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Hyperthermia and smart drug delivery systems for solid tumor therapy

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ABSTRACT

Chemotherapy is a cornerstone of cancer therapy. Irrespective of the administered drug, it is crucial that adequate drug amounts reach all cancer cells. To achieve this, drugs first need to be absorbed, then enter the blood circulation, diffuse into the tumor interstitial space and finally reach the tumor cells. Next to chemoresistance, one of the most important factors for effective chemotherapy is adequate tumor drug uptake and penetration. Unfortunately, most chemotherapeutic agents do not have favorable properties. These compounds are cleared rapidly, distribute throughout all tissues in the body, with only low tumor drug uptake that is heterogeneously distributed within the tumor. Moreover, the typical microenvironment of solid cancers provides additional hurdles for drug delivery, such as heterogeneous vascular density and perfusion, high interstitial fluid pressure, and abundant stroma. The hope was that nanotechnology will solve most, if not all, of these drug delivery barriers. However, in spite of advances and decades of nanoparticle development, results are unsatisfactory. One promising recent development are nanoparticles which can be steered, and release content triggered by internal or external signals. Here we discuss these so-called smart drug delivery systems in cancer therapy with emphasis on mild hyperthermia as a trigger signal for drug delivery.
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1. Introduction

Cancer is one of the leading causes of death and is expected to become even more prominent with the worldwide continuously increasing life span. While the improved understanding of the genetics and the molecular basis of cancer, together with advances in early diagnosis and therapy have resulted in improved clinical outcomes [1], cancer incidence and related mortality are still rising. Chemotherapy is one of the cornerstones in cancer treatment together with surgery and radiotherapy. Chemotherapeutic agents can be used as a single treatment or as a combination therapy with other drugs, or can be used in combination with radiotherapy or surgery. One less common combination is chemotherapy together with hyperthermia, since hyperthermia is one of the most widely studied chemo- and radiation sensitizer [2], and this combination will be discussed in more detail later. Chemotherapeutic approaches have advanced enormously after the Second World War, since the first application of mustard gas derivatives for treatment of lymphomas in the 1940s [3]. A vast number of new compounds were identified and successfully used in patients. In spite of these advances and the extensive research into new agents, chemotherapy suffers from significant limitations. Most of these compounds are highly cytotoxic to both cancer cells and normal tissue cells. The resulting morbidity is that severe, such that the administered dose is typically limited by toxicities (a.k.a. dose limiting toxicities). These toxicities are the result of (1) chemotherapeutics not being targeted to only reach cancer cells, and (2) because agents are not selectively cytotoxic to cancer cells. As a result of these dose limiting toxicities, relatively low drug levels are obtained in tumors. Furthermore, a significant number of chemotherapeutic agents is poorly water soluble, complicating formulation and administration of these compounds. Furthermore, the tumor microenvironment with the disorganized vasculature and blood supply often limits tumor drug uptake. The capacity of tumor cells to acquire resistance to different chemotherapeutics, (multidrug resistance (MDR)), is a factor that often leads to therapy failure [4,5]. Factors that contribute towards MDR are drug efflux pumps via p-glycoprotein, pro-survival signaling and interruption of apoptosis, and alterations in cell membrane composition that reduce drug uptake [6–9]. Taken together, there are a number of factors which are responsible for limiting chemotherapy efficacy. There is substantial evidence that the usually low and heterogeneous accumulation of drugs in tumors is a major reason for treatment failure, i.e. the suboptimal outcome in patients is to a large extend due to the inability to deliver adequate amounts of drug to all cancer cells [10–14]. Because of the mentioned dose-limiting toxicity, the administered dose cannot be further increased to achieve higher tumor drug levels. Therefore, alternate strategies to improve tumor drug delivery, while reducing systemic drug uptake are required.

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It is clear that adequate delivery to tumors is an important aspect but as important is reduction of co-morbidity. An effective method of targeted tumor drug delivery that is already in clinical use is infusion of the chemotherapeutic through the tumor feeding vessels (e.g. chemoembolization), and takes advantage of the rapid extraction of many chemotherapy agents, with the majority of drug extracted by tumors during one pass [15]. Another strategy is isolated perfusion of the tumor-bearing tissue or organ, where high drug concentration is maintained in part of the body with limited exposure of non-perfused tissues [16–18]. In this review we will focus on strategies via nano-carrier based drug delivery – a method that also allows treatment of metastatic disease. When first proposed about 30 years ago, nanoparticles carrying chemotherapeutics to the targeted tumors were considered to be the solution for the hurdles identified above [19–21], improving both delivery to tumors while also diminishing non-target toxicities due to the drug encapsulation. In addition, hydrophobic and poorly water soluble compounds can be formulated and render applicable for systemic administration. Finally, multiple active components could be incorporated into one nanoparticle, which enables simultaneous delivery of these multiple agents, to the same target tumor. Encapsulation of multiple compounds can for example deliver drugs that interact synergistically, or can deliver drugs together with imaging agents (e.g. MR contrast agents) to enable visualization and monitoring of delivery.

While there have been some successful translation of nanomedicines, these successes are mostly due to a more favorable toxicity profile and therefore better tolerance of the treatment by patients. However, rarely has improved clinical outcome been observed compared to unencapsulated drug (i.e. standard chemotherapy). While the clear advantages of nanomedicines in terms of reduced toxicity have been recognized, it has become increasingly clear that the traditional nanoparticle approaches have shown very limited success in enhancing drug uptake by cancer cells. In this paper we will discuss an alternate delivery strategy based on nano-sized smart drug delivery systems (SDDS), which allow control of particle movement (i.e. steering), as well as control of release – i.e. allowing spatial and temporal control (Fig. 1). Here, we will focus on SDDS with triggered release, i.e. where either internal (e.g. pH) or external signals (e.g. temperature) serve as release trigger. In addition, there have been considerable advances in devices that allow spatial control of the trigger signal, such as focused ultrasound devices or microwave devices for locally inducing hyperthermia that serves as trigger signal for SDDS. As we will discuss below, the combination of triggered SDDS with appropriate devices for controlling the external trigger signal can considerably enhance tumor drug uptake compared to traditional nanomedicine, and may achieve what prior nanoparticle approaches have failed by demonstrating improved therapeutic outcome compared to standard chemotherapy.

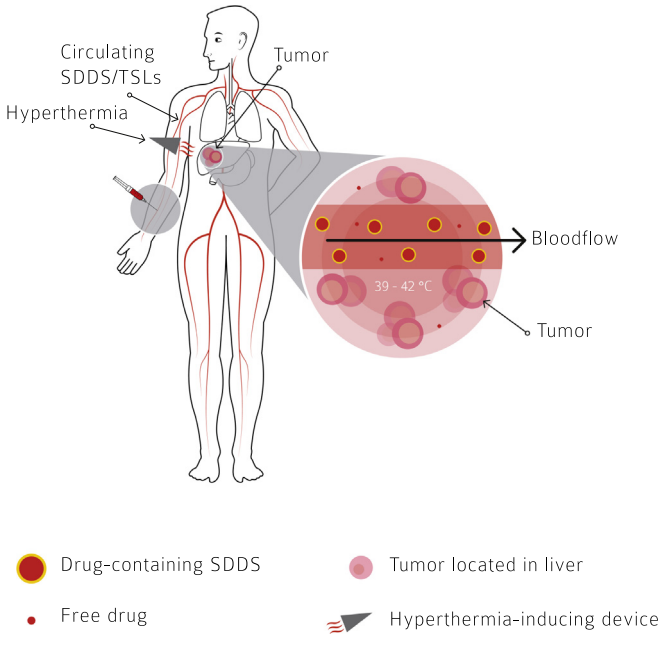

Fig. 1. Schematic representation of triggered drug release from smart drug delivery systems (SDDS)/thermosenstive liposomes (TSLs) by externally applied mild hyperthermia. SDDS/TSLs are systemically injected (syringe) and circulate throughout the body. When passing the heated area (light grey zone over the tumor in the liver), SDDS/TSLs are exposed to elevated temperatures of 39 to 42 °C and release content as a result. This procedure results therefore in a loco-regional exposure of the tumor to free chemotherapeutic.

2. Pharmacokinetics and tissue accumulation

2.1. Free chemotherapeutics

Chemotherapeutic agents can be administered by different routes, such as oral administration, intravenous or intra-arterial injection/infusion, local infusion or perfusion, direct intra-tumoral injection or by creating a (local) depot from which the drug is released over time. The mode of administration impacts the life-time of the drug, the tumor accumulation, and also the severity and type of toxicity and morbidity which accompanies the treatment. Low molecular weight chemotherapeutics tend to have short plasma half-lives when administered intravenously, and distribute throughout the body, thus having a large volume of distribution (Fig. 2). While drug distribution to healthy tissues causes undesired toxicity, it also limits tumor drug uptake, and together with fast clearance and metabolization reduces the effective concentration and exposure time of the drug in tumor tissue [22]. The interaction with proteins in serum, such as albumin, can lead to a prolonged plasma half-live and reduced dilution and degradation, which can have advantages for drug delivery to solid tumors. However, these interactions tend to be short-lived, and therefore do not prevent fast clearance and degradation; these interactions also makes the drug pharmacokinetics of more complex and patient dependent, since plasma composition is highly variable [23]. Furthermore, even when a chemotherapeutic agent reaches the tumor site, the pathophysiologic properties of the tumor microenvironment (see section 3), provide additional barriers that limit drug uptake at the tumor site. The heterogeneity of the tumor microenvironment, not only between individual tumors but also within the same tumor, provides additional challenges for an effective and homogeneous tumor drug distribution. As a result, cytotoxic drug concentrations often do not reach all cancer cells, and gradients of intratumoral drug concentrations exists [24]. Tumor regions with inadequate delivery contribute towards local tumor recurrence and may even result in drug resistance [25–31]. While this is true for free drug, it also applies to nanoparticles currently available for cancer treatment [32,33]. Importantly, chemotherapeutic agents have the least favorable therapeutic index of anticancer drugs currently being used, which limits the dose or dose schedule that can be administered. Increasing the chemotherapy dose to compensate for poor delivery is therefore typically not an option, as this also increases exposure of systemic tissues and therefore results in higher toxicity [34]. Therefore, either new and less toxic drugs have to be developed, or existing drugs with a proven activity need to be reformulated (e.g. with nanoparticles) to address the barriers limiting delivery, resulting in improved biodistribution and a better therapeutic index.

2.2. Nanoparticle-formulated chemotherapy

Nanoparticles are intended to protect the encapsulated chemotherapeutic agents from degradation, absorption, metabolism and excretion. In addition, nanoparticles should also improve distribution, by limiting the distribution volume to the blood volume, and thus improving

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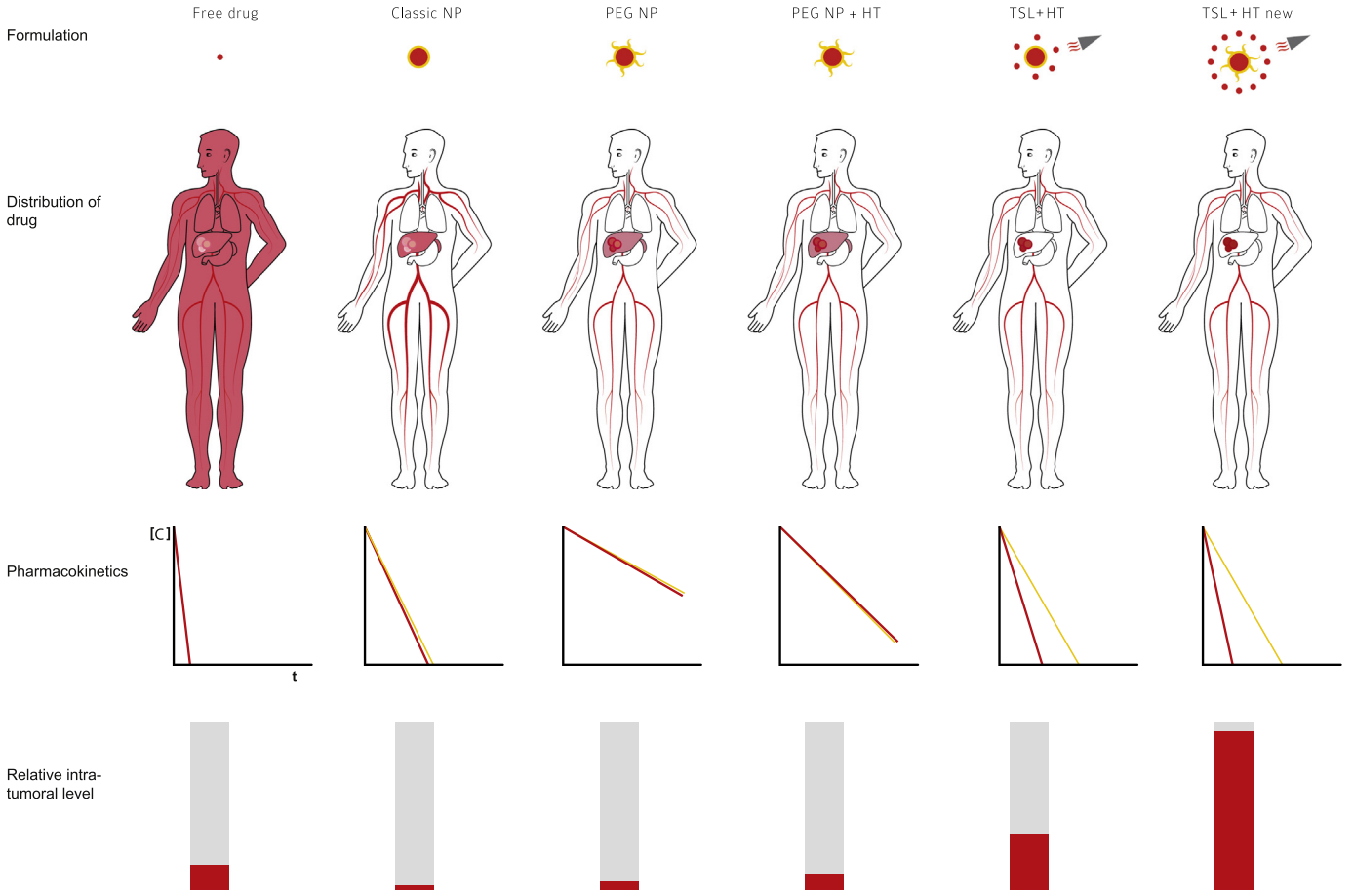

Fig. 2. Schematic representation of distribution, circulation time and tumor localization of chemotherapeutics in different administration settings. Free drug will generally distribute throughout the body with a short (minutes) residence time in circulation and marginal amounts localize in the tumor. Classic nanoparticles (NP), may prolong circulation time but most do not augment the amount of free drug in the tumor. Pegylation of NPs dramatically prolongs circulation time of the encapsulated drug. However, the amount of free drug in the tumor is still low due to poor accumulation of the NPs and slow release of content (i.e. chemotherapeutic). Preheating of the tumor for 15 to 30 min increases vascular leakage and promotes NP accumulation, although release of content is still slow. Exposing TSLs to mild hyperthermia triggers content release and when the heat is focused on the tumor elevated drug levels result. Several factors are involved which determine high and prolonged presence of the release chemotherapeutic is the tumor. Together, selection of the optimal chemotherapeutic, optimizing stability and circulation time of the nanoparticle, and optimizing response of the nanoparticle to a trigger (e.g. mild hyperthermia) need to be considered to achieve increased and effective (i.e. free) drug concentrations in the tumor. Drug is presented in red while the carrier in yellow. The pharmacokinetics are represented by red (drug) or yellow (carrier) lines in a log (concentration) versus time (linear) scale. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

tumor accumulation (Fig. 2) [20,21]. In addition, nanoparticles allow the administration of poorly water soluble and hydrophobic drugs [35,36]. Ideally, nanoparticles change the pharmacokinetics and biodistribution towards localization in the tumor while limiting uptake by other tissues. In addition, it is important that the activity of the agent at the target site is preserved [20,37,38]. This issue of target site activity is one of significance and will be discussed later in section 2.3. Initially, the hopes were high for nanoparticles and they were suggested to be the "Magic Bullet" previously postulated by Paul Ehrlich [39], which resulted in substantial investment in nanomedicine development over the recent decades. A large variety of organic and inorganic materials have been used in the fabrication of a numerous nanoparticles such as liposomes, solid lipid nanoparticles, micelles, polymeric nanoparticles, dendrimers, quantum dots, protein based nanoparticles, carbon based nanoparticles, and others. An155 assortment of nanoparticle design properties such as size, charge, shape, type of surface modification, and biocompatibility have been investigated [40–43], and resulted in nanoparticles with good stability and acceptable toxicity, some of which were successfully applied in the clinic [44,45]. One significant advance was the realization that rapid clearance of nanoparticles reduces their activity. In other words, prolonged circulation time was identified as an important factor. One way to achieve such prolonged circulation was by coating of nanoparticles with polyethylene glycol (PEG), which rendered nanoparticles unrecognizable by the immune system ("stealth"), therefore resulting in slower clearance and longer circulation time of up to several days (Fig. 2) [19,46,47]. PEGylated liposomal doxorubicin (PLD) was the first clinically approved type of pegylated nanoparticle. In patients receiving PLD, clearance and volume of distribution were, respectively, about 250-fold and 60-fold reduced [48]. Also the tumor accumulation was drastically improved compared to free doxorubicin [49]. Since cardiomyopathy is the main dose-limiting toxicity of free doxorubicin [50], the reduced drug accumulation in the heart with the use of PLDs was a major benefit. The shift of toxicity to a less hazardous, and better controlled palmar plantar syndrome makes prolonged drug dosing possible and renders PLDs suitable for combination therapies. Similarly, protein-bound paclitaxel (Abraxane®) or the polymeric micelle formulation of paclitaxel (Genexol-PM™) enable higher administered doses compared to the standard formulation of paclitaxel, Taxol™ of which Cremophor is used to solubilize paclitaxel, but causes hypersensitivity reactions [51]. A shorter infusion time and a reduced need for corticosteroid and/or antihistaminic co-medication are other advantages of Abraxane® over Taxol™ [36]. Liposomal vincristine sulfate (Marqibo®) has an increased therapeutic index versus free vincristine. This enables higher doses to be administered without increasing the neurotoxicity, even in extensively

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pretreated patients [52–54]. Encapsulation of irinotecan in liposomes (Onivyde®) improves pharmacokinetics and biodistribution of irinotecan and protects it from early conversion to SN-38. Compared to irinotecan, SN-38 is 100 to 1000 times more potent, but is susceptible to rapid hydrolysis and inactivation by nonspecific carboxylesterases [55–57]. Therefore, encapsulation provided benefits by extending availability of the active compounds at the site of action while maintaining a manageable safety profile. While patients mainly benefited from improved safety, tolerability and increased therapeutic windows of nanoformulated drugs [58], the limited impact on overall patient survival has become a major discussion point in the nanomedicine field. In summary, there have been several successful nanomedicines that provide various benefits in the clinic compared to the unencapsulated compound, but benefits are often related to an improved toxicity profile rather than a higher anti-tumor efficacy. Clearer insights into the relationship between cancer biology and nanomedicine behavior is instrumental to make meaningful progress in nanomedicines [59].

