presence of HSP70 and HSP90 on the cell surface is considered as a determinant of the immunogenicity of stressed or dying cells.

B. Calreticulin

Calreticulin is a protein that binds to Ca^{2+} ions. Calreticulin is mainly present in the endoplasmic reticulum (ER) lumen, participates in the homeostasis of Ca^{2+}, and controls Ca^{2+} dependent cell signals (Groenendyk et al., 2004). It is also a chaperone molecule and interacts with several proteins (Oliver et al., 1999). Similar to HSPs, calreticulin also locates on the plasma membrane of dying or stressed cells (Obeid et al., 2007). Calreticulin presence on the membrane of the cells determines the phagocytosis of dying tumor cells by macrophages and DCs. Although apoptotic cells that lack calreticulin on the surface can still die, phagocytes do not remove them efficiently (Gardai et al., 2006).

Studies show that translocation of calreticulin on the cell surface accounts for the initiation of an anti-tumor immune response both *in vitro* and *in vivo*. It interacts with various proteins such as thrombospondin, C1q, mannose-binding lectin (MBL), and the internalization receptor CD91 on phagocytes like DCs, leading to DC activation and engulfment of dying cells (Orr et al., 2003; Ogden et al., 2001; Gardai et al., 2005; Garg et al., 2010).

Tumor cells release several molecules into the extracellular matrix when they receive treatment and undergo cell death. These molecules can elicit an anti-tumor immune response. High mobility group box 1 (HMGB1) and adenosine triphosphate (ATP) are the two crucial ones that are discussed here (Tesniere et al., 2008).

C. High Mobility Group Box 1 (HMGB1).

HMGB1 is a protein that binds to the cell's chromatin and affects nuclear functions like transcription (Bianchi et al., 1989). The release of HMGB1 from the cells can induce an immune response. Both inflammatory cells and cancer cells that undergo necrosis can release HMGB1 (Scaffidi et al., 2002; Wang et al., 1999).

Released HMGB1 interacts with the toll-like receptor (TLR)-4 (TLR4)

receptor on DCs, which is responsible for controlling antigen presentation (Park et al., 2006). Besides, HMGB1 can play a role in stimulating TLR9, which leads to the production of interferon-α (INF-α) (Park et al., 2006). Interacting a complex of HMGB1 and DNA with the RAGE receptor can also produce INF-α through the same process (Tesniere et al., 2008; Rovere-Querini et al., 2004).

D. Adenosine Triphosphate (ATP).

Adenosine triphosphate (ATP) is a nucleotide that can be found in both intracellular and extracellular spaces. Inside the cells, ATP serves as the primary energy source for most cell functions. Extracellular ATP participates in cell signaling, the regulation of renal blood flow, vascular endothelium, and inflammatory responses. When released from damaged cells, ATP acts as a DAMP and informs the immune system of the presence of damaged tissue by binding to P2 purinergic receptors, which are classified as P2Y receptors (P2YR) and P2X receptors (P2XR) (Grazioli and Pugin, 2018).

Cells release ATP to the extracellular matrix through plasma membrane channel pannexin 1 when they undergo apoptosis. Released ATP promotes phagocytosis by binding to the macrophages' P2Y2R (Elliott et al., 2009; Chekeni et al., 2010). Interaction of ATP with P2Y2R leads to the release of proallergic biomolecules like the eosinophil cationic protein, interleukin 8 (IL-8), and IL-33 and, as a consequence, induces a T helper type 2 (Th2) immune response against cancer cells (Kouzaki et al., 2011; Idzko et al., 2003).

It has been demonstrated that the interaction of ATP with the P2X7 receptor can also cause tumor suppression. Several studies showed that released ATP binds to the P2X7 receptor on DCs and activates it. Then, inflammasomes are activated and result in IL-1β secretion and production of INF-γ by $CD8^+$ T-cells. Ultimately, this chain of processes promotes the clearance of the tumor cells (Grazioli and Pugin, 2018; Ghiringhelli et al., 2009). Fig. 10 illustrates the effect of ICD on the tumor microenvironment and the role of DAMPs in summary.

Despite the effect of ICD, which pushes the immune system to destroy the cancer cells, in many cases, the immune response that ICD induces is not enough, and better results might be observed if ICP reinforces the ICD effect. Our group has utilized nanoparticle-mediated PTT and combinatorial PTT/chemotherapy to induce the presentation/release of DAMPs as a way to elicit ICD (Aghda et al., 2020; Huff et al., 2020).

3.2.2.2. Induction of ICD. Temperature rise kills cells through two different pathways. It might either directly damage the cell because of the applied heat or indirectly stimulate cell death when the heating is ceased. The first pathway is proportional to the amount of provided thermal energy. Tumor biology and microenvironment also affect the efficacy of this method. A promising fact is that because of specific biological features like lower heat-dissipating ability and lower interstitial pH, cancer cells are more susceptible to heat injury in comparison to healthy cells (Nikfarjam et al., 2005). On the other hand, a chain of factors is involved in enabling the indirect cell death pathway, including apoptosis, microvascular damage, ischemia–reperfusion injury, altered cytokine expression, and alterations in the immune response (Nikfarjam et al., 2005). Immune response changes through dendritic cell (DC) activation, delivery of tumor-specific antigens (TSA) to the lymph nodes, and activation of T cells with T cell receptors (TCR) specific to the TSA which leads to upregulating inhibitory surface receptors (PD-1 and CTLA-4) resulting in the attack of remaining tumor cells. Therefore, treatments such as PTT, which are based on temperature elevation, are being considered as a method to induce ICD (Ott et al., 2017). Nanomedicines that are designed to function as photothermal agents can enable site-specific PTT for effective cancer eradication and activation of DCs.

Likewise, specific chemotherapeutic agents such as doxorubicin have been demonstrated to induce ICD, alleviate the immunosuppressive tumor microenvironment, and induce anti-tumor adaptive immunity (Mattarollo et al., 2011). Doxorubicin inhibits the replication of cancer cell's DNA by intercalation into DNA and inhibition of topoisomerase II and consequently hinders cell proliferation and growth. However, its cytotoxicity action is not specific to cancer cells. Therefore, it causes severe side effects, especially when administered with higher dosages (Yoo et al., 2000). Thus, a combinatory treatment approach that consists of mild dosages of both PTT and chemotherapy can result in desirable ICD induction that enhances tumor microenvironment immunogenicity. However, inhibitory ligands on tumor cells would inhibit a full response. Including ICP therapy in the explained combination therapy to block the immune checkpoints allows for an uninhibited immune response. The final ternary treatment is expected to lead to tumor cell killing and immune memory.

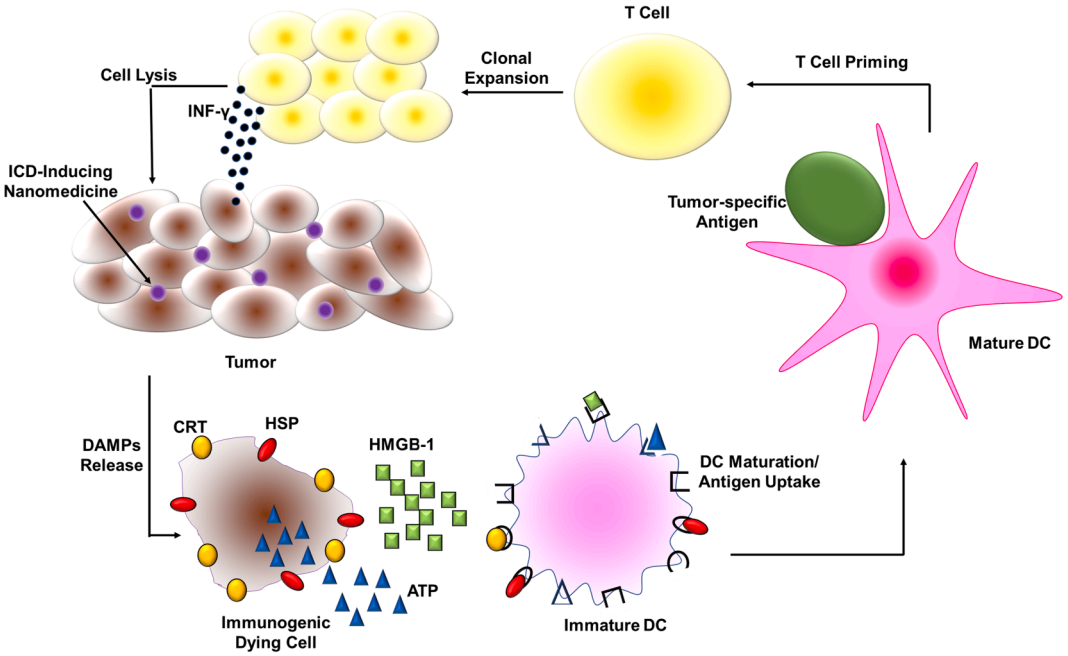

Fig. 10. Effect of ICD on tumor microenvironment.