2.3. Properties of nanoparticles for cancer therapy

The development of traditional nanoparticles has been primarily focused on creating a stable association of a drug with a nanoparticle in order to protect the drug while in circulation, with the goals of (1) decreasing the volume of distribution and (2) prolonging circulation time and/or retention at the diseased site. Ideally, this should result in higher tumor accumulation and lower toxicity to healthy tissues. The uniquely large surface-to-volume ratio of nanoparticles provides a large functional surface to enhance the solubility or to carry a variety of components. However, when initial nanoparticle formulations were administered these were identified as foreign bodies and were cleared rapidly by the reticuloendothelial system (RES), with only a small fraction reaching the diseased site. Studies in patients demonstrated preferential uptake of liposomes by the RES [60]. By adjusting the lipid composition, the circulation time of liposomes could be extended from hours to days. For example when doxorubicin was encapsulated, the volume of distribution was reduced from 365 L for doxorubicin to 5.9 L for liposomal doxorubicin (Doxil®) (both at a dose of 50 mg/m^2), but also resulted in a 4–16-fold enhanced accumulation in tumors [46]. Higher intratumoral drug levels and longer retention of the drug was observed both in preclinical models and in patients [61]. Improvement in delivery of the drug into the tumor site is believed to result from the enhanced permeability and retention effect [62] which will be discussed further below. Furthermore, this improved stability resulted in reduced cardiac drug uptake and thus lower cardiotoxicity [63,64]. Several methods have been used to prevent opsonisation and clearance, of which PEGylation is the best known and mostly widely used approach. Grafting nanoparticles with PEG (often referred to as stealth nanoparticles) provides steric hindrance on the particle surface, thereby minimizing aggregation, and reducing opsonization and macrophages uptake. PEGylation thus reduces clearance rate and enhances circulation time. Previously, Maruyama et al. observed that ganglioside GM1, comparable to PEGylation prolonged circulation of DPPC-based TSLs which resulted in 2.5-fold increased local drug delivery compared to liposomes not containing GM1 and a better tumor response [65].

Important however is that for drugs to become active, dissociation of the drug from the carrier has to occur. Papahadjopoulos and colleagues observed that liposomal doxorubicin localizes in the extracellular matrix of the tumor, and free doxorubicin enters the tumor cells upon degradation of the liposomes [66], or as recently proposed by Barenholz by means of remote release of doxorubicin due to reversed ammonium gradient in the tumor [67]. We observed in our studies however that release is a slow process taking place over several days [68]. Moreover, we demonstrated that tumor cells take up the intact liposomes, which are then trapped inside tumor cells while retaining doxorubicin inside lysosomes (Fig. 3A) [68,69]. We hypothesize that this intracellular trapped doxorubicin is not bioavailable since the drug either remains encapsulated or is retained in the lysosome/endosome, and therefore not available to perform cytotoxic actions. Doxorubicin - like most drugs - acts intracellularly. This means that the drug needs to pass the cell membrane, and in the case of doxorubicin, also the nuclear membrane. Measuring total levels of drug in tumors, as is common practice, provides inadequate information and knowledge of drug levels at the intracellular biological target is necessary; for doxorubicin, this drug target is the nucleus [68,70].

It has become increasingly clear that improved intratumoral delivery by nanoparticles does not necessarily imply improved delivery or interaction of the chemotherapeutic payload with the subcellular target. A good example is long circulating liposomal cisplatin where despite successful tumoral delivery, no therapeutic benefit over treatment with free cisplatin was observed because of the lack of release of cisplatin from liposomes [71]. Therefore, in addition enhanced tumor delivery, adequate bioavailability of the active compound is necessary, i.e. the chemotherapeutic agent has to dissociate from the nanoparticle in a timely fashion to assure an effective cytotoxic concentration at the biological target. Based on the discussion above, and to complicate the picture further, also vascular and tumoral barriers need to be taken into account since they greatly impact the accessibility of tumor cells to the nanoparticles, as will be discussed below. Clearer insights into the relationship between cancer biology and nanomedicine behavior is instrumental to make meaningful progress in nanomedicines [59].

Taking the above potential and limitations of drug carriers into account it becomes clear that the ideal properties of nanoparticles, i.e. great stability in circulation and rapid dissociation at the side of action, oppose each other and are difficult to realize in traditional nanoparticles. This realization initiated the development of advanced nanoparticles which we coined smart drug delivery systems (SDDS).

3. Tumor microenvironment

3.1. Introduction

For a drug to be effective it is important to reach the target, which is typically located within a specific compartment of the cancer cells. Irrespective of size, tumors do not solely exist of cancer cells but often also contain a large fraction of stromal cells (e.g. endothelial cells, pericytes, fibroblasts and immune infiltrating cells) and matrix components (e.g. basal membrane and extracellular matrix). This stroma is highly important in tumor development as it creates a connective and supporting framework and forms a reservoir of factors promoting tumor maintenance and growth. Stromal cells may support tumor growth, facilitate and promote the tumor vascular bed, and may protect the tumor from attacks by the immune system. Importantly, this tumor microenvironment plays also a pivotal role in chemotherapy delivery and therefore development of delivery systems must consider the tumor composition of the microenvironment [72]. A solid tumor has several key properties that are not found in normal tissues, including (1) an abnormal vascular network (i.e. heterogeneous and chaotic vessel growth, non-functional vessels and shunting of blood [73]), (2) accumulated solid stress because of the rapid tumor growth, and (3) an elevated interstitial fluid pressure (IFP) due to increased permeability of the tumor-associated vasculature in combination with the lack of a functional lymphatic drainage. IFP in turn causes blood flow stasis and reversed blood flow, which hinder drug uptake by tumor regions with high IFP. Chauhan et al. argue that in pancreatic cancer, IFP is driven by blood pressure, while solid stress causes vessel compression, and that relaxation of this stress improves therapeutic outcome [74,75]. Another barrier for effective drug uptake is the overproduction of extracellular matrix proteins, contributing to solid stress and compressed tumor vessels [76]. These barriers together with the perfusion defects result in hypoxia and acidosis, with necrotic and non-perfused tumor regions. Cancer cells are often more resistant to chemotherapeutic drugs in these regions.

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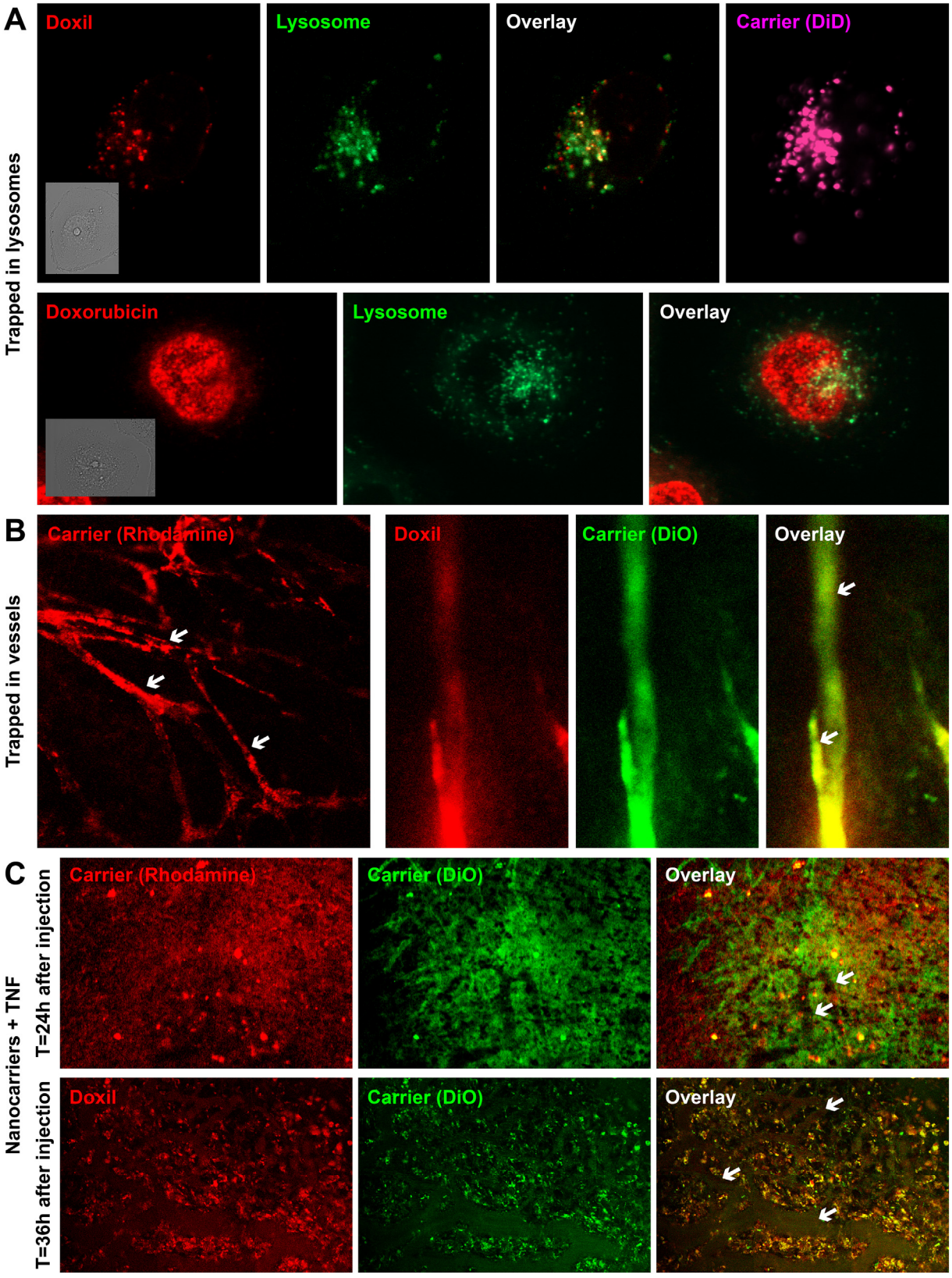

Fig. 3. Intravital images of nanoparticle fate in tumors. (A) Lysosomal sequestering of nanoparticles. Live cell imaging of human melanoma cells exposed for 24 h to Doxil with an incorporated DiD label or doxorubicin. Lysosomes are visualized using a live cell lysosomal marker-green. When administered as a nanoparticle doxorubicin and the carrier sequesters in lysosomes, whereas free administered doxorubicin is located in the nucleus. (B) Entrapment of nanoparticles in the vessels. Intravital imaging in a murine tumor 24 h and 36 h after administration of nanoparticles. Seen here is the presence of a placebo nanoparticle visualized with rhodamine or Doxil with an incorporated DiO label in the vasculature (white arrows) and no to minimal extravasation into the tumor tissue occured. (C) Extravasation of the same nanoparticle formulations combined with the vaso-active compound tumor necrosis factor alpha (TNF) 24 h and 36 h after systemic administration. Nanoparticles are found in the tumor interstitium with few nanoparticles remaining in the vasculature (white arrows). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

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3.2. Tumor-associated vasculature

Blood vessels consist of an endothelial cell lining surrounded by perivascular cells (i.e. smooth muscle cells or pericytes), and a basal membrane enveloping both cell layers. The endothelial cells form the inner lining of blood vessels, providing a dynamic barrier between the underlying tissue and the blood. Perivascular cells are wrapped around endothelial cells, provide structural support to the vessel tube and regulate vascular tone. However, the complex molecular association with endothelial cells suggests that perivascular cells serve more than just support [77,78]. Angiogenesis, the formation of new blood vessels from existing blood vessels, is tightly regulated under normal conditions and occurs in adults only under special circumstances such as wound healing and placental growth. However, under pathological conditions like tumor growth, the balance between pro and anti-angiogenic factors is in favor of angiogenesis, resulting in uninhibited, and importantly, uncontrolled angiogenesis. Because of this lack of control of tumor-associated vessels, many features of tumor vessels differ from normal vessels and display a lack of hierarchical branching organization in which the recognizable features of arterioles, capillaries and venules is lost [73]. Vessels are tortuous and unevenly dilated, with shunts being present between feeding vessels. As a result, tumor blood flow is chaotic, can be stationary, and can even change direction. Because of the relatively fast growth and abundance of pro-angiogenic factors such as VEGF, tumor vessels do not completely mature. Endothelial cells and pericytes are not nicely aligned [73,79] and gaps can be found in the vascular lining [80] making them leaky for fluid, molecules and nanoparticles. This vascular leakiness contributes, in combination with an ineffective lymphatic system, to an increased interstitial fluid pressure [81].

3.3. Tumor-associated stroma

Also stromal cells differ from healthy tissue in a way that limits drug delivery. Tumors tend to have an abundance of fibroblasts and infiltrating immune cells. While these normally provide regulatory, suppressive and constructive support, in tumors these cells contribute towards growth, as tumor cells may manipulate tumor-associated fibroblasts and immune cells towards a pro-tumoral status. These cells also serve vital roles in wound healing and it was Haddow who in 1972 asked the question, whether tumor growth can be considered a process of overhealing [82]. This question was later reexamined by Dvorak [83], seeing tumor stoma strongly resembling stroma of granulated tissue, and suggesting that tumors are equivalent to wounds going through a permanent healing response – or "a wound that never heals". During wound healing, fibroblasts synthesize extracellular matrix, maintain the microenvironment, and sustain cell growth. In later stages fibroblasts are responsible for remodeling the temporary extracellular matrix into a permanent composition which results in tissue contraction. Also in cancerous tissue these cells contribute to production of extracellular matrix components and remodeling enzymes. However, while in normal healing conditions, unwanted fibroblasts are removed via apoptosis, this safety feature is lost in the chronic proliferative tumor environment. Multiple layers of fibroblasts at high density are often found at the invasive front of a tumor [84], providing support and integrity of the tumor mass. These fibroblasts, together with overproduced matrix components, can form a dense wall between tumor cells and feeding vessels. This condition is referred to as desmoplasia and is for instance present in pancreatic cancer, where it is recognized as a major factor contributing to the poor response of pancreatic cancer to chemotherapy. Various approaches to reduce this barrier or enhance its permeability have been investigated to improve drug delivery [85,86]. In section 4 we will discuss how to improve nanoparticle accumulation in solid tumors using hyperthermia or vasoactive agents to manipulate the tumor microenvironment. Immune cells serve a pro-inflammatory role during the initial stages of wound healing and later have an anti-inflammatory role during the constructive processes of wound healing and tissue repair. As "a wound that never heals" tumor-associated immune cells are often polarized towards the anti-inflammatory pathway releasing several pro-tumorigenic cyto- and chemokines [87], as well as towards a tumor protective and tumor promoting direction. Immune cells present in the tumor can have a great impact on treatment outcome. Recent results clearly show that activation or modulation/manipulation of the immune system holds great promise and we think also in this field nanotechnology can play a significant and important role, which is however outside the scope of this review.

3.4. Enhanced permeability and retention (EPR)

Why would a nanoparticle, which is about a thousand-fold larger than the free drug, perform better in the treatment of solid cancer? As mentioned above, when accumulation of drugs in tumors was studied, circulation time directly correlated with intratumoral drug levels (i.e. the longer a drug circulated, the more was found inside a solid cancer). Notably, this longer circulation time is one of the main features provided by the nanoparticle. Matsumura et al. observed in 1986 that nanoparticles had the tendency to accumulate in murine solid tumors [62]. This phenomenon was termed the enhanced permeability and retention (EPR) effect and was attributed to the leaky tumor-associated vasculature and impaired lymphatic system, as recently reviewed by Golombek et al. [88]. Once a blood-born nanoparticle reaches the tumor site, as a result of the disorganized and permeable vasculature, the nanoparticle leaks out into the tumor interstitium and because of the lack of drainage has the tendency to remain there. This effect is mainly observed in experimental murine tumors and is less noticeable in human tumors. An effective tumor response solely based on the EPR effect requires a uniform permeability and retention throughout the tumor and this is usually not the case. Tumor heterogeneity is a major problem for effective drug delivery and is not only observed between tumors [89] but more importantly also spatially within a tumor [75,90]. Whether tumor areas are hypo- or hyperperfused, have mature vessels or leaky immature vessels, have functional or static blood flow, all these heterogeneities translate into the heterogeneity of the EPR effect. Matsumoto et al. argue that permeability of the vasculature also results from a dynamic process with bursts of extravasation occurring rather randomly [91]. The retention is attributed to the lack of drainage via a lymphatic system and due to a dense extracellular matrix compartment, and these mechanisms prevent nanoparticle penetration. Because a human cancer grows slower compared to experimental transplanted murine tumors, this heterogeneity in human cancers is even more prominent while vessels appear to be less leaky compared to animal models. Recently, Sindhwani et al. stated that nanoparticle extravasation does not proceed via endothelial gaps, but through a dynamic and active process possibly including transcellular channels [92]. If true, this may suggest alternate approaches to enhance nanoparticle based tumor uptake. The therapeutic efficacy of Doxil®, the first nanodrug approved for human trials, is superior to free doxorubicin in AIDS-related Kaposi sarcoma and advanced ovarian cancer [93,94]. For other cancer types however, the efficacy compared to free drug is rather modest [95–97]. Strikingly, administration of Doxil® gives an area under the curve (AUC) 600-fold higher compared to free drug [46,98], and this was thought to improve clinical outcome. The general conviction was that with a higher AUC in blood, more drug will get to the tumor because of the EPR, and thus a better tumor response is achieved. However, it turned out that the AUC in blood of a drug-loaded nanoparticle does not predict outcome. This is an important observation that relates to the bioavailability of nanomedicines, and will be discussed in more detail below. In our studies with murine tumors where we focused specifically on the location of both the carriers and the chemotherapeutic drug, we observed that nanoparticles remained predominantly in the vasculature and extravasation into the tumor interstitium was minimal during the first hours (Fig. 3B) [69]. In addition to the barriers limiting

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drug delivery discussed above, non-tumor stromal cells impair drug activity directly by absorbing a significant fraction of a drug in the tumor. By doing so, these cells sequester drug and thus lower the drug amount available for cancer cells, while also restricting drug penetration further into the tumor. This phenomenon is important to consider as resistance to chemotherapeutics is especially noticeable in the lower concentration range. Even drug delivery strategies using active targeting, in which nanoparticles are grafted with a specific ligand, still rely on passive extravasation and homogenous distribution throughout the tumor to effectively target all tumor cells, and therefore active targeting cannot overcome any inherent limitations of the EPR effect. Currently, there is a lot of controversy in regards to relevance of the EPR effect of Danhier [99] versus Man [100]. Therefore smart drug delivery systems that do not rely on the EPR effect are becoming of considerable interest.

A recent review paper by Wilhelm et al. suggested that the delivery efficiency of nanoparticles has remained low and did not improve throughout the last decade of intense research with an average tumor nanoparticle uptake of 0.7% injected dose per tumor in 2015, the same as it was in 2005 [101]. These results further suggest that the inherent limitation of nanoparticles based on the EPR effect are difficult to overcome by novel nanoparticle designs, and that an alternate strategy that does not depend on the EPR effect may be necessary to improve on this modest tumor uptake.

In addition to any limitations of the EPR effect, inadequate release or dissociation of the drug from the nanoparticle at the target site is a major limitation of many nanoparticles. Even if nanoparticles extravasate from the blood circulation into the tumor microenvironment, migrate across stromal compartments, and accumulate in high amounts in the tumor for extended duration, the encapsulated drug still needs to be released to become biologically active. Release from the carrier can be extra- or intracellularly, and for many chemotherapeutics, as is for instance the case for intercalating agents, the drug needs not only to enter the cell but also the nucleus. While commonly ignored, efficient and timely release of content by the nanoparticles is not trivial to achieve, and is a major focus in drug delivery research. For example, requirements for a liposomal carrier to achieve long circulation time and high stability are PEG coating, and either a robust bilayer of rigid phospholipids or cholesterol to reinforce the bilayer. In general, the required rigidity of nanoparticles for stable drug encapsulation becomes a limitation after nanoparticles enter the tumor interstitium, as most of the drug remains encapsulated and release is limited and too slow [68,69]. The resulting low bioavailable drug level is in part accountable for the low therapeutic efficiency compared to free drug administration and the need for repeated administration. Possible strategies to address this particular issue are discussed in the next section.

4. Improving drug and nanoparticle accumulation

4.1. Tumoral delivery of nanoparticles

As described above, intratumoral accumulation of nanoparticles is thought to result from the EPR effect. As also noted, EPR is a stochastic process and is now considered to be quite inefficient. One way to improve nanoparticle accumulation in tumors is by active targeting via ligands attached to the outer surface of the nanoparticles. It was assumed that decoration of nanoparticles with targeting ligands towards receptors that are highly overexpressed on tumor cells or tumor vasculature will improve intratumoral accumulation and increase cellular internalization [102]. However, there is now consensus that active targeting does not necessarily improve tumor accumulation of nanoparticles [103], and a recent review paper found on average an only modestly improved tumor drug uptake of 0.9% injected dose/tumor for actively targeted compared to 0.6% for passively targeted nanoparticles [101]. One disadvantage is that the addition of any antigen or recognizable moiety at the nanoparticle surface causes augmented clearance. This shortens circulation time [104,105], and since circulation time dictates tumor accumulation, tumor uptake is reduced [103,106,107]. We demonstrated that ligand modification of nanoparticles not only reduces penetration depth, but also that endocytosed doxorubicin-loaded liposomes remain inside lysosomes for extended duration [108]. Based on these observations, additional research has been conducted in an attempt to modify or exploit the tumor pathophysiology to improve or bypass EPR-driven accumulation.

Accumulation of a nanoparticles or drugs in tumors can be enhanced by improving perfusion. Strikingly, antiangiogenic therapy with VEGF neutralizing antibodies results in better perfusion of the tumor [109–111], and as most drugs are blood born, the augmented bulk fluid through a tumor results likewise in a higher drug delivery to the tumor. This however only helps the delivery of small (i.e. free drug) compounds as inhibiting VEGF results in vascular normalization and with that closing of the gaps between endothelial cells, thus eliminating the EPR effect [111,112]. We have demonstrated that the opposite approach is more effective, and showed that enhancing vascular permeability with Tumor Necrosis Factor alpha (TNF-a) – an effect we termed “vascular abnormalization” [113] - improved intratumor accumulation of free drug during isolated perfusion [114,115], and also improved the accumulation of nanoparticles when administered systemically [69,116]. This approach is based in part on the realization that tumor vessels less firmly attached to the matrix, which renders the endothelial cells more sensitive to certain cytokines, vasoactive agents such as TNF-a, and histamines [117–119].

4.2. Strategies to enhance tumor uptake

4.2.1. Modification of vascular function or vascular integrity

As noted, tumors have both features that can impair drug uptake as well features that can enhance uptake. Importantly, abnormalities in tumor vasculature, stroma and other microenvironmental conditions can be targeted and manipulated to specifically augment tumor drug uptake and thus outcome. Several strategies have been suggested in which the tumor-associated vasculature was exploited to improve drug delivery. Anti-angiogenic therapy not only inhibits new vessel growth, but also changes the tumor-associated vasculature more resembling normal vascular [110,111,120]. This normalization is associated with a reduction in interstitial fluid pressure and increased oxygenation, which both result in a better penetration of chemotherapy agents, as well as higher cytotoxicity of chemo- and radiotherapy [110,120]. This normalizing strategy is applicable to nanoparticles and agents less than 40 nm in size (e.g. free chemotherapeutic agents, or micelles), since larger nanoparticles are dependent on the abnormal tumor vasculature and associated EPR effect [111,121]. To enhance the accumulation of such larger nanoparticles requires alternate strategies, such as enhancing the permeability of the tumor-associated vasculature. We and others have demonstrated that co-administering of vasoactive compounds or external hyperthermia further enhances the already increased vascular permeability to obtain a better and more homogeneous nanoparticle distribution [69,122]. This strategy is particularly relevant for augmenting extravasation of larger particles, like liposomes. We demonstrated that a low, non-toxic dose of TNF-α specifically augments the intratumoral drug accumulation of doxorubicin-containing liposomes, and by doing so, renders a prior ineffective dose into an effective one. Specifically, a dose regimen of Doxil® that initially had 100% non-responders, produced a partial or complete response in 75% of the subjects when combined with TNF-α [69,123,124]. We also found that the addition of TNF-α augmented intratumoral drug concentrations more than 6-fold by increasing permeability of the endothelial lining (Fig. 3C) [69,116]. Others demonstrated that nanoparticles can be used to deliver plasmids to modify pro- to anti-tumorigenic properties of cancer-infiltrating fibroblasts, as demonstrated by Miao et al. [125]. Furthermore, reducing the extracellular matrix decreases the interstitial pressure, resulting in a better tumor perfusion and improved drug uptake [126]. As an example, Losartan, an angiotensin II receptor

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antagonist, augments nanoparticle accumulation not only by degrading collagen and thereby enhancing tumor perfusion [72], but also through inhibiting cancer-associated fibroblasts that are responsible for collagen production [127]. In addition to sequestration of drugs, fibroblast can also physically block drug penetration. This is the case for example in pancreatic cancer, where fibroblasts together with the tumor matrix form a wall between tumor vessels and tumor cells. Olive et al. show that depletion of this stromal barrier in pancreatic cancer greatly improves drug delivery and improves survival in a mouse model [128]. Particularly relevant for this review is that mild hyperthermia is able to manipulate the tumor-associated vasculature to enhance uptake [32], and this topic will be discussed in the next section.

4.2.2. Mild hyperthermia as facilitator of nanoparticle delivery

Localized hyperthermia therapy, which consists of artificially raising of the temperature in a part of the body, is used clinically in various forms (Fig. 1). At higher temperatures, above 50 °C [129], it is used to directly kill tumor cells, and is termed "thermal ablation" [130,131]. At lower temperatures of around 42 °C, it is referred to as mild hyperthermia, with a number of clinical applications and physiological responses as documented by Issels et al. [2]. In their review, the 'hallmarks of hyperthermia' are listed as: (1) blocking cell survival, (2) inducing cellular stress response, (3) modulating immune response, (4) evading DNA repair, (5) changing tumor microenvironment, and (6) sensitization to radiation and chemotherapy. To this we can add mild hyperthermia as a trigger for controlled drug release from thermosensitive nanoparticles as described in detail in section 6. Raising the whole body temperature as happens during fever, or locally raising the temperature through an external energy source, induces a number responses, some likely still unknown. When hyperthermia is applied to tumors, either direct cell kill may be achieved, or the cells become sensitized towards radiotherapy and chemotherapy, possibly in part due to interference with DNA repair mechanisms by degradation of BRCA2 [132,133]. A combination of standard chemotherapy with regional hyperthermia improved both short-time but and long-time (10 years) survival in sarcoma patients [134,135]. As Killock states, regional hyperthermia affects a range of cellular targets and processes, including DNA repair, the tumor microenvironment, and anticancer immunity, which might explain the consistent prolonged benefit [136]. We will later also discuss the effect that hyperthermia has on the tumor microenvironment with respect to nanoparticle-mediated drug delivery.

As already mentioned hyperthermia can be used to augment the EPR effect. For example, Huang et al. observed that intratumoral drug levels where 1.5-fold higher when tumors were exposed for 30 min to 42 °C after injection of liposomal doxorubicin compared to 37 °C (Fig. 2). In comparison to free drug, drug levels after liposomal doxorubicin administration was 15-fold higher, suggesting that hyperthermia is most beneficial when combined with a long circulating drug or formulation [137]. Nevertheless, hyperthermia also improves accumulation of drug and outcome when combined with free drug through modulation of intratumoral fluid dynamics such as increased blood flow and vascular permeability [138,139]. Kong et al. show that exposing tumors in vivo to 42 °C for 1 h increases the pore cutoff size of tumor vessels to >400 nm allowing all tested liposomes (100 to 400 nm) to extravasate, whereas at normothermia cutoff size was between 7 and 100 nm and liposomal preparations did not extravasate [140,141]. We previously observed that large gaps between endothelial cells occur after mild hyperthermia in all tumor types tested and that this process is reversible with tumor vessels returning to the initial condition within approximately 8 h [32]. This hyperthermia response is absent in normal vessels. While hyperthermia has shown benefits for nanoparticle delivery, it still relies nanoparticle extravasation, and only a small fraction (~1 to 5% of the injected dose per gram tumor tissue) are taken up by tumors [142,143]. In addition, the limited bioavailability of the still encapsulated drug is not addressed by this approach, and section 6 focuses specifically on this topic.

5. Devices for local hyperthermia

A wide variety in systems exists for the application of local hyperthermia, employing various energy sources, and for different treatment volumes. The differences are in the method of energy transfer to tissue, the size of the volume that can be heated, externally or internally applied energy and finally the ability to control the temperature within the desired range of a few degrees Celsius. In general, hyperthermia systems providing better spatial control of heating involve more complex technology for heating and temperature monitoring, and are more costly. Other relevant factors related to the integration into the clinical workflow are discussed elsewhere [144–146].

5.1. Devices for externally applied hyperthermia

Most clinical hyperthermia systems are based on electromagnetic (EM) energy to heat tumor and the surrounding tissue [147]. The interaction of EM fields with tissue results in drift of ions and oscillation of electric dipoles (i.e. water). The resulting friction produces tissue heating. The specific heating mechanism depends on the frequency and direction of the EM field as well as on the electrical properties of tissue. A benefit of EM based hyperthermia systems is their ability to heat large (up to 10–15 cm, Fig. 4) tissue volumes independent on location within the body. At frequencies of >50 MHz transfer of the EM energy is radiative whereby increasing the frequency results in a smaller heating focus and reduced penetration depth. Small and large sized superficially located tumors with depths up to 4 cm from the skin are in general heated at the frequencies approved for medical use, which are of 434 MHz in Europe and 915 MHz in the USA. Optimal spatial control is obtained by using multiple (2–24) applicators, while controlling the energy output of each individual applicator. Annular phased array applicator systems consisting of 4–12 applicators with constructive interference are used to heat advanced, deep seated tumors in the abdomen or pelvis region. Hyperthermia treatment planning is often employed to calculate the optimal phase and amplitude setting to maximize tumor heating. In general, radiative hyperthermia systems are considered the most advanced technology as they allow for dynamic adaptation of the spatial energy distribution. Alternatively, radiofrequency capacitive hyperthermia systems are available that can heat both superficial and deep located tumors. Capacitive hyperthermia systems use less complex technology, but lack spatial control of the energy distribution. A disadvantage of capacitive systems is that only the total amount of applied energy can be controlled, and during deep hyperthermia preferential heating of the fatty tissue occur. The latter limits the use of this technology for heating of deep seated tumors in the pelvic region to patients with a fat layer less than 2 cm thickness [148].

High intensity focused ultrasound (HIFU) is increasingly clinically used for high-temperature application (i.e. thermal ablation), but less widely employed for mild hyperthermia therapies [149]. The pressure wave applied during HIFU causes small tissue vibrations, and the resultant friction produces heat. Clear advantages of HIFU over EM heating are the deep penetration and the ability of very focused heating [130]. One disadvantage of HIFU is the high reflection at air (99%) and bone (60%) interface as well as the high absorption in bone. Therefore, not all locations are accessible by HIFU since it requires that no air or bone (e.g. lung, rib cage) are present between the ultrasound transducer and the target tissue. With current HIFU systems, small tumors with a diameter up to 3 cm at deep locations up to 15 cm can be heated. For larger tumors with a size up to 15 cm, planar multisource ultrasound applicators maybe be used. Alternatively, by applying HIFU with a blurred focus in combination with rapid electronic scanning of the focus it has been shown that superficially located tumors with a diameter up to 5 to 6 cm can be heated (Fig. 4). Enhancing the ability to heat large tumors at depth is still subject of ongoing research [150].

Several studies have investigated the combination of HIFU hyperthermia with heat-triggered SDDS [150–154], and results of a Phase I

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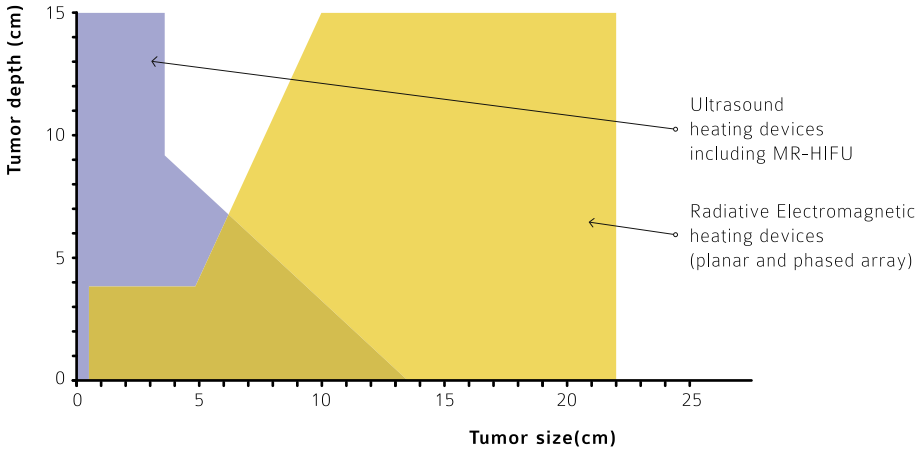

Fig. 4. Heating properties of ultrasound (US) and radiative electromagnetic (EM) heating devices. Capacity to heat efficiently tumors of certain size (x-axis) and at certain tumor depth (y-axis) is depicted. EM allows heating of large tumors at most, if not all, body sites, while US can be used for smaller, or more superficial tumors.

trial in liver cancer patients have recently been reported (Clinical trial number NCT02181075) [155]. The ability of accurate spatial targeting combined with guidance of hyperthermia by MR thermometry allows for accurate control of tumor temperature within the ideal temperature range, and very promising tumor responses have been achieved with complete regression reported by two recent animal studies [153,154]. Another subject of research has been the co-encapsulation of MR contrast agents together with a drug in heat-triggered SDDS [138,150,156], allowing MR imaging of contrast agent release to serve as surrogate for drug release [157–160].

5.2. Devices for internally applied hyperthermia

In devices for internally applied hyperthermia, an applicator is placed in the tumors (i.e. interstitially), usually guided by medical imaging such as ultrasound, computed tomography (CT), or MR imaging. As the device is placed directly in the tumor, heat is localized within the tumor with limited heating of distant tissues [161]. Various devices for internal hyperthermia have been described [162], and particularly those based on ultrasound and microwave heating have achieved promising results. Typically, such devices require placement of a probe or catheter (usually ~1–3 mm in diameter) in or near the targeted tissue region (e.g. tumor). Internal ultrasound based devices may employ multiple transducers and are able to provide directional heating [163–166], and such devices have been clinically investigated for treatment of prostate cancer and benign prostate hyperplasia by hyperthermia [167,168]. A recent microwave based device provides directional heating as well [169], and both ultrasound and microwave based internal hyperthermia devices have been combined with MR thermometry to provide real-time feedback on tissue temperature [164,166,169]; this aspect is important when combined with heat-triggered SDDS, since target tissue temperature needs to be controlled within a relatively narrow temperature range (ideally ~40–43 °C).

To limit damage to tissue during placement of the hyperthermia device, the applicator is ideally small enough in diameter to allow a minimally invasive approach. Magnetic nanoparticles (MNPs), like iron oxide particles, have been investigated for hyperthermia because of several specific features [170]. The small size allows them to reach the tumor cell, they can be tagged with tumor antibodies, the magnetic properties can be used to target the MNPs to the tumor, and in combination with a time-varying magnetic field the MNPs can be used to heat the tissue. Depending upon the goal, MNPs have been administered by various routes. Direct intratumoral injection of the MNPs is reported to be most effective for bulk heating of the tumor in animals, but is problematic in larger tumors due to heterogenous MNP distribution. MNPs can improve drug uptake by: 1) facilitating extravasation of the chemotherapeutic drug when applied in a systemic way, i.e. heat from the MNPs increases vascular permeability, or as packaged in thermosensitive liposomes (TSL), i.e. heat from the MNPs trigger the release of content from TSLs. And 2) heat from the MNPs present in the tumors may cause thermal sensitization of the tumor cells to the chemotherapy. When MNPs are applied intravenously the tumor concentration of MNPs achieved is usually insufficient to induce adequate tumor heating. An alternate strategy that has been examined is the encapsulation of MNPs in TSLs to enable triggering of drug release from TSL by magnetic fields [171].

5.3. Thermometry

Accurate thermometry during hyperthermia requires either the insertion of interstitial catheter for invasive temperature measurements using multi-sensor probes, or some type of image-based thermometry. When a hyperthermia system is integrated with magnetic resonance imaging (MRI), a 3-dimensional temperature distribution can be measured using non-invasively based on MR-thermometry [172,173]. Typically, MR thermometry is based on the temperature dependence of the proton resonance frequency [174]. A disadvantages of MR thermometry is the susceptibility to motion artifacts, which is problematic in some organs where movement is prevalent such as the liver, or pelvic and abdominal regions where movement of intestines is an issue. MR-thermometry works well in locations without movement, such as in soft tissue sarcomas in the extremities, temperature measurement in the pelvic and abdomen region are more affected by movement of intestines and the patient. In addition, research is ongoing to investigate the potential of the MRI relaxation parameters R1 and R2 as a parameter to quantify cargo release of TSLs [159,160].