3.2.3. Nanomedicine in photothermal therapy (PTT)

PTT is one treatment approach that has been proposed to induce ICD. PTT consists of the use of electromagnetic radiation of NIR wavelengths for the treatment of cancer. An agent that absorbs the light in the NIR range is introduced into the body. This agent accumulates in the tumor site through the means which were earlier explained (active and passive targeting). A laser irradiates the tumor site containing the PTT agent at the wavelength that it absorbs the most. By converting the laser energy to heat, the PTT agent increases the tumor temperature by over 43 ℃, which is detrimental to cells (Huang et al., 2006).

The irradiated light passes through the tissues as deep as a few centimeters in depth (3.4 cm in bovine tissue for 808 nm light at 1 mW/cm^2) (Hudson et al., 2013) to reach the photothermal agent accumulated in the tumor. If other substances in this path, such as hemoglobin, water, etc. absorb the light, these not only decrease the treatment's efficacy by reducing the intensity of light that reaches the target agent but also result in off-target damage caused by heating the absorbing substance in noncancerous tissues. NIR wavelength is the most appropriate choice to address this issue since main tissue chromophores are transparent to light in the NIR window of ~ 650–950 nm (Smith et al., 2009).

Nanoparticles used for PTT purposes are classified into four major types:

1) Metallic nanoparticles: Metallic nanoparticles have a photothermal effect due to surface plasmon resonance (SPR). Plasmon absorption is efficiently converted to heat through electron–electron and electron–phonon relaxations (Jain et al., 2007). This ultrafast heat generation can be harnessed for photothermal therapy through laser irradiation at a wavelength that overlaps the nanoparticles SPR absorption. The ideal nanoparticles for this purpose have an optimized size and a high absorption but low scattering. Optical properties of the parent metal, incident light, surrounding medium, nanoparticles size, and shape affect the heat production of metallic nanoparticles (Jain et al., 2007). Gold nanoshells, gold nanorods, and other gold/silver nanostructures have been constructed to have their SPR in the NIR range and have been successfully utilized as PTT agents. AuroShell particles (Nanospectra Biosciences) consist of core–shell NPs with a silica core and gold shell that is being investigated in clinical trials as PTT agents for cancer treatment.
2) Carbon nanomaterials: Carbon nanomaterials have been extensively used in biomedical applications due to their biocompatibility. Graphite-based nanomaterials, including graphene oxide (GO), carbon nanotubes (CNTs), carbon nanohorns (CNHs), carbon dots (CDs), graphene dots (GDs), and fullerenes have been utilized for photothermal applications (Yu et al., 2019). The π-plasmon absorbance background at the NIR range and low luminance make graphite-based nanomaterials a great candidate for photothermal applications. Vibration in carbon lattice due to the optical transitions and relaxations upon laser irradiation elevates the medium temperature. However, the toxicity of these materials limits their biomedical applications (Yu et al., 2019).
3) Conductive polymer nanoparticles: Various conductive polymer nanoparticles have shown an excellent photothermal conversion effect in the NIR range. Polyaniline is the first conductive polymer that was reported to be utilized as a photothermal agent (Xu et al., 2014). Polypyrrole and poly(3,4-ethylene dioxythiophene)-poly(styrene sulfonate) (PEDOT:PSS) polymers' maximum absorbance occur in the NIR region which makes them potent PTT agents (Xu et al., 2014). Our group has utilized PEDOT nanoparticles for PTT and reported promising *in-vitro* results (Huff et al., 2020; Cantu et al., 2017; Cantu et al., 2016).
4) Dye encapsulating nanoparticles: Several organic dyes, especially the ones that absorb the NIR light wavelengths such as tetrapyrrole structures, cyanine dyes, squaraine derivatives, and boron-dipyrromethane (BODIPY) dyes have been readily studied for biomedical applications including imaging and photothermal therapy (Cai et al., 2018). Fig. 11 Shows the chemical structure of a representative dye from each group. Our group has utilized the cyanine dye indocyanine green (ICG) as a PTT agent within nanomedicines (Heshmati Aghda et al., 2020).