5.4. Devices for thermochemotherapy

All hyperthermia systems can be used in combination with systemic applied chemotherapy or with more advanced nanoparticles, such as thermosensitive liposomes as will be discussed in section 6. The difference between the hyperthermia systems is in their ability to provide preferential heating of the target volume, i.e. the bulk tumor with a safety margin around it, and the heterogeneity in the temperature distribution. Typically, HIFU provides the most targeted heating volume, but at the same time still has clinically relevant limitations in tumor size and location. Of the EM based systems only the radiative hyperthermia systems possess the ability to adapt the heating volume to the tumor and minimize normal tissue heating. Given the ability to heat

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large tumors, radiative EM hyperthermia systems can be considered to combine with nanoparticle smart drug delivery systems without limitations for tumor size and location. The latter does not apply for radiofrequency capacitive systems as these systems lack the ability to direct the EM energy to the tumor volume. Hence, for radiofrequency (RF)-capacitive systems, preferential tumor heating is only possible when the tumor has a lower blood perfusion than the surrounding normal tissue. The latter requirement of a low perfusion is however conflicting with the ability of the nanoparticles to reach the tumor center. For the combination of smart drug delivery systems with MNPs high expectations exists with respect to its features for tumor specific heating, increased drug delivery via magnetic targeting and of triggered drug release via encapsulation of MNPs in TSLs [175].

6. Smart drug delivery systems (SDDS) in hyperthermia

6.1. Introduction to smart drug delivery systems

Smart Drug Delivery Systems (SDDS) can be defined as structures which incorporate chemotherapeutics, or agents which have an activity that benefits tumor therapy, and combine that with an additional functionality in order to improve treatment outcome. An example would be a nanoparticle containing a chemotherapeutic agent that by a tumor specific trigger, or responds to an external trigger applied in the tumor region, releases content. Tumor specific, internal triggers include a lower pH [176,177], increased redox [178] or enzymatic activities [179]. External triggers to which SDDS respond include temperature, light, ultrasound, electromagnetic fields, and x-rays [180–185].

The properties of the encapsulated drug, such as pharmacokinetics and biodistribution, are determined by the carrier. After exposure to the trigger, for instance mild hyperthermia (~40–43 °C) [186], the encapsulated drug is released. The intratumoral concentration of free drug is therefore determined by the locally inherently present or locally externally applied trigger.

Improvement of site specific accumulation with subsequent cellular or subcellular delivery of the drug into tumor cells with a spatiotemporal control of drug release has long been an unsolved problem for the scientific community [187–189]. Using unique pathophysiological features of tumor environment combined with the knowledge of design and fabrication of nanoparticles enabled scientists to equip nanoparticles with a variety of different kinds of functionalities to improve cellular drug delivery. To date, a variety of stimuli responsive nanoparticles with one or multi-stimuli responsiveness have been designed and fabricated [190,191].

Endogenous trigger-sensitive nanoparticles mainly suffer from a lack of defined and site specific response due to diminutive and heterogeneous differences between normal and malignant tissue as tumor-characteristics tend to be broad and overlap with conditions in healthy tissue. Besides, the kinetics of enzyme activity or redox reactions are relatively slow, limiting responsiveness. Importantly, the delivery of these particles mainly relies on the EPR effect and the stimulus is passive, i.e. active spatiotemporal control is not possible (Fig. 5). Exogenous stimuli such as light [192,193], ultrasound [194–196], electromagnetic waves [180,185] and heat on the other hand not only provide an active spatiotemporal control of drug release, but it has been demonstrated that some external stimuli such as sonoporation [197,198] or hyperthermia [32,66,199] improve tumor permeability for nanoparticles. Thus, a more precise and controlled release of content from trigger-responsive nanoparticles can be achieved through the use of a non-invasive triggers such as mild hyperthermia as discussed in section 5 (Figs. 1, 6).

Here, we will focus on heat-responsive nanoparticles as this type has been studied most widely and progressed the furthest towards clinical translation. Such nanoparticles with heat-triggered release functionality can be broadly divided into two main groups: liposomal based and polymeric based nanoparticles. For both types, the driving force for drug release is a physical phase transition in response to temperature.

Thermal responsiveness of thermosensitive liposomes (TSLs) mainly relies on permeabilization of the lipid bilayer at grain boundary defects formed between solid phase domains and liquid phase domains during phase transition of DPPC [200,201]. While liposomes composed of pure 1,2-dipalmitoyl-sn-glycero-3-phosphocholine (DPPC, membrane transition temperature (Tm) 41.5 °C) have a slow release rate over a wide temperature range, by addition of other phospholipids (e.g. 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), Tm 54 °C), alkylphosphocholines (e.g. hexadecylphosphocholine (HePC)) [202] or lysophospholipids (e.g. 1-palmitoyl-sn-glycero-3-phosphocholine, 1-stearoyl-sn-glycero-3-phosphocholine) [203] one may adjust both transition temperature and release rate [204]. DPPC-based TSLs can be tuned to release content fast (within seconds), and release rate is affected by presence of serum components as well as percentage of PEG; in our studies, 5 mol% of PEG provided the best results [205]. Pegylation not only provides steric hindrance and the prolonged circulation time discussed earlier, but also stabilizes the leakiness of TSLs at physiological conditions.

In polymer based nanoparticles, thermal responsiveness results from a change in solubility of polymers in aqueous medium in response to a temperature changes [206]. Two types of polymers, those exhibiting a lower critical solution temperature (LCST), having lower solubility at

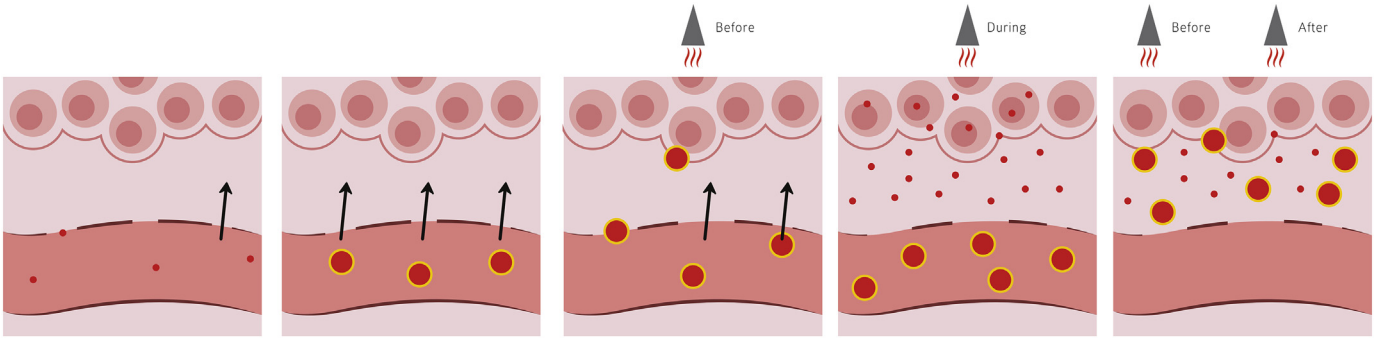

Fig. 5. Depiction of intratumoral drug delivery when using different treatment strategies. Only limited free drug will pass the tumor but will have, when unbound, easy access to enter the tumor because of the small size (sub nm range). When encapsulated in long circulating nanoparticles (NPs) more drug will pass the tumor and more could enter the tumor interstitial space. However, tumor characteristics discussed in the section 3 impair extravasation. When mild hyperthermia is applied before administration gaps between endothelial cells become larger and NPs are able to extravasate. Drug release occurs after that passively. Alternatively, drug release can be initiated by locally applied hyperthermia. First, during and after administration the tumor region is heated causing instant release of content while NPs are still in the bloodstream. Free drug diffuses into the tumor interstitial space and is taken up by tumor cells. Secondly, preheating is combined with heating during administration. The pre-heating promotes extravasation of NPs and when maximum accumulation is reached a second heat does is given to trigger release of drug.

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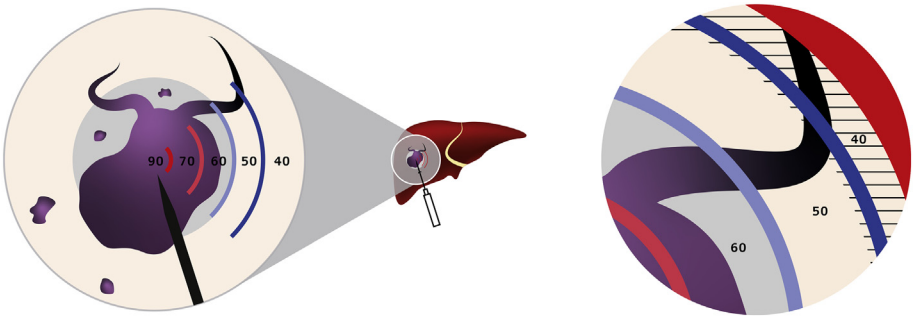

Fig. 6. Graphic illustration of radiofrequency ablation (RFA) of a liver tumor in combination with doxorubicin-loaded thermosensitive liposomes (DTSLs). The liver tumor is heated centrally causing a temperature gradient outwards leading to direct cell kill in the grey colored area. The pushing front at the bottom of the tumor, the infiltrating tumor parts at the top, as well as metastases outside of the ablation zone are not directly affected. At the periphery and around the tumor a zone exists in which tumor cells are not killed directly by the heat but a mild hyperthermia is reached which triggers DTSLs to release content causing cell kill in that region. In the zoom in on the right the ablation zone (grey), mild hyperthermia zone (beige) and zone in which doxorubicin release is maximum (red) is depicted. As DTSLs have a sharp optimum release-temperature release outside this temperature region, both above and below, is impaired or absent. This may cause insufficient drug levels in the region between ablation and triggered drug release (stripped area) as well as in the region close to body temperature. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

increased temperatures, and those exhibiting an upper critical solution temperature (UCST), having higher solubility at increased temperatures, have been employed for fabrication of temperature-sensitive polymeric nanoparticles, such as micelles, nanogels and nanoparticles. Poly-N-isopropylacrylamide (PNIPAAm) is of the most studied polymer in this field. At temperatures below the LCST, hydrogen bonding interactions with water keep this polymer in an expanded coil state due to the dominant effect of the hydrophilic part of PNIPAAm. An increase in temperature weakens the hydrophilic hydrogen bonds making the hydrophobic effect predominant, in which polymer-polymer interactions outbalance polymer-water interactions; as a result, polymers phase-out from the solution resulting in a collapsed globule state. Upon this temperature dependent transition in polymer solubility a swollen hydrated polymer turns into a shrunken dehydrated polymer accompanied with about 90% volume loss, accompanied by drug release. However, PNIPAAm alone is not suitable for heat triggered release nanoparticles. Introduction of more hydrophilic residues by *co*-polymerization of PNIPAAm with hydrophilic monomers [207,208] successfully increased the LCST. Copolymerization with hydrophobic monomers [208–210] enhances micellar formation, incorporation yield of hydrophobic chemotherapeutics and stability of nanoparticles in aqueous media. Importantly, almost all these thermosensitive polymeric nanoparticles exhibit a release at temperature below the LSCT and require long duration of hyperthermia, up to few hours, to release a significant amount of their payload, which is difficult to translate to the clinical setting and which limits successful testing in preclinical investigations. While the response rates of purely polymeric nanoparticles were not encouraging, the introduction of thermosensitive polymers on the outer surface of liposomes provided much faster release rates, however at a relatively high temperature of 45 °C [211,212], where vascular destruction/shutdown may impair blood perfusion and thus limit TSL supply to the target region. Thermosensitive polymer-modified liposomes have been reviewed by Kono [213] and Al-Ahmady et al. [214].

More sophisticated hybrid nanoparticles in which TSLs or thermosensitive polymers were combined with a metallic nanoparticle have also attracted considerable attention. Such systems do not rely on direct heat application, but heat is generated by the metallic nanoparticle in response to other external stimuli such as electromagnetic fields (EMF) or light. While the use of light has limitations related to a limited penetration depth in tissue, EMF provide more precise spatiotemporal control on drug release and offer magnetic guided targeting and theranostic applications. Iron oxide nanoparticles can be encapsulated inside [215] or incorporated in the bilayer [216] of DPPC-based liposomes for EMF-induced triggered release. Gold nanoparticles have also been associated with DPPC-based liposomes for release triggered by ultra violet [217,218] or near infrared light [219,220]. However, in addition to the complexity in formulation of stable preparations of those types, the release rate of these hybrid systems is relatively slow (i.e. a few minutes for a significant release) and still needs to be improved.

6.2. Intravascular triggered release from SDDS

The intravascular triggered release paradigm is based on drug release from the nanoparticle within the vasculature, i.e. while blood and nanoparticle transit through the tumor. It has been established that for this intravascular triggered release paradigm, triggered nanoparticles with rapid release (i.e. within seconds) are required [221].

Yatvin et al. published the first design of a lipid-based nanoparticle which responds to mild hyperthermia by triggered release of the contents [222]. This TSL consisted of DPPC:DSPC (3:1 by weight) with maximum release over ~30 min, at a temperature range of 42.5–44.5 °C. Over the recent decades this prototypical formulation has considerably evolved in order to improve its therapeutic potential, with the goal of improving stability and enhancing the release rate. By increasing the DPPC to DSPC ratio, a faster and sharper release at lower temperatures was achieved [223–226]. However, release kinetics were still relatively slow, circulation time in animal models short and aggregation occurred [137]. Incorporation of GM1 increases circulation time of liposomes [65]. However, the release rate was not sufficient as only 45% of encapsulated doxorubicin was released after 5 min incubation at 42 °C. To reduce the premature release, Gaber et al. incorporated 16% cholesterol (half of what is required to abolish phase transition) and show that 60% of content was released within 30 min [227]. We and others incorporated PEGylated phospholipids [205,227], which not only prevented aggregation and prolonged circulation time, but also accelerated triggered drug release at the membrane transition temperature (Tm). It has been postulated that PEG stabilizes membrane deformation and grain boundaries and therefore facilitates rapid transfer of the amphiphilic drug doxorubicin [228].

For nanoparticles based on the intravascular triggered release paradigm to be most effective, TSLs have to fulfil two basic requirements. First, after injection and during subsequent circulation the formulation should be as stable as possible with minimal clearance, minimal release of content and minimal accumulation in off-target sites. Second, TSLs in this setting need to release content fast and efficient, ideally within seconds as is discussed elsewhere in this issue. In addition, the properties of the encapsulated drug affect delivery efficacy. Ideally, the released drug easily penetrates the tumor, crosses the vascular wall rapidly, and has a fast diffusion in the tumor interstitial space, with rapid cellular uptake. As shown in Fig. 5, TSLs enter a preheated region and while traversing through this region release content within the bloodstream. Clearly,

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transit time through the heated area is short demanding fast release. Moreover, as all drug is released in the blood, transport away from the tumor by blood flow is likely, hence the need for fast extravasation and diffusion of the released drug. We demonstrated using intravital microscopy that optimized DPPC-DSPC pegylated TSLs release instantly massive amounts of drug at 42 °C, either carboxyfluorescein (a model drug), or the agent doxorubicin, resulting in over 30-fold delivery enhancement of doxorubicin compared to doxorubicin administered as a free drug [122,205]. Manzoor et al. observed by intravital microscopy that intravascular triggered release from TSLs resulted in deep penetration and homogeneous intratumor distribution of doxorubicin, while administration of free doxorubicin, and hyperthermia, only resulted in low levels in some parts of the tumor [33]. Additionally, when doxorubicin-loaded TSLs were combined with local hyperthermia, we observed by intravital microscopy massive uptake of doxorubicin by endothelial cells [122]. Resulting vascular damage could very well explain part of the improved tumor response we and others have reported [122,229,230]. An important step forward in the application of TSLs for solid tumor treatment is the introduction of lysophospholipids into liposomes, which based on their characteristics render fast (within seconds), release of doxorubicin. Needham et al. incorporated lysolipids in so-called low temperature sensitive liposomes (LTSLs) [231] resulting in the thus far most successful TSL formulation that is currently being commercialized under the name Thermodox® [228]. First clinical trials have been conducted using Thermodox® (doxorubicin loaded TSLs) in combination with radiofrequency ablation (RFA) for liver cancer (Clinical trial number NCT02181075) [232], as well as together with microwave hyperthermia for recurrent chest wall cancer [233]. With RFA the tumor is heated to a temperatures above 50 °C, directly killing tumor cells by heat [234]. For liver-confined liver cancer (Fig. 6) such as hepatocellular carcinoma (HCC) RFA might provide a possibility to control local disease [235,236]. However, as the tumor spreads in surrounding tissue effective ablation of all tumor tissue may not be reached. To this end TSLs are co-administered as around the ablative zone a region with mild hyperthermia is established in which TSLs are triggered to release content [237–239]. The first Phase III trial of this combination therapy (HEAT trial; clinical trial number NCT00617981) shows no therapeutic benefit of this combination in HCC patients, with the exception of a subgroup of patients with solitary tumors and a RFA dwell time of more than 45 min [240]. Further analysis of this trial identified several issues which may have contributed to the trial failure [241]. More so, the intrinsic instability of LTSLs together with the late start of heating may have been crucial. Plasma clearance of doxorubicin in patients receiving 50 mg/m^2 Thermodox® shows a rapid buildup of free doxorubicin of about a third of the total doxorubicin administered, reaching maximum at 30 min, which is also the end of infusion of Thermodox® [228]. Thus Thermodox® instantly releases a significant portion of the encapsulated doxorubicin when in contact with blood, which will be cleared fast and is not likely to reach the tumor. Together these factors, treatment setup and plasma clearance, indicate that a significant fraction of LTSLs passing the tumor had already released doxorubicin before getting to the heated area, i.e. the tumor, certainly if the tumor is heated after Thermodox® is injected. Secondly, elaborating on the sufficiently heated area concept, in our vision combining RFA with a lipid-based nanoparticle is not a happy marriage. Liver cancer, for instance HCC and metastasis of colorectal cancer, have a infiltrative or expansive growth pattern [242], and may be multifocal [243]. As boundaries may not be clear, tumor may extend into the liver or metastasis may be present and as a result not all tumor tissue is ablated. To solve this LTSLs are added which release content in the sub 50 °C heated area; or at least that is the hypothesis. In Fig. 6 we show RFA of HCC, showing both infiltrative growth and metastasis. The ablated region is indicated as well as the temperature zones around this region in which temperature drops until it reaches body temperature. It is crucial to realize that lipid-based thermosensitive SDDS have an optimal temperature, the membrane transition temperature (Tm), at which release is maximum [203,204,226]. Below, but also above the Tm release drops rapidly, both in rate and in maximum amount. This means that only in a defined and limited area doxorubicin is efficiently released resulting in regrowth of the cancer from those parts. Finally, as we discuss below, doxorubicin might not be the best drug choice for liver cancer [199].

Nevertheless, based on the response of a sub-group of patients in the RFA + Thermodox® trial (HEAT trial) where RFA duration was above 45 min, pre-clinical follow-up studies were performed. These studies demonstrated that drug delivery is enhanced at longer heating durations [237,239]. Results are expected from a follow-up phase III trial (OPTIMA) combining RFA with Thermodox® which completed enrollment in August 2018 (clinical trial number NCT02112656) [244]. The Data Monitoring Committee recommended recently to continue the trial as progression free survival was better than observed in the HEAT trial while other data is consistent which what was observed in the HEAT trial subgroup [245]. This suggests that a longer RFA dwell time of 45 min or more may render better results and may reduce local recurrence.

Recently the TARDOX phase I trial using HIFU-induced mild hyperthermia demonstrated that local HT results in a 3.7-fold increased intratumoral drug concentration comparing drug levels before HIFU induced drug release and after HIFU [155,246]. While these results are not as promising as prior pre-clinical studies, this was the first study demonstrating in human tumors that tumor drug uptake can be enhanced with thermosensitive liposomes. For example, prior studies in a rabbit liver tumor model with HIFU hyperthermia and Thermodox® showed a 26.7-fold increase in tumor drug uptake [247]. One limitation of the TARDOX trial likely contributing to the lower tumor uptake than in preclinical studies was, that tumor temperature in this trial was not accurately controlled or monitored [241,248]. Another contributing factor was the delay after injection of Thermodox® before heating was started [155]. And this is a crucial aspect in intravascular triggered drug release. As stipulated above and depicted in Fig. 2, TSLs are in general unstable in circulation, irrespective of size, pegylation or other long circulating properties. For instance, as mentioned above, Thermodox® leaks part of the contents during infusion [249,250], which can however be reduced by adding up to 10% cholesterol without affecting release rate [251]. In addition, TSLs tend to have significantly shorter plasma halflives (typically around 1 h) compared to a liposomal stealth formulation like Doxil® (i.e. days) [46,142]. Thus, pre-heating of the tumor prior to injection may be beneficial; in the two mentioned trials, hyperthermia was applied for 12 min to 1 h when combined with RFA (HEAT trial), and around 40 min when used with HIFU hyperthermia (Tardox trial) [155,252]. A direct correlation exists between the duration of hyperthermia, and the locally delivered drug concentration [253], although the used temperatures of 45 and 50 °C are relatively high and vascular damage is likely in close proximity of the heating probe. The instability of TSLs and the need for optimal temperature at the target zone (i.e. tumor) preferably at the Tm and such that tumor vessels are not damaged introduces another important factor. When TSLs pass through regions with inadequately low temperature, triggered release is slow and partial. Uneven heating, unheated tumor zones, and zones with too much cooling are examples which negatively affect triggered release and therefore outcome [241]. This is in addition to heterogeneous distribution of the TSLs because of above discussed tumor vasculature related inadequacies. If one would argue, and unfortunately this does happen, that therefore it would be better to set the local target temperature higher, this is for several reasons ill-advised. First, overheating a region is often accompanied by a higher chance of unwanted side-effects such as burns, heating duration limiting pains and damage to healthy tissues. Second, when local temperatures are above 42 °C, endothelial damage in tumors occurs, resulting in destruction of vessels, stasis and thus poor perfusion of that region, resulting in poor drug delivery. Thirdly, as mentioned above, TSLs show impaired triggered drug release when temperatures are applied above the Tm, and show fastest release at

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the Tm as explained by Papahadjopoulos et al. [204] and Lu et al. [226]. More recently the group of Lindner et al. developed a new non-PEGylated TSL in which 1.2-dipalmitoyl-sn-glycero-3-phosphoglyceroglycerol (DPPGOG or DPPG2) was used to enhance the circulation time of liposomes, with promise of no reduction by accelerated blood clearance upon repeated injection as is shown to result from the use of PEGylated products [254]. Like PEG, DPPGOG also facilitates temperature-triggered drug release and shows comparable release rates as that observed in lysolipid-based TSLs with however a higher degree of stability at 37 °C [255]. Since the optimum size for long circulation is between 70 and 200 nm they used 200 nm liposome size to take the advantage of higher drug/lipid ratio where doubling the size increases available loading volume by eightfold that leads to more efficient intravascular drug release. These allow the DPPG2 TSL to circulate long and therefore the possibility to pass the hyperthermic area after injection more often. Doxorubicin-containing DPPG2-TSL combined with local hyperthermia indicated promising therapeutic effects in treatment of feline soft tissue sarcoma in advanced stage of disease [256]. Interestingly the maximal tolerated dose was not reached in this trial indicating that possibly higher doses can be used with the chance of higher response rates. We previously published a better response when using optimized DPPC based TSLs with doxorubicin compared to LTSLs [122]. This may result from the reduced stability of LTSLs mentioned above resulting in a significant level of free doxorubicin in circulation while no hyperthermia is applied. Moreover, that could also explain why in this study mice treated with LTSLs without heat show a better tumor response compared to DPPC-based TSLs. The group of Dewhirst compared different TSLs: classic cholesterol containing TSL responding optimally to 42°-45 °C, LTSLs responding to a lower temperature of 39–40 °C and non-temperature sensitive liposomes [257]. They found LTSLs to be superior in drug delivery and tumor response, which may be explained by the slow release from the classic TSLs, which contained 16% cholesterol as well as a relatively low percentage of DPPC (54%) [257]. To ensure fast release from DPPC-based TSLs a DPPC content of 70–80 mol% is optimal, and cholesterol should not be included [258].

Interestingly, intravascular release may introduce an aspect not encountered when drugs are injected in the free form: a local concentration too high to be accumulated in time by tumor cells. Intravascular triggered release as explained above results in a rapid buildup of free drug in a relatively small volume. We and others observed a decline in drug levels after heating was stopped and drug not yet taken up by cells diffused back to tumor vessel [122]. One way to deal with that is using drugs which are rapidly taken up by cells (Fig. 7). We published recently fast and efficient uptake by tumor cells of idarubicin, a more hydrophobic anthracycline, and when incorporated in TSLs a superior local drug accumulation and tumor response results (Fig. 2) [199].

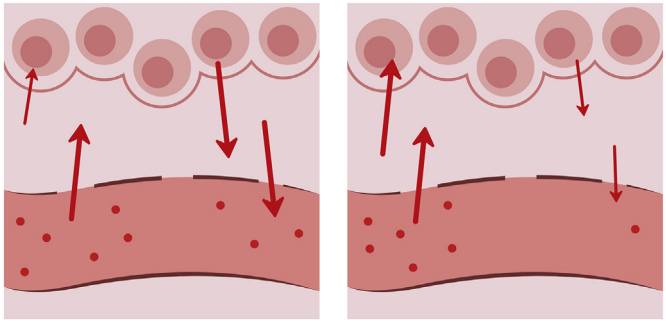

Fig. 7. Depiction of the effect of drug uptake and retention in tumor cells on intratumoral drug kinetics. In the left panel a drug is represented with fast diffusion but slow cellular uptake and poor intracellular retention. The net result is a relatively low concentration in tumor cells and a high exposure to healthy tissues. The right panel represents a drug with comparable diffusion but fast cellular uptake and high intracellular retention. Here the concentration in cell will be higher and more likely capable of killing while systemic levels remain lower.

These observations are in agreement with a different local drug delivery method, hepatic artery infusion (HAI) which has been employed for treatment of liver cancers. For HAI, it is clinically accepted that optimal results are achieved with agents that are rapidly extracted by tissue [15,259]. For example, the agent 5-fluorouracil (5-FU) with moderate extraction fraction (30–40% of drug are extracted during a single pass through the liver) increases tumor drug exposure only 5–10 fold when administered by HAI compared to systemic delivery, and administration via HAI does not provide a therapeutic benefit. However, 5-fluoro-2′-deoxyuridine, a drug analog of 5-FU, enhances tumor drug exposure ~100–400 fold due to rapid extraction (94–99% are extracted during a single pass through the liver), and does provide therapeutic benefit over systemic administration. These results are directly applicable to localized delivery by intravascular triggered SDDS, since the release of bioavailable drug within the tumor vasculature can be considered as direct infusion of bioavailable drug into the tumor (i.e. similar to HAI).

Alternatively, the cellular uptake of chemotherapeutics can be improved. We and others observed a faster intracellular accumulation of doxorubicin when these cells were exposed to short chain sphingolipids such as glucosylceramide [260,261]. Others used ultrasound to permeabilize cell membranes to facilitate intracellular accumulation of a cell impermeable test drug released from TSLs [262]. Together these examples show that aiding or improving drug accumulation may be an essential part of intravascular triggered drug delivery to be optimally effective.

Importantly, computational modeling of intravascular release using optimally tuned TSLs indicates that intravascular triggered release method is superior in delivery of doxorubicin when compared to other methods including the two step approach [221,263]. The group of Papahadjopoulos reported that heating of a tumor to 42–45 °C increased both liposome content (47-times versus unheated) and doxorubicin content (38–76-fold versus unheated) in the tumor [66].

6.3. Extravascular triggered release from SDDS

A major aspect which drove the development of nanoparticles for drug delivery in cancer is the tendency of particles to accumulate in tumors. A direct correlation between tumor accumulation and circulation time has been demonstrated; the longer a particle circulates the more ends up in a tumor. This EPR effect can be considered as the holy grail in nanoparticle-mediated drug delivery, however as stated above is under debate. We and others observed that the EPR effect plays actually only a minor role, seems to occur mainly in fast growing tumors and if present is rather heterogeneous [32,69]. In humans, particularly the leakiness of vessels, and thus the EPR effect, is much less pronounced as compared to the often fast growing mouse tumors. Irrespective of that, the tumor associated vasculature presents an immature makeup, does have gaps between endothelial cells and preferential accumulation is seen [61,73]. Importantly, the endothelial lining of tumor vessels responds to internal and external triggers different from mature and quiescent endothelial cells in normal vessels. As outlined above the degree of leakiness, and thus EPR effect, is augmented by certain cytokines, vaso-active agents, but also hyperthermia [32,69]. Combination of hyperthermia and long circulating nanoparticles (Fig. 1) therefore results in higher intratumoral delivery and improved outcome in animal studies [66,122,199,264]. We and others proposed to combine hyperthermia-mediated extravasation with hyperthermia-mediated triggered drug release and coined this a two-step approach as demonstrated by Li et al. (Fig. 5) [263,265]. In this setting the tumor is first heated mildly to about 42 °C and allowed to regain body temperature. This results in changes in the tumor vasculature allowing higher accumulation of subsequently injected nanoparticles. When maximum accumulation has been achieved, which is for long circulating

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nanoparticles around 24 h after systemic injection, a second local mild hyperthermia is applied triggering release of contents from the intratumoral particles. Li et al. show that this treatment setting is however less effective with respect to tumor response as compared to the above discussed intravascular triggered release approach, while local drug levels reached in the two methods were the same [263]. It is important to note that the nanoparticles used in the two settings are different. So-called slow release thermosensitive liposomes (sTSLs) where used in the two-step method. These sTSLs only release their content over minutes at 42 °C while a significant fraction of the sTSLs retain contents even after 1 h of heating. Possibly another TSLs, better equipped for the two-step method rendered better results. Together these results indicate that possibly intact doxorubicin-containing TSLs are present in the interstitial space when the two-step method is combined with slow release TSLs. Therefore, this slow release method is likely not the best choice to deliver a chemotherapeutic compound like doxorubicin, but may be an interesting option for other drugs. Similarly, Cha et al. used HIFU to initially increase vascular permeability followed by injection of TSLs containing doxorubicin [266]. After 6 h, when maximum tumor accumulation was achieved, tumors were heated to 42 °C. They show that this approach achieved a better tumor response compared to intravascular release.

For a drug to be active, a local drug concentration needs to be established which is high enough while the drug needs to be present for adequate time to act. This drug exposure can be expressed by the AUC of the drug concentration over time. That means that a high but short exposure will produce the same AUC compared to a low concentration present for a longer time. What is better really depends on the drug used. Some drugs need to be converted or are taken up by cells slowly, have poor diffusion profiles, or are accompanied by severe side-effects. The above described one-step intravascular triggered release approach is intended to deliver, in a short time-frame, massive amounts of drug in a relatively small volume. It can be argued that for most chemotherapeutics this method is preferred. However, the two step method may provide an interesting possibility to deliver in a controlled manner compounds which benefit from intratumoral release. First, when a drug enters a tumor the first layers of cells accumulate most, with deeper tumoral regions receiving less drug. Nanoparticles, especially sterically stabilized for instance with PEG, are taken up by cells slower and could therefore penetrate deeper and hence when drug is released this also reaches cells further away from the vessel. Second, deposition of particles which respond in a slow manner to a tumor-intrinsic release trigger could establish sustained drug delivery in the tumor over extended periods of time. Thirdly, if the particle is equipped with more than one active component, presence deep in the tumor tissue guarantees simultaneous exposure of the tumor cell to these active components at the same time. This may be of value in combination therapies, vaccination or immunologic treatments. Fourth, the blood brain barrier (BBB) inhibits delivery of drugs or nanoparticles to brain cancer. Mild hyperthermia transiently opens the BBB and allows drug to pass. Here the two step-method may be useful to first open the BBB and secondly release drug from interstitially present liposomes. More so, this can also be achieved in one hyperthermia dose [253].

7. Future of SDDS and hyperthermia: a marriage for life?

While nanotechnology developed rapidly and nanoparticles underwent several generations of evolution (for liposomes since the discovery by Bangham in the 60s), successes in the cancer field have been limited. Currently only a few nanoparticles carrying chemotherapeutics are approved for patient use, and Doxil® - the most successful formulation – was mainly approved because of a favorable toxicity profile rather than better efficacy [48,49,267–273]. Clearly, further improvement, but also a different way of thinking is required to realize the promise of nanoparticles. The nanoparticles currently dominating nanomedicine are relatively stable and therefore release slowly, or establish sustained release depots. Here, a comparison with thermosensitive hydrogels can be made which at body temperature release a steady level of drug over long duration [274,275]. While this steady and slow release may be useful in some settings, for effective tumor cell kill high drug levels and thus rapid release are more effective. A recent proposed hypothesis is that a more controlled, so-called immunologic cell death may result in a systemic response and possibly cure. When the tumor is killed in this rather subtle way an immunologic response may occur which may kill not-targeted metastases and render immunity towards the cancer [276–278]. In spite of this, bringing adequate drug amounts to all tumor cells is still a goal.

The question is whether combination of nanodevice-mediated drug delivery through the use of SDDS in combination with mild hyperthermia is a viable approach. This question raises several concerns and issues which need to be addressed. First, a question often encountered when results with controlled locally triggered drug release is: what to do about micrometastasis? The rationale is that patients do not generally die from the primary or locally advanced tumor but from progression of micrometastases. Do we need additional infusion of free drug to kill micrometastasis? Can we use a drug which is released from SDDS to attack these? Or can we improve non-invasive detection and target smaller, currently undetectable tumors? Or is it feasible to achieve regional delivery with SDDS in organ or tissue volumes where micrometastases are suspected? And if so, can we repeat treatment again and again to achieve local control as soon as micrometastases become detectable? If this is not possible currently or in the near future, is local control a clinically sufficient goal for continuing SDDS research? As discussed above, a combination that already underwent a trial, with an ongoing follow-up trial is TSLs together with ablation. While this combination may reduce recurrences in the margin of the ablation zone and thus reduce overall local recurrence rates, there are several concerns as discussed above.

Another important factor complicating cancer therapy through hyperthermia-triggered drug release from SDDS is that a hyperthermia device is required, and that device performance is as important as SDDS properties. As described above there are several methods to heat regions in the body but all have advantages as well as limitations and drawbacks. Currently, there is no ideal heating protocol and therefore the field has not developed to its full potential. Providing homogeneous and tumor specific heating to the required temperature without damaging surrounding health tissues is still a distant future goal, since exposure of large tissue volumes to a relatively narrow temperature range (~40–42 °C) is technically very challenging. This together with the already discussed heterogeneity of solid tumors, which affects SDDS presence, confronts the field with complex issues that still need to be resolved. Possibly, treatment parameters need to be optimized in a patient-specific manner to be effective. This will make clinical studies difficult to conduct as it will be hard to recruit enough patients. Here, more recent developments could provide at least part of an answer. By computational modeling of drug delivery, drug distribution, response to heat triggering, impact of perfusion, patient characteristics and behavior of different TSLs with different drugs, insights into treatment options can be studied and the best selected or even tuned per patient. More so, if we could validate the different processes modeled and could improve on the models devised, this approach could well be a crucial element in making the SDDS + hyperthermia combination successful. An important question which needs to be looked at is if doxorubicin is the best drug for this setting. At the moment this drug is by far the most widely used in thermosensitive nanodevices for cancer therapy. As discussed above, we hypothesized recently that the SDDS-Hyperthermia approach is actually a local therapy, and therefore should be looked at as such. We argue that drugs need to be selected with characteristics which are especially of benefit in such a setting. Another question, and likely related to the one just asked, is: why is the tumor response not as good as expected, since we do get more drug in the tumor when SDDS are used in combination with hyperthermia?

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The future of hyperthermia-mediated triggered drug release from SDDS for the treatment of cancer is therefore obscured by the many aspects which determine success. In other words, there are many aspects which could all, independently or in combination, result in failure. Current research is and needs to be focused on how to get the most synergistic interaction between SDDS, hyperthermia, patient and tumor. For this a solid interaction between the different disciplines is key.