Tetrapyrrole Structures: Tetrapyrrole dyes usually have two distinct absorption bands. The main absorbance peak appears at around 400 nm. In comparison, a minor absorption band, termed the Q-band, exists at longer absorption wavelengths around 600 nm and confers photothermal properties to the dye. Tetrapyrrole dyes also have interesting chemical properties that allow them to form a complex with transition metals that are required for magnetic resonance imaging. Natural examples of tetrapyrrole structure include some colored biomolecules such as chlorophyll, heme, and bacteriochlorophyll. Porphyrin and phthalocyanine derivatives are other common examples that have been frequently used for photothermal applications. However, due to the presence of the four phenyl groups or four naphthyl groups in their chemical structure, they highly tend to aggregate in aqueous environments which leads to low solubility and decreases their bioavailability (Cai et al., 2018).

3.2.3.1. Cyanine Dyes. Cyanine dyes are small organic molecules that generally exhibit trans geometry. Most of the cyanine dyes absorb light in the NIR region. They have shown a high molar extinction coefficient and high fluorescence quantum yields, which makes them potent candidates for bioimaging, photodynamic therapy, and photothermal therapy (Cai et al., 2018). A well-known example of these dyes is indocyanine green (ICG) that has been approved by the U.S. Food and Drug Administration (FDA) for biological imaging (Sheng et al., 2013) However, their application is limited by their low photostability, uncontrolled aggregation in physiological fluids, and high rate of binding to the proteins in the human serum (Sheng et al., 2013).

3.2.3.2. Squaraine Derivatives. The main feature of squaraine dyes is their high absorbance in the 650–700 nm range and sharp fluorescent emission peak in the NIR region. This unique optical property can be utilized for imaging and PTT. However, poor water solubility resulting from their hydrophobic π-conjugated planar structures hinders their functionality in physiological environments (Cai et al., 2018).

BODIPY Dyes: BODIPY dyes are good candidates for use in PTT owing to their unique properties, such as high thermal and photostability, high molar extinction coefficient, and high fluorescence quantum yields. However, most BODIPY derivatives' maximum absorbance occurs at short wavelengths in the visible range. Furthermore, their hydrophobicity reduces their bioavailability. Aza-BODIPY is a modified structure that can be obtained by replacing the carbon atom at the meso position with a nitrogen atom in the chemical structure of BODIPY. This modification leads to the bandgap reduction and shifts the spectral bands to

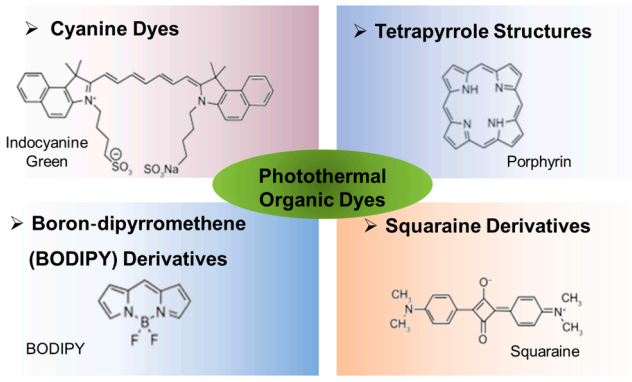

Fig. 11. Chemical structure of examples of each of the four major classes of photothermal organic dyes.

the right to the NIR region. Our group has utilized aza-BODIPY entrapped within polymeric nanoparticles for NIR imaging (Cai et al., 2018).

Most of the organic dyes described above are hydrophobic and can be eliminated readily from the body since they are small molecules. Some of them absorb light at the visible wavelengths. Two main strategies have been utilized to address these problems. Chemical modification of the dye and introduction of hydrophilic functional groups increases the solubility of the organic dye. However, the delivery of the dye to the tumor site remains unsolved. Encapsulation of the dye within water dispensable nanoparticles is a well-known strategy to increase the organic dye's stability. Nanoparticles can also deliver the dye to the tumor sites via either passive or active targeting. Moreover, nanoparticles facilitate the combination of two therapeutic agents. For example, two organic dyes, one dye, and either one of the photothermal materials discussed earlier can be loaded within the nanoparticles to reinforce the PTT effect of the nanoparticles. Moreover, PTT can be combined with other treatment modalities such as photodynamic therapy, chemotherapy, or imaging by co-loading the agents within the nanoparticles.

Table 2 listed some examples of ICD inducing nanomedicines.