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References

[1] S.B. Park, D. Goldstein, A.V. Krishnan, C.S. Lin, M.L. Friedlander, J. Cassidy, M. Koltzenburg, M.C. Kiernan, Chemotherapy-induced peripheral neurotoxicity: a critical analysis, CA Cancer J. Clin. 63 (2013) 419–437.
[2] R. Issels, E. Kampmann, R. Kanaar, L.H. Lindner, Hallmarks of hyperthermia in driving the future of clinical hyperthermia as targeted therapy: translation into clinical application, Int. J. Hyperth. 32 (2016) 89–95.
[3] V.T. DeVita Jr., E. Chu, A history of cancer chemotherapy, Cancer Res. 68 (2008) 8643–8653.
[4] C. Holohan, S. Van Schaeybroeck, D.B. Longley, P.G. Johnston, Cancer drug resistance: an evolving paradigm, Nat. Rev. Cancer 13 (2013) 714–726.
[5] R.W. Robey, K.M. Pluchino, M.D. Hall, A.T. Fojo, S.E. Bates, M.M. Gottesman, Revisiting the role of ABC transporters in multidrug-resistant cancer, Nat. Rev. Cancer 18 (2018) 452–464.
[6] B.C. Baguley, Multiple drug resistance mechanisms in cancer, Mol. Biotechnol. 46 (2010) 308–316.
[7] S.N. Aleksakhina, A. Kashyap, E.N. Imyanitov, Mechanisms of acquired tumor drug resistance, Biochim. Biophys. Acta Rev. Cancer 1872 (2019) 188310.
[8] S. Zalba, T.L. Ten Hagen, Cell membrane modulation as adjuvant in cancer therapy, Cancer Treat. Rev. 52 (2017) 48–57.
[9] D.J. Konieczkowski, C.M. Johannessen, L.A. Garraway, A convergence-based framework for cancer drug resistance, Cancer Cell 33 (2018) 801–815.
[10] S.M. Tolaney, Y. Boucher, D.G. Duda, J.D. Martin, G. Seano, M. Ancukiewicz, W.T. Barry, S. Goel, J. Lahdenrata, S.J. Isakoff, E.D. Yeh, S.R. Jain, M. Golshan, J. Brock, M. Snuderl, E.P. Winer, I.E. Krop, R.K. Jain, Role of vascular density and normalization in response to neoadjuvant bevacizumab and chemotherapy in breast cancer patients, Proc. Natl. Acad. Sci. U. S. A. 112 (2015) 14325–14330.
[11] H.I. Hurwitz, L. Fehrenbacher, J.D. Hainsworth, W. Heim, J. Berlin, E. Holmgren, J. Hambleton, W.F. Novotny, F. Kabbinavar, Bevacizumab in combination with fluorouracil and leucovorin: an active regimen for first-line metastatic colorectal cancer, J. Clin. Oncol. 23 (2005) 3502–3508.
[12] L. Simpson-Herren, P.E. Noker, S.D. Wagoner, Variability of tumor response to chemotherapy. II. Contribution of tumor heterogeneity, Cancer Chemother. Pharmacol. 22 (1988) 131–136.
[13] F. Fu, M.A. Nowak, S. Bonhoeffer, Spatial heterogeneity in drug concentrations can facilitate the emergence of resistance to cancer therapy, PLoS Comput. Biol. 11 (2015), e1004142.
[14] J. Liu, S. Liao, B. Diop-Frimpong, W. Chen, S. Goel, K. Naxerova, M. Ancukiewicz, Y. Boucher, R.K. Jain, L. Xu, TGF-beta blockade improves the distribution and efficacy of therapeutics in breast carcinoma by normalizing the tumor stroma, Proc. Natl. Acad. Sci. U. S. A. 109 (2012) 16618–16623.
[15] P.G. de Takats, D.J. Kerr, C.J. Poole, H.W. Warren, C.S. McArdle, Hepatic arterial chemotherapy for metastatic colorectal carcinoma, Br. J. Cancer 69 (1994) 372–378.
[16] F.O. Stephens, Pharmacokinetics of intra-arterial chemotherapy, Recent Results Cancer Res. 86 (1983) 1–12.
[17] T. de Baere, L. Tselikas, V. Boige, M. Ducreux, D. Malka, D. Goere, E. Benahim, F. Deschamps, Intra-arterial therapies for colorectal cancer liver metastases (radioembolization excluded), Bull. Cancer 104 (2017) 402–406.
[18] A.M. Eggermont, J.H. de Wilt, T.L. ten Hagen, Current uses of isolated limb perfusion in the clinic and a model system for new strategies, Lancet Oncol. 4 (2003) 429–437.
[19] D. Papahadjopoulos, T.M. Allen, A. Gabizon, E. Mayhew, K. Matthay, S.K. Huang, K.D. Lee, M.C. Woodle, D.D. Lasic, C. Redemann, et al., Sterically stabilized liposomes: improvements in pharmacokinetics and antitumor therapeutic efficacy, Proc. Natl. Acad. Sci. U. S. A. 88 (1991) 11460–11464.
[20] A.S. Thakor, S.S. Gambhir, Nanooncology: the future of cancer diagnosis and therapy, CA Cancer J. Clin. 63 (2013) 395–418.
[21] A.Z. Wang, R. Langer, O.C. Farokhzad, Nanoparticle delivery of cancer drugs, Annu. Rev. Med. 63 (2012) 185–198.
[22] H.M. Kieler-Ferguson, J.M. Frechet, F.C. Szoka Jr., Clinical developments of chemotherapeutic nanomedicines: polymers and liposomes for delivery of camptothecins and platinum (II) drugs, Wiley Interdiscip. Rev. Nanomed. Nanobiotechnol. 5 (2013) 130–138.
[23] S. Garattini, Pharmacokinetics in cancer chemotherapy, Eur. J. Cancer 43 (2007) 271–282.
[24] A.J. Primeau, A. Rendon, D. Hedley, L. Lilge, I.F. Tannock, The distribution of the anticancer drug doxorubicin in relation to blood vessels in solid tumors, Clin. Cancer Res. 11 (2005) 8782–8788.
[25] B.A. Teicher, G. Ara, S.R. Keyes, R.S. Herbst, E. Frei 3rd, Acute in vivo resistance in high-dose therapy, Clin. Cancer Res. 4 (1998) 483–491.
[26] A.K. Larsen, A.E. Escargueil, A. Skladanowski, Resistance mechanisms associated with altered intracellular distribution of anticancer agents, Pharmacol. Ther. 85 (2000) 217–229.
[27] A. Gartung, J. Yang, V.P. Sukhatme, D.R. Bielenberg, D. Fernandes, J. Chang, B.A. Schmidt, S.H. Hwang, D. Zurakowski, S. Huang, M.W. Kieran, B.D. Hammock, D. Panigrahy, Suppression of chemotherapy-induced cytokine/lipid mediator surge and ovarian cancer by a dual COX-2/sEH inhibitor, Proc. Natl. Acad. Sci. U. S. A. 116 (2019) 1698–1703.
[28] J. Chang, S.S. Bhasin, D.R. Bielenberg, V.P. Sukhatme, M. Bhasin, S. Huang, M.W. Kieran, D. Panigrahy, Chemotherapy-generated cell debris stimulates colon carcinoma tumor growth via osteopontin, FASEB J. 33 (2019) 114–125.
[29] K.J. Seelig, L. Revesz, Effect of lethally damaged tumour cells upon the growth of admixed viable cells in diffusion chambers, Br. J. Cancer 14 (1960) 126–138.
[30] Q. Tan, J.K. Saggar, M. Yu, M. Wang, I.F. Tannock, Mechanisms of drug resistance related to the microenvironment of solid tumors and possible strategies to inhibit them, Cancer J. 21 (2015) 254–262.
[31] A.I. Minchinton, I.F. Tannock, Drug penetration in solid tumours, Nat. Rev. Cancer 6 (2006) 583–592.
[32] L. Li, T.L. Ten Hagen, M. Bolkestein, A. Gasselhuber, J. Yatvin, G.C. van Rhoon, A.M. Eggermont, D. Haemmerich, G.A. Koning, Improved intratumoral nanoparticle extravasation and penetration by mild hyperthermia, J. Control. Release 167 (2013) 130–137.
[33] A.A. Manzoor, L.H. Lindner, C.D. Landon, J.Y. Park, A.J. Simnick, M.R. Dreher, S. Das, G. Hanna, W. Park, A. Chilkoti, G.A. Koning, T.L. ten Hagen, D. Needham, M.W. Dewhirst, Overcoming limitations in nanoparticle drug delivery: triggered, intravascular release to improve drug penetration into tumors, Cancer Res. 72 (2012) 5566–5575.
[34] G. Powis, Dose-dependent metabolism, therapeutic effect, and toxicity of anticancer drugs in man, Drug Metab. Rev. 14 (1983) 1145–1163.
[35] A. Bhakay, M. Rahman, R.N. Dave, E. Bilgili, Bioavailability enhancement of poorly water-soluble drugs via nanocomposites: formulation(-)processing aspects and challenges, Pharmaceutics 10 (2018).
[36] S. Kalepu, V. Nekkanti, Insoluble drug delivery strategies: review of recent advances and business prospects, Acta Pharm. Sin. B 5 (2015) 442–453.
[37] A. Rodallec, R. Fanciullino, B. Lacarelle, J. Ciccolini, Seek and destroy: improving PK/PD profiles of anticancer agents with nanoparticles, Expert. Rev. Clin. Pharmacol. 11 (2018) 599–610.
[38] S. Onoue, S. Yamada, H.K. Chan, Nanodrugs: pharmacokinetics and safety, Int. J. Nanomedicine 9 (2014) 1025–1037.
[39] K. Strebhardt, A. Ullrich, Paul Ehrlich's magic bullet concept: 100 years of progress, Nat. Rev. Cancer 8 (2008) 473–480.
[40] J. Zhang, H. Tang, Z. Liu, B. Chen, Effects of major parameters of nanoparticles on their physical and chemical properties and recent application of nanodrug delivery system in targeted chemotherapy, Int. J. Nanomedicine 12 (2017) 8483–8493.
[41] N.P. Truong, M.R. Whittaker, C.W. Mak, T.P. Davis, The importance of nanoparticle shape in cancer drug delivery, Expert Opin. Drug Deliv. 12 (2015) 129–142.
[42] S.M. Moghimi, A.C. Hunter, T.L. Andresen, Factors controlling nanoparticle pharmacokinetics: an integrated analysis and perspective, Annu. Rev. Pharmacol. Toxicol. 52 (2012) 481–503.
[43] T.J. Anchordoquy, Y. Barenholz, D. Boraschi, M. Chorny, P. Decuzzi, M.A. Dobrovolskaia, Z.S. Farhangrazi, D. Farrell, A. Gabizon, H. Ghandehari, B. Godin, N.M. La-Beck, J. Ljubimova, S.M. Moghimi, L. Pagliaro, J.H. Park, D. Peer, E. Ruoslahti, N.J. Serkova, D. Simberg, Mechanisms and barriers in cancer nanomedicine: addressing challenges, looking for solutions, ACS Nano 11 (2017) 12–18.
[44] C.L. Ventola, Progress in nanomedicine: approved and investigational nanodrugs, P T 42 (2017) 742–755.
[45] D. Bobo, K.J. Robinson, J. Islam, K.J. Thurecht, S.R. Corrie, Nanoparticle-based medicines: a review of FDA-approved materials and clinical trials to date, Pharm. Res. 33 (2016) 2373–2387.
[46] A. Gabizon, R. Catane, B. Uziely, B. Kaufman, T. Safra, R. Cohen, F. Martin, A. Huang, Y. Barenholz, Prolonged circulation time and enhanced accumulation in malignant exudates of doxorubicin encapsulated in polyethylene-glycol coated liposomes, Cancer Res. 54 (1994) 987–992.
[47] J.S. Suk, Q. Xu, N. Kim, J. Hanes, L.M. Ensign, PEGylation as a strategy for improving nanoparticle-based drug and gene delivery, Adv. Drug Deliv. Rev. 99 (2016) 28–51.
[48] A. Gabizon, H. Shmeeda, Y. Barenholz, Pharmacokinetics of pegylated liposomal doxorubicin: review of animal and human studies, Clin. Pharmacokinet. 42 (2003) 419–436.
[49] B. Uziely, S. Jeffers, R. Isacson, K. Kutsch, D. Wei-Tsao, Z. Yehoshua, E. Libson, F.M. Muggia, A. Gabizon, Liposomal doxorubicin: antitumor activity and unique toxicities during two complementary phase I studies, J. Clin. Oncol. 13 (1995) 1777–1785.
[50] Y. Barenholz, Doxil(R)–the first FDA-approved nano-drug: lessons learned, J. Control. Release 160 (2012) 117–134.
[51] M. Picard, M.C. Castells, Re-visiting hypersensitivity reactions to taxanes: a comprehensive review, Clin. Rev. Allergy Immunol. 49 (2015) 177–191.
[52] D. Douer, Efficacy and safety of vincristine sulfate liposome injection in the treatment of adult acute lymphocytic Leukemia, Oncologist 21 (2016) 840–847.
[53] O.R. Deitcher, J. Glaspy, R. Gonzalez, T. Sato, A.Y. Bedikian, K. Segarini, J. Silverman, S.R. Deitcher, High-dose vincristine sulfate liposome injection (Marqibo) is not

Please cite this article as: A.L.B. Seynhaeve, M. Amin, D. Haemmerich, et al., Hyperthermia and smart drug delivery systems for solid tumor therapy, Adv. Drug Deliv. Rev., https://doi.org/10.1016/j.addr.2020.02.004

associated with clinically meaningful hematologic toxicity, Clin. Lymphoma Myeloma Leuk 14 (2014) 197–202.
[54] J.A. Silverman, S.R. Deitcher, Marqibo(R) (vincristine sulfate liposome injection) improves the pharmacokinetics and pharmacodynamics of vincristine, Cancer Chemother. Pharmacol. 71 (2013) 555–564.
[55] F.C. Passero Jr., D. Grapsa, K.N. Syrigos, M.W. Saif, The safety and efficacy of Onivyde (irinotecan liposome injection) for the treatment of metastatic pancreatic cancer following gemcitabine-based therapy, Expert. Rev. Anticancer. Ther. 16 (2016) 697–703.
[56] H. Zhang, Onivyde for the therapy of multiple solid tumors, Oncol. Targets Ther. 9 (2016) 3001–3007.
[57] Y.N. Lamb, L.J. Scott, Liposomal irinotecan: a review in metastatic pancreatic adenocarcinoma, Drugs 77 (2017) 785–792.
[58] (!!! INVALID CITATION!!! [50, 51]).
[59] J.I. Hare, T. Lammers, M.B. Ashford, S. Puri, G. Storm, S.T. Barry, Challenges and strategies in anti-cancer nanomedicine development: an industry perspective, Adv. Drug Deliv. Rev. 108 (2017) 25–38.
[60] A. Gabizon, R. Chisin, S. Amselem, S. Druckmann, R. Cohen, D. Goren, I. Fromer, T. Peretz, A. Sulkes, Y. Barenholz, Pharmacokinetic and imaging studies in patients receiving a formulation of liposome-associated adriamycin, Br. J. Cancer 64 (1991) 1125–1132.
[61] K.J. Harrington, S. Mohammadtaghi, P.S. Uster, D. Glass, A.M. Peters, R.G. Vile, J.S. Stewart, Effective targeting of solid tumors in patients with locally advanced cancers by radiolabeled pegylated liposomes, Clin. Cancer Res. 7 (2001) 243–254.
[62] Y. Matsumura, H. Maeda, A new concept for macromolecular therapeutics in cancer chemotherapy: mechanism of tumoritropic accumulation of proteins and the antitumor agent smancs, Cancer Res. 46 (1986) 6387–6392.
[63] A. Gabizon, A. Meshorer, Y. Barenholz, Comparative long-term study of the toxicities of free and liposome-associated doxorubicin in mice after intravenous administration, J. Natl. Cancer Inst. 77 (1986) 459–469.
[64] A. Gabizon, R. Shiota, D. Papahadjopoulos, Pharmacokinetics and tissue distribution of doxorubicin encapsulated in stable liposomes with long circulation times, J. Natl. Cancer Inst. 81 (1989) 1484–1488.
[65] K. Maruyama, S. Unezaki, N. Takahashi, M. Iwatsuru, Enhanced delivery of doxorubicin to tumor by long-circulating thermosensitive liposomes and local hyperthermia, Biochim. Biophys. Acta 1149 (1993) 209–216.
[66] M.H. Gaber, N.Z. Wu, K. Hong, S.K. Huang, M.W. Dewhirst, D. Papahadjopoulos, Thermosensitive liposomes: extravasation and release of contents in tumor microvascular networks, Int. J. Radiat. Oncol. Biol. Phys. 36 (1996) 1177–1187.
[67] L. Silverman, Y. Barenholz, In vitro experiments showing enhanced release of doxorubicin from Doxil(R) in the presence of ammonia may explain drug release at tumor site, Nanomedicine 11 (2015) 1841–1850.
[68] A.L. Seynhaeve, B.M. Dicheva, S. Hoving, G.A. Koning, T.L. Ten Hagen, Intact Doxil is taken up intracellularly and released doxorubicin sequesters in the lysosome: evaluated by in vitro/in vivo live cell imaging, J. Control. Release 172 (2013) 330–340.
[69] A.L. Seynhaeve, S. Hoving, D. Schipper, C.E. Vermeulen, G. de Wiel-Ambagtsheer, S.T. van Tiel, A.M. Eggermont, T.L. Ten Hagen, Tumor necrosis factor alpha mediates homogeneous distribution of liposomes in murine melanoma that contributes to a better tumor response, Cancer Res. 67 (2007) 9455–9462.
[70] K.M. Laginha, S. Verwoert, G.J. Charrois, T.M. Allen, Determination of doxorubicin levels in whole tumor and tumor nuclei in murine breast cancer tumors, Clin. Cancer Res. 11 (2005) 6944–6949.
[71] N. Seetharamu, E. Kim, H. Hochster, F. Martin, F. Muggia, Phase II study of liposomal cisplatin (SPI-77) in platinum-sensitive recurrences of ovarian cancer, Anticancer Res. 30 (2010) 541–545.
[72] B. Diop-Frimpong, V.P. Chauhan, S. Krane, Y. Boucher, R.K. Jain, Losartan inhibits collagen I synthesis and improves the distribution and efficacy of nanotherapeutics in tumors, Proc. Natl. Acad. Sci. U. S. A. 108 (2011) 2909–2914.
[73] A.L.B. Seynhaeve, D. Oostinga, R. van Haperen, H.M. Eilken, S. Adams, R.H. Adams, T.L.M. Ten Hagen, Spatiotemporal endothelial cell - pericyte association in tumors as shown by high resolution 4D intravital imaging, Sci. Rep. 8 (2018) 9596.
[74] V.P. Chauhan, Y. Boucher, C.R. Ferrone, S. Roberge, J.D. Martin, T. Stylianopoulos, N. Bardeesy, R.A. DePinho, T.P. Padera, L.L. Munn, R.K. Jain, Compression of pancreatic tumor blood vessels by hyaluronan is caused by solid stress and not interstitial fluid pressure, Cancer Cell 26 (2014) 14–15.
[75] H. Lee, A.F. Shields, B.A. Siegel, K.D. Miller, I. Krop, C.X. Ma, P.M. LoRusso, P.N. Munster, K. Campbell, D.F. Gaddy, S.C. Leonard, E. Geretti, S.J. Blocker, D.B. Kirpotin, V. Moyo, T.J. Wickham, B.S. Hendriks, (64)cu-MM-302 positron emission tomography quantifies variability of enhanced permeability and retention of nanoparticles in relation to treatment response in patients with metastatic breast cancer, Clin. Cancer Res. 23 (2017) 4190–4202.
[76] P.A. Netti, S. Roberge, Y. Boucher, L.T. Baxter, R.K. Jain, Effect of transvascular fluid exchange on pressure-flow relationship in tumors: a proposed mechanism for tumor blood flow heterogeneity, Microvasc. Res. 52 (1996) 27–46.
[77] K.D. Barlow, A.M. Sanders, S. Soker, S. Ergun, L.J. Metheny-Barlow, Pericytes on the tumor vasculature: jekyll or hyde? Cancer Microenviron. 6 (2013) 1–17.
[78] C. Schrimpf, O.E. Teebken, M. Wilhelmi, J.S. Duffield, The role of pericyte detachment in vascular rarefaction, J. Vasc. Res. 51 (2014) 247–258.
[79] S. Morikawa, P. Baluk, T. Kaidoh, A. Haskell, R.K. Jain, D.M. McDonald, Abnormalities in pericytes on blood vessels and endothelial sprouts in tumors, Am. J. Pathol. 160 (2002) 985–1000.
[80] H. Hashizume, P. Baluk, S. Morikawa, J.W. McLean, G. Thurston, S. Roberge, R.K. Jain, D.M. McDonald, Openings between defective endothelial cells explain tumor vessel leakiness, Am. J. Pathol. 156 (2000) 1363–1380.
[81] T. Stylianopoulos, J.D. Martin, M. Snuderl, F. Mpekris, S.R. Jain, R.K. Jain, Coevolution of solid stress and interstitial fluid pressure in tumors during progression: implications for vascular collapse, Cancer Res. 73 (2013) 3833–3841.
[82] A. Haddow, Molecular repair, wound healing, and carcinogenesis: tumor production a possible overhealing? Adv. Cancer Res. 16 (1972) 181–234.
[83] H.F. Dvorak, Tumors: wounds that do not heal. Similarities between tumor stroma generation and wound healing, N. Engl. J. Med. 315 (1986) 1650–1659.
[84] N. Erez, M. Truitt, P. Olson, S.T. Arron, D. Hanahan, Cancer-associated fibroblasts are activated in incipient neoplasia to orchestrate tumor-promoting inflammation in an NF-kappaB-dependent manner, Cancer Cell 17 (2010) 135–147.
[85] D.F. Mardhian, G. Storm, R. Bansal, J. Prakash, Nano-targeted relaxin impairs fibrosis and tumor growth in pancreatic cancer and improves the efficacy of gemcitabine in vivo, J. Control. Release 290 (2018) 1–10.
[86] M.A. Jacobetz, D.S. Chan, A. Neesse, T.E. Bapiro, N. Cook, K.K. Frese, C. Feig, T. Nakagawa, M.E. Caldwell, H.I. Zecchini, M.P. Lolkema, P. Jiang, A. Kultti, C.B. Thompson, D.C. Maneval, D.I. Jodrell, G.I. Frost, H.M. Shepard, J.N. Skepper, D.A. Tuveson, Hyaluronan impairs vascular function and drug delivery in a mouse model of pancreatic cancer, Gut 62 (2013) 112–120.
[87] E.C. Carron, S. Homra, J. Rosenberg, S.B. Coffelt, F. Kittrell, Y. Zhang, C.J. Creighton, S.A. Fuqua, D. Medina, H.L. Machado, Macrophages promote the progression of premalignant mammary lesions to invasive cancer, Oncotarget 8 (2017) 50731–50746.
[88] S.K. Golombek, J.N. May, B. Theek, L. Appold, N. Drude, F. Kiessling, T. Lammers, Tumor targeting via EPR: strategies to enhance patient responses, Adv. Drug Deliv. Rev. 130 (2018) 17–38.
[89] A. Eberhard, S. Kahlert, V. Goede, B. Hemmerlein, K.H. Plate, H.G. Augustin, Heterogeneity of angiogenesis and blood vessel maturation in human tumors: implications for antiangiogenic tumor therapies, Cancer Res. 60 (2000) 1388–1393.
[90] E. El Emir, U. Qureshi, J.L. Dearling, G.M. Boxer, I. Clatworthy, A.A. Folarin, M.P. Robson, S. Nagl, M.A. Konerding, R.B. Pedley, Predicting response to radioimmunotherapy from the tumor microenvironment of colorectal carcinomas, Cancer Res. 67 (2007) 11896–11905.
[91] Y. Matsumoto, J.W. Nichols, K. Toh, T. Nomoto, H. Cabral, Y. Miura, R.J. Christie, N. Yamada, T. Ogura, M.R. Kano, Y. Matsumura, N. Nishiyama, T. Yamasoba, Y.H. Bae, K. Kataoka, Vascular bursts enhance permeability of tumour blood vessels and improve nanoparticle delivery, Nat. Nanotechnol. 11 (2016) 533–538.
[92] S. Sindhwani, A.M. Syed, J. Ngai, B.R. Kingston, L. Maiorino, J. Rothschild, P. MacMillan, Y. Zhang, N.U. Rajesh, T. Hoang, J.L.Y. Wu, S. Wilhelm, A. Zilman, S. Gadde, A. Sulaiman, B. Ouyang, Z. Lin, L. Wang, M. Egeblad, W.C.W. Chan, The entry of nanoparticles into solid tumours, Nat. Mater. (2020 Jan 13) https://doi.org/10.1038/s41563-019-0566-2[Epub ahead of print].
[93] S.E. Krown, D.W. Northfelt, D. Osoba, J.S. Stewart, Use of liposomal anthracyclines in Kaposi's sarcoma, Semin. Oncol. 31 (2004) 36–52.
[94] M. Markman, A.N. Gordon, W.P. McGuire, F.M. Muggia, Liposomal anthracycline treatment for ovarian cancer, Semin. Oncol. 31 (2004) 91–105.
[95] S.T. Duggan, G.M. Keating, Pegylated liposomal doxorubicin: a review of its use in metastatic breast cancer, ovarian cancer, multiple myeloma and AIDS-related Kaposi's sarcoma, Drugs 71 (2011) 2531–2558.
[96] E. Rivera, V. Valero, F.J. Esteva, L. Syrewicz, M. Cristofanilli, Z. Rahman, D.J. Booser, G.N. Hortobagyi, Lack of activity of stealth liposomal doxorubicin in the treatment of patients with anthracycline-resistant breast cancer, Cancer Chemother. Pharmacol. 49 (2002) 299–302.
[97] M.E. O'Brien, N. Wigler, M. Inbar, R. Rosso, E. Grischke, A. Santoro, R. Catane, D.G. Kieback, P. Tomczak, S.P. Ackland, F. Orlandi, L. Mellars, L. Alland, C. Tendler, C.B.C.S. Group, Reduced cardiotoxicity and comparable efficacy in a phase III trial of pegylated liposomal doxorubicin HCl (CAELYX/Doxil) versus conventional doxorubicin for first-line treatment of metastatic breast cancer, Ann. Oncol. 15 (2004) 440–449.
[98] A. Gabizon, A. Dagan, D. Goren, Y. Barenholz, Z. Fuks, Liposomes as in vivo carriers of adriamycin: reduced cardiac uptake and preserved antitumor activity in mice, Cancer Res. 42 (1982) 4734–4739.
[99] F. Danhier, To exploit the tumor microenvironment: since the EPR effect fails in the clinic, what is the future of nanomedicine? J. Control. Release 244 (2016) 108–121.
[100] F. Man, T. Lammers, T.M. De Rosales, Imaging nanomedicine-based drug delivery: a review of clinical studies, Mol. Imaging Biol. 20 (2018) 683–695.
[101] S. Wilhelm, A.J. Tavares, Q. Dai, S. Ohta, J. Audet, H.F. Dvorak, W.C.W. Chan, Analysis of nanoparticle delivery to tumours, Nat. Rev. Mater. 1 (2016).
[102] D.B. Kirpotin, D.C. Drummond, Y. Shao, M.R. Shalaby, K. Hong, U.B. Nielsen, J.D. Marks, C.C. Benz, J.W. Park, Antibody targeting of long-circulating lipidic nanoparticles does not increase tumor localization but does increase internalization in animal models, Cancer Res. 66 (2006) 6732–6740.
[103] T.M. Allen, P.R. Cullis, Liposomal drug delivery systems: from concept to clinical applications, Adv. Drug Deliv. Rev. 65 (2013) 36–48.
[104] M.P. Melancon, M. Zhou, R. Zhang, C. Xiong, P. Allen, X. Wen, Q. Huang, M. Wallace, J.N. Myers, R.J. Stafford, D. Liang, A.D. Ellington, C. Li, Selective uptake and imaging of aptamer- and antibody-conjugated hollow nanospheres targeted to epidermal growth factor receptors overexpressed in head and neck cancer, ACS Nano 8 (2014) 4530–4538.
[105] J.I. Hare, E.H. Moase, T.M. Allen, Targeting combinations of liposomal drugs to both tumor vasculature cells and tumor cells for the treatment of HER2-positive breast cancer, J. Drug Target. 21 (2013) 87–96.
[106] M. Amin, A. Badiee, M.R. Jaafari, Improvement of pharmacokinetic and antitumor activity of PEGylated liposomal doxorubicin by targeting with N-methylated cyclic RGD peptide in mice bearing C-26 colon carcinomas, Int. J. Pharm. 458 (2013) 324–333.

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[107] R. van der Meel, L.J. Vehmeijer, R.J. Kok, G. Storm, E.V. van Gaal, Ligand-targeted particulate nanomedicines undergoing clinical evaluation: current status, Adv. Drug Deliv. Rev. 65 (2013) 1284–1298.

[108] M. Amin, M. Bagheri, M. Mansourian, M.R. Jaafari, T.L. Ten Hagen, Regulation of in vivo behavior of TAT-modified liposome by associated protein corona and avidity to tumor cells, Int. J. Nanomedicine 13 (2018) 7441–7455.

[109] A.G. Sorensen, K.E. Emblem, P. Polaskova, D. Jennings, H. Kim, M. Ancukiewicz, M. Wang, P.Y. Wen, P. Ivy, T.T. Batchelor, R.K. Jain, Increased survival of glioblastoma patients who respond to antiangiogenic therapy with elevated blood perfusion, Cancer Res. 72 (2012) 402–407.

[110] F. Winkler, S.V. Kozin, R.T. Tong, S.S. Chae, M.F. Booth, I. Garkavtsev, L. Xu, D.J. Hicklin, D. Fukumura, E. di Tomaso, L.L. Munn, R.K. Jain, Kinetics of vascular normalization by VEGFR2 blockade governs brain tumor response to radiation: role of oxygenation, angiopoietin-1, and matrix metalloproteinases, Cancer Cell 6 (2004) 553–563.

[111] V.P. Chauhan, T. Stylianopoulos, J.D. Martin, Z. Popovic, O. Chen, W.S. Kamoun, M.G. Bawendi, D. Fukumura, R.K. Jain, Normalization of tumour blood vessels improves the delivery of nanomedicines in a size-dependent manner, Nat. Nanotechnol. 7 (2012) 383–388.

[112] A.A. Van der Veldt, M. Lubberink, I. Bahce, M. Walraven, M.P. de Boer, H.N. Greuter, N.H. Hendrikse, J. Eriksson, A.D. Windhorst, P.E. Postmus, H.M. Verheul, E.H. Serne, A.A. Lammertsma, E.F. Smit, Rapid decrease in delivery of chemotherapy to tumors after anti-VEGF therapy: implications for scheduling of anti-angiogenic drugs, Cancer Cell 21 (2012) 82–91.

[113] A.L. Seynhaeve, A.M. Eggermont, T.L. ten Hagen, TNF and manipulation of the tumor cell-stromal interface: "ways to make chemotherapy effective", Front. Biosci. 13 (2008) 3034–3045.

[114] A.H. van der Veen, J.H. de Wilt, A.M. Eggermont, S.T. van Tiel, A.L. Seynhaeve, T.L. ten Hagen, TNF-alpha augments intratumoural concentrations of doxorubicin in TNF-alpha-based isolated limb perfusion in rat sarcoma models and enhances anti-tumour effects, Br. J. Cancer 82 (2000) 973–980.

[115] J.H. de Wilt, T.L. ten Hagen, G. de Boeck, S.T. van Tiel, E.A. de Bruijn, A.M. Eggermont, Tumour necrosis factor alpha increases melphalan concentration in tumour tissue after isolated limb perfusion, Br. J. Cancer 82 (2000) 1000–1003.

[116] S. Hoving, A.L. Seynhaeve, S.T. van Tiel, A.M. Eggermont, T.L. ten Hagen, Addition of low-dose tumor necrosis factor-alpha to systemic treatment with STEALTH liposomal doxorubicin (Doxil) improved anti-tumor activity in osteosarcoma-bearing rats, Anti-Cancer Drugs 16 (2005) 667–674.

[117] F. Brunstein, S. Hoving, A.L. Seynhaeve, S.T. van Tiel, G. Guetens, E.A. de Bruijn, A.M. Eggermont, T.L. ten Hagen, Synergistic antitumor activity of histamine plus melphalan in isolated limb perfusion: preclinical studies, J. Natl. Cancer Inst. 96 (2004) 1603–1610.

[118] C. Ruegg, A. Yilmaz, G. Bieler, J. Bamat, P. Chaubert, F.J. Lejeune, Evidence for the involvement of endothelial cell integrin alphaVbeta3 in the disruption of the tumor vasculature induced by TNF and IFN-gamma, Nat. Med. 4 (1998) 408–414.

[119] A.L. Seynhaeve, C.E. Vermeulen, A.M. Eggermont, T.L. ten Hagen, Cytokines and vascular permeability: an in vitro study on human endothelial cells in relation to tumor necrosis factor-alpha-primed peripheral blood mononuclear cells, Cell Biochem. Biophys. 44 (2006) 157–169.

[120] R.T. Tong, Y. Boucher, S.V. Kozin, F. Winkler, D.J. Hicklin, R.K. Jain, Vascular normalization by vascular endothelial growth factor receptor 2 blockade induces a pressure gradient across the vasculature and improves drug penetration in tumors, Cancer Res. 64 (2004) 3731–3736.

[121] B. Zhang, W. Shi, T. Jiang, L. Wang, H. Mei, H. Lu, Y. Hu, Z. Pang, Optimization of the tumor microenvironment and nanomedicine properties simultaneously to improve tumor therapy, Oncotarget 7 (2016) 62607–62618.

[122] L. Li, T.L. ten Hagen, M. Hossann, R. Suss, G.C. van Rhoon, A.M. Eggermont, D. Haemmerich, G.A. Koning, Mild hyperthermia triggered doxorubicin release from optimized stealth thermosensitive liposomes improves intratumoral drug delivery and efficacy, J. Control. Release 168 (2013) 142–150.

[123] T.L. Ten Hagen, A.H. Van Der Veen, P.T. Nooijen, S.T. Van Tiel, A.L. Seynhaeve, A.M. Eggermont, Low-dose tumor necrosis factor-alpha augments antitumor activity of stealth liposomal doxorubicin (DOXIL) in soft tissue sarcoma-bearing rats, Int. J. Cancer 87 (2000) 829–837.

[124] T.L. Ten Hagen, A.L. Seynhaeve, S.T. van Tiel, D.J. Ruiter, A.M. Eggermont, Pegylated liposomal tumor necrosis factor-alpha results in reduced toxicity and synergistic antitumor activity after systemic administration in combination with liposomal doxorubicin (Doxil) in soft tissue sarcoma-bearing rats, Int. J. Cancer 97 (2002) 115–120.

[125] L. Miao, Q. Liu, C.M. Lin, C. Luo, Y. Wang, L. Liu, W. Yin, S. Hu, W.Y. Kim, L. Huang, Targeting tumor-associated fibroblasts for therapeutic delivery in desmoplastic tumors, Cancer Res. 77 (2017) 719–731.

[126] H. Gong, Y. Chao, J. Xiang, X. Han, G. Song, L. Feng, J. Liu, G. Yang, Q. Chen, Z. Liu, Hyaluronidase to enhance nanoparticle-based photodynamic tumor therapy, Nano Lett. 16 (2016) 2512–2521.

[127] C. Hu, X. Liu, W. Ran, J. Meng, Y. Zhai, P. Zhang, Q. Yin, H. Yu, Z. Zhang, Y. Li, Regulating cancer associated fibroblasts with losartan-loaded injectable peptide hydrogel to potentiate chemotherapy in inhibiting growth and lung metastasis of triple negative breast cancer, Biomaterials 144 (2017) 60–72.

[128] K.P. Olive, M.A. Jacobetz, C.J. Davidson, A. Gopinathan, D. McIntyre, D. Honess, B. Madhu, M.A. Goldgraben, M.E. Caldwell, D. Allard, K.K. Frese, G. Denicola, C. Feig, C. Combs, S.P. Winter, H. Ireland-Zecchini, S. Reichelt, W.J. Howat, A. Chang, M. Dhara, L. Wang, F. Ruckert, R. Grutzmann, C. Pilarsky, K. Izeradjene, S.R. Hingorani, P. Huang, S.E. Davies, W. Plunkett, M. Egorin, R.H. Hruban, N. Whitebread, K. McGovern, J. Adams, C. Iacobuzio-Donahue, J. Griffiths, D.A. Tuveson, Inhibition of Hedgehog signaling enhances delivery of chemotherapy in a mouse model of pancreatic cancer, Science 324 (2009) 1457–1461.

[129] C.J. Diederich, Thermal ablation and high-temperature thermal therapy: overview of technology and clinical implementation, Int. J. Hyperth. 21 (2005) 745–753.

[130] G.T. Haar, C. Coussios, High intensity focused ultrasound: physical principles and devices, Int. J. Hyperth. 23 (2007) 89–104.

[131] G. Mauri, L. Nicosia, Z. Xu, S. Di Pietro, L. Monfardini, G. Bonomo, G.M. Varano, F. Prada, P. Della Vigna, F. Orsi, Focused ultrasound: tumour ablation and its potential to enhance immunological therapy to cancer, Br. J. Radiol. 91 (2018) 20170641.

[132] A.L. Oei, V.R. Ahire, C.M. van Leeuwen, R. Ten Cate, L.J.A. Stalpers, J. Crezee, H.P. Kok, N.A.P. Franken, Enhancing radiosensitisation of BRCA2-proficient and BRCA2-deficient cell lines with hyperthermia and PARP1-i, Int. J. Hyperth. 34 (2018) 39–48.

[133] N. van den Tempel, C. Laffeber, H. Odijk, W.A. van Cappellen, G.C. van Rhoon, M. Franckena, R. Kanaar, The effect of thermal dose on hyperthermia-mediated inhibition of DNA repair through homologous recombination, Oncotarget 8 (2017) 44593–44604.

[134] R.D. Issels, L.H. Lindner, J. Verweij, P. Wust, P. Reichardt, B.C. Schem, S. Abdel-Rahman, S. Daugaard, C. Salat, C.M. Wendtner, Z. Vujaskovic, R. Wessalowski, K.W. Jauch, H.R. Durr, F. Ploner, A. Baur-Melnyk, U. Mansmann, W. Hiddemann, J.Y. Blay, P. Hohenberger, R. European Organisation for, T. Treatment of Cancer Soft, G. Bone Sarcoma, O. European Society for Hyperthermic, Neo-adjuvant chemotherapy alone or with regional hyperthermia for localised high-risk soft-tissue sarcoma: a randomised phase 3 multicentre study, Lancet Oncol. 11 (2010) 561–570.

[135] R.D. Issels, L.H. Lindner, J. Verweij, R. Wessalowski, P. Reichardt, P. Wust, P. Ghadjar, P. Hohenberger, M. Angele, C. Salat, Z. Vujaskovic, S. Daugaard, O. Mella, U. Mansmann, H.R. Durr, T. Knosel, S. Abdel-Rahman, M. Schmidt, W. Hiddemann, K.W. Jauch, C. Belka, A. Gronchi, R. European Organization for the, T. Treatment of Cancer-Soft, G. Bone Sarcoma, O. the European Society for Hyperthermic, Effect of neoadjuvant chemotherapy plus regional hyperthermia on long-term outcomes among patients with localized high-risk soft tissue sarcoma: the EORTC 62961-ESHO 95 randomized clinical trial, JAMA Oncol. 4 (2018) 483–492.