3.2.4. Nanomedicine in gene therapy

Gene therapy is a novel promising cancer treatment modality that ultimately aims to repair the genetic defect that causes cancer. Recent studies in this field are mostly focused on genetically engineering cancer cells to either inhibit or reduce the cancer cells' growth and proliferation. Gene therapy requires efficient delivery of several types of polynucleotides such as DNA, mRNA, and RNA to the tumor cells (Zuckerman and Davis, 2015). Nanomedicine facilitates gene delivery to the tumor by efficient encapsulation of polynucleotides within nanocarriers, which preserves them from enzymatic degradation and immune system evasion. Entrapment within a nanocarrier also enhances the transfection efficiency into target cells by presenting proper positive surface charge or ligands that allow receptor-mediated cell entry (Green et al., 2008). Therefore, gene carriers are commonly viral vectors that endogenously possess a proper structure for cell internalization or engineered nanoparticles. Nanoparticle gene carriers commonly have cationic regions that can entrap the negative polynucleotide through electrostatic interactions (Hwang and Davis, 2001). Lipid-based nanoparticles such as solid nanoparticles and liposomes, polypeptides such as poly(L-lysine) nanoparticles, and polyethyleneimine-based nanoparticles are common types of nonviral gene carriers used in this application (Briolay et al., 2021). For example, Shobaki *et al.* made siRNA-loaded lipid nanoparticles to target the M2 phenotypes of tumor-associated macrophages for gene silencing and repolarizing the cells to M1 phenotype which unlike the M2 phenotype can eliminate the cancer cells (Shobaki et al., 2020).

3.3. Nanomedicine in diagnosis and imaging

Early detection and diagnosis of cancer have a pivotal role in the treatment success. Conventional cancer diagnosis methods, which include imaging techniques such as magnetic resonance imaging (MRI) and computed tomography (CT) scans, are associated with a few challenges. The mass has to be large enough to be detected by these methods, which means that the tumor would have to have already proliferated significantly and perhaps even metastasized for detection. Also, further tests are required to determine whether the detected mass is malignant. Detection of cancer biomarkers such as cancer-specific proteins, polynucleotides, exosomes, and vesicles opened a new window in early cancer diagnosis. Highly accurate and sensitive methods are required to analyze cancer biomarkers since their concentration in biological fluids is very low. Nanoparticles exhibit exceptional properties that have been extensively used for highly sensitive and precise biomarker detection. The high surface-to-volume ratio of the nanoparticles allows dense immobilization of bioreceptors that can efficiently capture and detect the cancer biomarker in the specimen.

Cancer-specific proteins such as carcinoembryonic antigen (CEA), secreted cancer DNA fragments, cancer vesicles, and circulating cancer cells are the main biomarkers of cancer that can be found in the blood or other biological fluids (Zhang et al., 2019). The most common method to detect these biomarkers in a biological specimen is a sandwich method in which the target attaches to a bioreceptor which is bound to a nanoparticle that is capable of producing a signal such as light absorbance, fluorescence, luminescence, etc. The bioreceptor can be an antibody, complementary DNA, and enzyme, or aptamer that have a high affinity to the biomarker. Quantum dots, gold nanoparticles, iron oxide nanoparticles, and polymeric nanoparticles are examples of nanoparticles that have been frequently used in this field due to their unique optical and electrochemical properties (Xiao et al., 2017; Pang et al., 2018; Zayed et al., 2019; Bao et al., 2018; Li et al., 2011; Harmsen et al., 2017). Nanoparticles' capability for active and passive targeting, their relatively long circulation time in the body, and biocompatibility make them excellent candidates for *in vivo* imaging agents. Superparamagnetic iron oxide nanoparticles (SPIONPs) are the most popular example which can accumulate in the tumor and are utilized for MRI imaging (Wang et al., 2017; Deh et al., 2020; Brigger et al., 2012; Guan et al., 2020). *In vivo* imaging nanoparticles have also been investigated for immunoimaging as an efficient tool to assist immunotherapeutic treatment modalities. Immunoimaging nanoparticles provide a clear visualization of the tumor microenvironment's immunogenic state by enabling imaging of the immune cells and of markers, and also allow monitoring of the treatment progression (Ou et al., 2020). Different examples of *in vitro* and *in vivo* imaging nanoparticles are provided in Table 3.

4. Regulatory considerations and commercialization of nanomedicines

As nanomedicines are finding their way into clinical translation and commercialization, they must pass regulatory standards that are set by the FDA in the U.S.A. to prove their safety and therapeutic effectiveness through premarket approval and acceptance, and postmarket surveillance. Initially, all possible associated risks must be determined and evaluated by the manufacturer and presented to the FDA. The manufacturer must also present the strategies to avoid or reduce the risks. After the product is released to the market and administered to a large population of patients, it is monitored by postmarket surveillance. For each approval procedure, the FDA may inspect the manufacturing platform to ensure that it meets all the good manufacturing practice (GMP) standards. It is worth mentioning that FDA has not issued any concerns about the nanoparticles size in general. Table 4 provides a list of some of the cancer nanomedicines that are approved for clinical use by the FDA.

Nanoparticles are also associated with secondary environmental and health risks as well as ethical issues. However, there is not sufficient data to prove/reject the proposed hypothesis such as adverse health effects through unintended adsorption of therapeutic nanoparticles that are accumulated in the environment (Hammond and Kompella, 2006).

5. Conclusion

Nanotechnology is still considered a young emerging field of science that has benefited several other fields including electronics, environmental technologies, and medicine. The application of nanotechnology in cancer medicine has been extensively studied in the past two decades. Unique features of cancer cells and tumor tissues such as unique metabolic activity, vasculature, and physicochemical properties in combination with exceptional properties of nanomaterials including small size and surface chemistry must be considered in the design of engineered nanomedicines for cancer therapy or diagnosis (or a combination of

Table 2
ICD-inducing nanomedicines.

Treatment modality/ies	Nanoparticle	Active Agent	Target tumor cells	Studied DAMPs	Reference
Chemotherapy, Immunotherapy	A folate-targeted PEG modified amphiphilic cyclodextrin	Ginsenoside Rg3 and quercetin and anti-PD-L1	CT26 and HCT116 colorectal cancer cell lines	ATP, HMGB1 and CRT	(Sun et al., 2021)
PDT, PTT, Immunotherapy	PEG modified human serum albumin NPs	IR820 and anti-CD47 antibody (αCD47)	4 T1 breast cancer cells	CRT	(Lu et al., 2022)
Radiotherapy	Au NPs	–	MDA-MB-231 breast cancer cells	CRT	(Janic et al., 2021)
Photodynamic Immunotherapy	NPs assembled from 9-fluorenyl methoxycarbonyl (Fmoc)-KCRGDK-phenylboronic acid, poly(vinyl alcohol) and chlorin e6-decorated PEI	TL3 agonist polyinosinic-polycytidylic acid (Poly(I:C)) and chlorin e6 (Ce6)	4 T1 breast cancer cells	CRT, HMGB1, ATP	(Fang et al., 2021)
Chemotherapy, PTT, Immunotherapy	Hollow prussian blue NPs conjugated with Cy5.5 and targeted with SP94 peptide	Sorafenib (SF) and Cyanine (Cy)5.5 anti-PD-L1	HepG2 and Hepa1 − 6 Hepatocellular Carcinoma (HCC) cell lines	CRT, HMGB1, ATP	(Zhou et al., 2020)
Photothermal-Immunotherapy.	Thermosensitive liposomes of 1,2-dipalmitoyl-*sn*-glycerol-3-phosphocholine (DPPC) and 1,2-distearoyl-*sn*-glycero-3-phosphoethanolamine-PEG2k loaded with BSA-coated CuS NPs	Copper sulfide, TLR-9 agonist, cytosine-phospho-guanine oligodeoxynucleotides, and PD-L1 inhibitors (JQ1)	Panc02 pancreatic cancer cells and 4 T1 breast cancer cells	CRT, HMGB1, ATP	(Sun et al., 2021)
Chemotherapy, PTT	BSA NPs	Dox, ICG	B16-F10 melanoma cells	CRT, HSP70, HSP90	(Heshmati Aghda et al., 2021)
PTT	Poly(3,4-ethylenedioxythiophene) (PEDOT) NPs	–	MDA-MB-231 breast cancer cell	HMGB1, CRT	(Huff et al., 2020)
PTT Immunotherapy	A semiconducting polymer NP core coated with a thermally responsive lipid shell	A NIR-II absorbing semiconducting polymer for PTT and TLR agonist	4 T1 breast cancer cell	CRT, HMGB1, ATP	(Li et al., 2021)
Radiotherapy, PTT, Immunotherapy	$WO_{2.9}$-WSe_2-PEG NPs	Anti-PD-L1	4 T1 breast cancer cell	CRT	(Dong et al., 2020)
Chemotherapy Immunotherapy	pH responsive NPs made from amphiphilic stearyl alcohol linked to D-type peptide antagonist of PD-L1	Dox, a PD-L1 binding peptide	CT26 colorectal cancer cells and 4 T1 breast cancer cells	CRT	(Zhu et al., 2021)
PDT, PTT	Gold nanorods	Ce6	B16-OVA melanoma and EMT6 carcinoma cells	-	(Kang et al., 2020)
Chemotherapy, PTT	PLA-PEG NP	ICG, Dox	MDA-MB-231 breast cancer cells	ATP, HMGB1, CRT	(Aghda et al., 2020)
Chemotherapy, PTT	PLGA polymeric core and cancer cell membrane cloaking	ICG and decitabine	4 T1 breast cancer cells	-	(Zhao et al., 2020)
Cell disruption by laser generated nanobubbles	Au nanorods	–	MDA-MB-231 and 4 T1 breast cancer cells	HMGB1, HSP70 and ATP	(Nguyen et al., 2021)
Photodynamic Immunotherapy	Ovalbumin NP coated with cancer cell membrane	Ce6	B16-OVA melanoma cells	-	(Wang et al., 2020)
Chemotherapy Sonodynamic Therapy	Chondroitin sulfate NPs linked via disulfide bonds to Rhein and perfluorocarbon	Docetaxel (DTX) and ROS-generating Rhein	B16-F10 melanoma cells	CRT	(Zhang et al., 2021)
Chemotherapy Immunotherapy	Lipid bilayer coated mesoporous silica nanoparticle (Silicosome)	Irinotecan Anti-PD-1	KPC Pancreatic ductal adenocarcinoma cells	CRT HMGB1	(Liu et al., 2021)
Immunotherapy , Metabolism interfering	Folic acid-conjugated 1,2-distearoyl-*sn*-glycero-3-phosphoethanolamine-N-[PEG_{2k}] and polyethyleneimine–poly(epsilon-caprolactone) NP	Shikonin (SK) PD-L1 knockdown siRNA	CT26 colorectal cancer cells	CRT, HMGB1, ATP	(Li et al., 2020)
Chemotherapy Immunotherapy	PLA-mPEG NP	PTX anti-PD-1	CT26 colorectal cancer cells	CRT, ERp57, HMGB1, ATP	(Yang et al., 2020)
Immunochemotherapy	Hyaluronic acid NP	Dox, cisplatin, and resiquimod (R848)	K7M2 osteosarcoma cells	CRT, HMGB1	(Zhang et al., 2021)
PDT	Core-shell gold nanocage coated with manganese dioxide and hyaluronic acid	–	CT26.WT colorectal cancer cells	CRT, ATP	(He et al., 2020)
Chemotherapy, PTT	Poly(*N*,*N*-diethyl acrylamide) and poly(2-(diisopropylamino) ethyl methacrylate) NP	Celastrol (CLT) and ICG	B16F10 melanoma cells	CRT, HMGB1, ATP	(Li et al., 2021)
Sonodynamic Therapy	Lipid-Perfluorohexane NP	–	Murine breast cancer 4 T1 cells	CRT, HMGB1, ATP	(Si et al., 2021)
Chemotherapy Gene/Immunotherapy	PEGylated PEI-PLGA NP	CRISPR/Cas9 and paclitaxel	B16F10 melanoma cells	CRT, HMGB1, ATP	(Tu et al., 2020)
PTT	Gold nanodot swarms aggregated with glycol chitosan	–	CT26 colorectal cancer cells	HSP70 HMGB1	(Jo et al., 2021)

Abbreviations: BSA: Bovine serum albumin, ce6: chlorin e6, ICG: indocyanine green, NP/s: nanoparticle/s, PEG: poly(ethylene glycol), PLA: poly(lactic acid), PLGA: poly(lactic-co-glycolic acid), PEI: poly(ethyleneimine), TLR: toll like receptor.

Table 3
Examples of *in vitro* and *in vivo* diagnostic and imaging nanoparticles.

Detection class	Diagnosis mode	Target	Nanoparticle	Detection modality	Remarks	References
Circulating tumor cells	*In vitro*	HER2	Au NP	Electrochemical	Aptamer bioreceptor Detection limit of 26 cells/mL	(Zhu et al., 2013)
	In vitro	CD2/CD3	Au NP	ICP-MS	Antibody bioreceptor Detection limit of 86 cells	(Zhang et al., 2014)
	In vitro	PTK7	ZnO nanodisks@g-C3N4 QD	Photocurrent	Aptamer bioreceptor Detection limit of 20 cells/mL	(Pang et al., 2018)
	In vitro	EpCAM EGFR HER2 CK	Au shell/Iron oxide core NP	Magnetic/Plasmonic	Antibody bioreceptor for all the targeting molecules High capture yields	(Wu et al., 2013)
Cancer biomarker	*In vitro*	CEA and NSE	ZnO Fluorescent QD	Fluorescent	Antibody bioreceptor Detection limit of 1.0 ng/mL	(Li et al., 2011)
	In vitro	A single exon in the BRCA1 gene	Fluorescent silver nanocluster	Fluorescent	DNA hybridization Optimized LOD = 6.4×10^{-11} M	(Borghei et al., 2017)
	In vitro	Exosome	Au NP	Colorimetry (Absorbance)	Uses CD63 aptamer as bioreceptor	(Jiang et al., 2017)
	In vitro	miR-141 (microRNA)	CdSe/ZnS QD	Fluorescent/ Chemiluminescent	Detection limit of 2.8×10^{-13} M	(A.F.-j. Jou, C.-H. Lu, Y.-C. Ou, S.-S. Wang, S.-L. Hsu, I. Willner, J.-a.A. , 2015)
Tumor mass	*In vivo*	Cancerous lymph nodes	Iodinated NP	CT		(Wisner et al., 1996)
	In vivo	Gliosarcoma model	Dextran-coated iron oxide NP	MRI		(Moore et al., 2000)
	In vivo	Metastatic brain tumors	Ultra-small superparamagnetic iron oxide (USPIO) NP	MRI		(Enochs et al., 1999)

* HER2: Human epidermal growth factor receptor 2, Au: Gold, EpCAM: Epithelial cell adhesion molecule, EGFR: Epidermal growth factor receptor, CK: Cytokeratin, PTK7: Protein tyrosine kinase 7, CD2/CD3: Cluster of differentiation 2/3, QD: Quantum Dot, NSE: Neuron-specific enolase, CEA: Carcinoembryonic antigen, BRCA1: BReast CAncer gene 1, ICP-MS: inductively coupled plasma mass spectrometry.

Table 4
Examples of FDA-approved nanomedicines for cancer therapy.

Trade Name	Carrier	API	Cancer indication	Approval date
DaunoXome®	45 nm liposome	Daunorubicin	HIV-related Kaposi's Sarcoma	1996
Doxil®	100 nm liposome	Doxorubicin	HIV-related Kaposi's Sarcoma, Multiple Myloma, Ovarian cancer	1995
Marqibo®	100 nm liposome	Vincristine sulfate	Acute lymphoid leukemia	2012
Oncaspar®	PEG shell	L-Asparginase	Acute lymphoblastic leukemia	1994
Eligard®	PLGA NP	Leuprolide acetate	Advanced prostate cancer	2002
Abraxane®	130 nm human serum albumin NP	Paclitaxel	Metastatic breast cancer	2005

both) so that they not only exhibit enhanced efficacy but also overcome the multiple barriers that the conventional modalities encountered. Besides all the advantages that nanomedicines present, they are also associated with a number of challenges and limitations that several research studies are focusing to address. These challenges include but are not limited to biological complications, mass production of nanoparticles, their reproducibility, and stability. As discussed in this review, nanomedicine design is highly dependent on the biological properties of the tumor. Biological differences in testing animals and humans, as well as individual patient differences may cause severe errors and lead to nanomedicine failure. This fact raises the demand for designing personalized therapies aided by real-time imaging nanomedicines.

CRediT authorship contribution statement

Niloofar Heshmati Aghda: Conceptualization, Investigation, Data curation, Writing – original draft, Writing – review & editing, Visualization, Project administration, Funding acquisition. **Maedeh Dabbaghianamiri:** Conceptualization, Investigation, Data curation, Writing – original draft, Writing – review & editing, Visualization. **James W. Tunnell:** Conceptualization, Writing – review & editing. **Tania Betancourt:** Conceptualization, Investigation, Writing – review & editing, Visualization, 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.

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