[136] D. Killock, Sarcoma: local hyperthermia improves survival, Nat. Rev. Clin. Oncol. 15 (2018) 266.

[137] S.K. Huang, P.R. Stauffer, K. Hong, J.W. Guo, T.L. Phillips, A. Huang, D. Papahadjopoulos, Liposomes and hyperthermia in mice: increased tumor uptake and therapeutic efficacy of doxorubicin in sterically stabilized liposomes, Cancer Res. 54 (1994) 2186–2191.

[138] A.M. Ponce, B.L. Viglianti, D. Yu, P.S. Yarmolenko, C.R. Michelich, J. Woo, M.B. Bally, M.W. Dewhirst, Magnetic resonance imaging of temperature-sensitive liposome release: drug dose painting and antitumor effects, J. Natl. Cancer Inst. 99 (2007) 53–63.

[139] S. Stapleton, M. Dunne, M. Milosevic, C.W. Tran, M.J. Gold, A. Vedadi, T.D. McKee, P.S. Ohashi, C. Allen, D.A. Jaffray, Radiation and heat improve the delivery and efficacy of nanotherapeutics by modulating intratumoral fluid dynamics, ACS Nano 12 (2018) 7583–7600.

[140] G. Kong, R.D. Braun, M.W. Dewhirst, Hyperthermia enables tumor-specific nanoparticle delivery: effect of particle size, Cancer Res. 60 (2000) 4440–4445.

[141] G. Kong, R.D. Braun, M.W. Dewhirst, Characterization of the effect of hyperthermia on nanoparticle extravasation from tumor vasculature, Cancer Res. 61 (2001) 3027–3032.

[142] B.M. Dicheva, A.L. Seynhaeve, T. Soulie, A.M. Eggermont, T.L. Ten Hagen, G.A. Koning, Pharmacokinetics, tissue distribution and therapeutic effect of cationic thermosensitive liposomal doxorubicin upon mild hyperthermia, Pharm. Res. 33 (2016) 627–638.

[143] A.H. van der Veen, A.M. Eggermont, A.L. Seynhaeve, T. Van, T.L. Ten Hagen, Biodistribution and tumor localization of stealth liposomal tumor necrosis factor-alpha in soft tissue sarcoma bearing rats, Int. J. Cancer 77 (1998) 901–906.

[144] R.J. Myerson, E.G. Moros, C.J. Diederich, D. Haemmerich, M.D. Hurwitz, I.C. Hsu, R.J. McGough, W.H. Nau, W.L. Straube, P.F. Turner, Z. Vujaskovic, P.R. Stauffer, Components of a hyperthermia clinic: recommendations for staffing, equipment, and treatment monitoring, Int. J. Hyperth. 30 (2014) 1–5.

[145] J.C. Peeken, P. Vaupel, S.E. Combs, Integrating hyperthermia into modern radiation oncology: what evidence is necessary? Front. Oncol. 7 (2017) 132.

[146] P. Wust, B. Hildebrandt, G. Sreenivasa, B. Rau, J. Gellermann, H. Riess, R. Felix, P.M. Schlag, Hyperthermia in combined treatment of cancer, Lancet Oncol. 3 (2002) 487–497.

[147] G.C. van Rhoon, M.M. Paulides, J.M. van Holthe, M. Franckena, Hyperthermia by electromagnetic fields to enhanced clinical results in oncology, Conf. Proc. IEEE Eng. Med. Biol. Soc. 2016 (2016) 359–362.

[148] H.P. Kok, F. Navarro, L. Strigari, M. Cavagnaro, J. Crezee, Locoregional hyperthermia of deep-seated tumours applied with capacitive and radiative systems: a simulation study, Int. J. Hyperth. 34 (2018) 714–730.

[149] L. Zhu, M.B. Altman, A. Laszlo, W. Straube, I. Zoberi, D.E. Hallahan, H. Chen, Ultrasound hyperthermia technology for radiosensitization, Ultrasound Med. Biol. 45 (2019) 1025–1043.

[150] N. Hijnen, S. Langereis, H. Grull, Magnetic resonance guided high-intensity focused ultrasound for image-guided temperature-induced drug delivery, Adv. Drug Deliv. Rev. 72 (2014) 65–81.

[151] N. Hijnen, E. Kneepkens, M. de Smet, S. Langereis, E. Heijman, H. Grull, Thermal combination therapies for local drug delivery by magnetic resonance-guided high-intensity focused ultrasound, Proc. Natl. Acad. Sci. U. S. A. 114 (2017) E4802–E4811.

[152] A. Ranjan, G.C. Jacobs, D.L. Woods, A.H. Negussie, A. Partanen, P.S. Yarmolenko, C.E. Gacchina, K.V. Sharma, V. Frenkel, B.J. Wood, M.R. Dreher, Image-guided drug

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delivery with magnetic resonance guided high intensity focused ultrasound and temperature sensitive liposomes in a rabbit Vx2 tumor model, J. Control. Release 158 (2012) 487–494.
[153] R.M. Staruch, K. Hynynen, R. Chopra, Hyperthermia-mediated doxorubicin release from thermosensitive liposomes using MR-HIFU: therapeutic effect in rabbit Vx2 tumours, Int. J. Hyperth. 31 (2015) 118–133.
[154] A. Kheirolomoom, C.Y. Lai, S.M. Tam, L.M. Mahakian, E.S. Ingham, K.D. Watson, K.W. Ferrara, Complete regression of local cancer using temperature-sensitive liposomes combined with ultrasound-mediated hyperthermia, J. Control. Release 172 (2013) 266–273.
[155] P.C. Lyon, M.D. Gray, C. Mannaris, L.K. Folkes, M. Stratford, L. Campo, D.Y.F. Chung, S. Scott, M. Anderson, R. Goldin, R. Carlisle, F. Wu, M.R. Middleton, F.V. Gleeson, C.C. Coussios, Safety and feasibility of ultrasound-triggered targeted drug delivery of doxorubicin from thermosensitive liposomes in liver tumours (TARDOX): a single-centre, open-label, phase 1 trial, Lancet Oncol. 19 (2018) 1027–1039.
[156] A.H. Negussie, P.S. Yarmolenko, A. Partanen, A. Ranjan, G. Jacobs, D. Woods, H. Bryant, D. Thomasson, M.W. Dewhirst, B.J. Wood, M.R. Dreher, Formulation and characterisation of magnetic resonance imageable thermally sensitive liposomes for use with magnetic resonance-guided high intensity focused ultrasound, Int. J. Hyperth. 27 (2011) 140–155.
[157] E. Kneepkens, E. Heijman, J. Keupp, S. Weiss, K. Nicolay, H. Grull, Interleaved mapping of temperature and longitudinal relaxation rate to monitor drug delivery during magnetic resonance-guided high-intensity focused ultrasound-induced hyperthermia, Investig. Radiol. 52 (2017) 620–630.
[158] M. Peller, L. Willerding, S. Limmer, M. Hossann, O. Dietrich, M. Ingrisch, R. Sroka, L.H. Lindner, Surrogate MRI markers for hyperthermia-induced release of doxorubicin from thermosensitive liposomes in tumors, J. Control. Release 237 (2016) 138–146.
[159] S. Ray, C.A. Cheng, W. Chen, Z. Li, J.I. Zink, Y.Y. Lin, Magnetic heating stimulated cargo release with dose control using multifunctional MR and thermosensitive liposome, Nanotheranostics 3 (2019) 166–178.
[160] S.Y. Yeo, M. de Smet, S. Langereis, L. Vander Elst, R.N. Muller, H. Grull, Temperature-sensitive paramagnetic liposomes for image-guided drug delivery: Mn(2+) versus [Gd(HPDO3A)(H2O)], Biochim. Biophys. Acta 1838 (2014) 2807–2816.
[161] J. Beik, Z. Abed, F.S. Ghoreishi, S. Hosseini-Nami, S. Mehrzadi, A. Shakeri-Zadeh, S.K. Kamrava, Nanotechnology in hyperthermia cancer therapy: from fundamental principles to advanced applications, J. Control. Release 235 (2016) 205–221.
[162] D.C.S. PR, M.H. Seegenschmiedt, Interstitial heating technologies, in: F.P.S. MH, C.C. Vernon (Eds.),Thermoradiotherapy and Thermochemotherapy: Volume 1, Biology, Physiology and Physics 1995, pp. 279–320.
[163] V.A. Salgaonkar, C.J. Diederich, Catheter-based ultrasound technology for image-guided thermal therapy: current technology and applications, Int. J. Hyperth. 31 (2015) 203–215.
[164] R. Chopra, M. Burtnyk, M.A. Haider, M.J. Bronskill, Method for MRI-guided conformal thermal therapy of prostate with planar transurethral ultrasound heating applicators, Phys. Med. Biol. 50 (2005) 4957–4975.
[165] D. Liu, M.S. Adams, E.C. Burdette, C.J. Diederich, Transurethral high-intensity ultrasound for treatment of stress urinary incontinence (SUI): simulation studies with patient-specific models, Int. J. Hyperth. 34 (2018) 1236–1247.
[166] E. Ozhinsky, V.A. Salgaonkar, C.J. Diederich, V. Rieke, MR thermometry-guided ultrasound hyperthermia of user-defined regions using the ExAblate prostate ablation array, J. Ther. Ultrasound 6 (2018) 7.
[167] Z. Petrovich, F. Ameye, M. Pike, S. Boyd, L. Baert, Relationship of response to transurethral hyperthermia and prostate volume in BPH patients, Urology 40 (1992) 317–321.
[168] M.D. Hurwitz, I.D. Kaplan, G.K. Svensson, K. Hynynen, M.S. Hansen, Feasibility and patient tolerance of a novel transrectal ultrasound hyperthermia system for treatment of prostate cancer, Int. J. Hyperth. 17 (2001) 31–37.
[169] S. Curto, P. Faridi, T.B. Shrestha, M. Pyle, L. Maurmann, D. Troyer, S.H. Bossmann, P. Prakash, An integrated platform for small-animal hyperthermia investigations under ultra-high-field MRI guidance, Int. J. Hyperth. 34 (2018) 341–351.
[170] Q.A. Pankhurst, J. Connolly, S.K. Jones, J. Dobson, Applications of magnetic nanoparticles in biomedicine, J. Phys. D. Appl. Phys. 36 (2003) R167–R181.
[171] I. Hilger, In vivo applications of magnetic nanoparticle hyperthermia, Int. J. Hyperth. 29 (2013) 828–834.
[172] L. Winter, E. Oberacker, K. Paul, Y. Ji, C. Oezerdem, P. Ghadjar, A. Thieme, V. Budach, P. Wust, T. Niendorf, Magnetic resonance thermometry: methodology, pitfalls and practical solutions, Int. J. Hyperth. 32 (2016) 63–75.
[173] P. Wust, C.H. Cho, B. Hildebrandt, J. Gellermann, Thermal monitoring: invasive, minimal-invasive and non-invasive approaches, Int. J. Hyperth. 22 (2006) 255–262.
[174] V. Rieke, K. Butts Pauly, MR thermometry, J. Magn. Reson. Imaging 27 (2008) 376–390.
[175] R. Tietze, J. Zaloga, H. Unterweger, S. Lyer, R.P. Friedrich, C. Janko, M. Pottler, S. Durr, C. Alexiou, Magnetic nanoparticle-based drug delivery for cancer therapy, Biochem. Biophys. Res. Commun. 468 (2015) 463–470.
[176] E.S. Lee, Z. Gao, Y.H. Bae, Recent progress in tumor pH targeting nanotechnology, J. Control. Release 132 (2008) 164–170.
[177] M.B. Yatvin, W. Kreutz, B.A. Horwitz, M. Shinitzky, pH-sensitive liposomes: possible clinical implications, Science 210 (1980) 1253–1255.
[178] W. Ong, Y. Yang, A.C. Cruciano, R.L. McCarley, Redox-triggered contents release from liposomes, J. Am. Chem. Soc. 130 (2008) 14739–14744.
[179] T.L. Andresen, D.H. Thompson, T. Kaasgaard, Enzyme-triggered nanomedicine: drug release strategies in cancer therapy, Mol. Membr. Biol. 27 (2010) 353–363.
[180] S. Mura, J. Nicolas, P. Couvreur, Stimuli-responsive nanocarriers for drug delivery, Nat. Mater. 12 (2013) 991–1003.
[181] A.Y. Rwei, W. Wang, D.S. Kohane, Photoresponsive nanoparticles for drug delivery, Nano Today 10 (2015) 451–467.
[182] M.S. Yavuz, Y. Cheng, J. Chen, C.M. Cobley, Q. Zhang, M. Rycenga, J. Xie, C. Kim, K.H. Song, A.G. Schwartz, L.V. Wang, Y. Xia, Gold nanocages covered by smart polymers for controlled release with near-infrared light, Nat. Mater. 8 (2009) 935–939.
[183] Y. Li, K. Xiao, W. Zhu, W. Deng, K.S. Lam, Stimuli-responsive cross-linked micelles for on-demand drug delivery against cancers, Adv. Drug Deliv. Rev. 66 (2014) 58–73.
[184] W. Deng, W. Chen, S. Clement, A. Guller, Z. Zhao, A. Engel, E.M. Goldys, Controlled gene and drug release from a liposomal delivery platform triggered by X-ray radiation, Nat. Commun. 9 (2018) 2713.
[185] S. Senapati, A.K. Mahanta, S. Kumar, P. Maiti, Controlled drug delivery vehicles for cancer treatment and their performance, Signal Transduct. Target Ther. 3 (2018) 7.
[186] B. Kneidl, M. Peller, G. Winter, L.H. Lindner, M. Hossann, Thermosensitive liposomal drug delivery systems: state of the art review, Int. J. Nanomedicine 9 (2014) 4387–4398.
[187] N.D. Donahue, H. Acar, S. Wilhelm, Concepts of nanoparticle cellular uptake, intracellular trafficking, and kinetics in nanomedicine, Adv. Drug Deliv. Rev. 43 (2019) 68–96.
[188] S. Barua, S. Mitragotri, Challenges associated with penetration of nanoparticles across cell and tissue barriers: a review of current status and future prospects, Nano Today 9 (2014) 223–243.
[189] S.N. Tammam, H.M.E. Azzazy, A. Lamprecht, How successful is nuclear targeting by nanocarriers? J. Control. Release 229 (2016) 140–153.
[190] D. Liu, F. Yang, F. Xiong, N. Gu, The smart drug delivery system and its clinical potential, Theranostics 6 (2016) 1306–1323.
[191] M. van Elk, B.P. Murphy, T. Eufrasio-da-Silva, D.P. O'Reilly, T. Vermonden, W.E. Hennink, G.P. Duffy, E. Ruiz-Hernandez, Nanomedicines for advanced cancer treatments: transitioning towards responsive systems, Int. J. Pharm. 515 (2016) 132–164.
[192] S.J. Leung, M. Romanowski, Light-activated content release from liposomes, Theranostics 2 (2012) 1020–1036.
[193] A. Bansal, Y. Zhang, Photocontrolled nanoparticle delivery systems for biomedical applications, Acc. Chem. Res. 47 (2014) 3052–3060.
[194] S. Mo, C.C. Coussios, L. Seymour, R. Carlisle, Ultrasound-enhanced drug delivery for cancer, Expert Opin. Drug Deliv. 9 (2012) 1525–1538.
[195] S. Eggen, S.M. Fagerland, Y. Morch, R. Hansen, K. Sovik, S. Berg, H. Furu, A.D. Bohn, M.B. Lilledahl, A. Angelsen, B. Angelsen, C. de Lange Davies, Ultrasound-enhanced drug delivery in prostate cancer xenografts by nanoparticles stabilizing microbubbles, J. Control. Release 187 (2014) 39–49.
[196] S.L. Huang, Liposomes in ultrasonic drug and gene delivery, Adv. Drug Deliv. Rev. 60 (2008) 1167–1176.
[197] P. Nittayacharn, H.X. Yuan, C. Hernandez, P. Bielecki, H. Zhou, A.A. Exner, Enhancing tumor drug distribution with ultrasound-triggered nanobubbles, J. Pharm. Sci. (2019) 3091–3098.
[198] S. Rizzitelli, P. Giustetto, J.C. Cutrin, D. Delli Castelli, C. Boffa, M. Ruzza, V. Menchise, F. Molinari, S. Aime, E. Terreno, Sonosensitive theranostic liposomes for preclinical in vivo MRI-guided visualization of doxorubicin release stimulated by pulsed low intensity non-focused ultrasound, J. Control. Release 202 (2015) 21–30.
[199] T. Lu, W.J.M. Lokerse, A.L.B. Seynhaeve, G.A. Koning, T.L.M. Ten Hagen, Formulation and optimization of idarubicin thermosensitive liposomes provides ultrafast triggered release at mild hyperthermia and improves tumor response, J. Control. Release 220 (2015) 425–437.
[200] O.G. Mouritsen, K. Jorgensen, Dynamical order and disorder in lipid bilayers, Chem. Phys. Lipids 73 (1994) 3–25.
[201] O.G. Mouritsen, M.J. Zuckermann, Model of interfacial melting, Phys. Rev. Lett. 58 (1987) 389–392.
[202] L.H. Lindner, M. Hossann, M. Vogeser, N. Teichert, K. Wachholz, H. Eibl, W. Hiddemann, R.D. Issels, Dual role of hexadecylphosphocholine (miltefosine) in thermosensitive liposomes: active ingredient and mediator of drug release, J. Control. Release 125 (2008) 112–120.
[203] J.K. Mills, D. Needham, Lysolipid incorporation in dipalmitoylphosphatidylcholine bilayer membranes enhances the ion permeability and drug release rates at the membrane phase transition, Biochim. Biophys. Acta 1716 (2005) 77–96.
[204] D. Papahadjopoulos, K. Jacobson, S. Nir, T. Isac, Phase transitions in phospholipid vesicles. Fluorescence polarization and permeability measurements concerning the effect of temperature and cholesterol, Biochim. Biophys. Acta 311 (1973) 330–348.
[205] L. Li, T.L. ten Hagen, D. Schipper, T.M. Wijnberg, G.C. van Rhoon, A.M. Eggermont, L.H. Lindner, G.A. Koning, Triggered content release from optimized stealth thermosensitive liposomes using mild hyperthermia, J. Control. Release 143 (2010) 274–279.
[206] A. Bordat, T. Boissenot, J. Nicolas, N. Tsapis, Thermoresponsive polymer nanocarriers for biomedical applications, Adv. Drug Deliv. Rev. 138 (2019) 167–192.
[207] J. Zhang, Z. Qian, Y. Gu, In vivo anti-tumor efficacy of docetaxel-loaded thermally responsive nanohydrogel, Nanotechnology 20 (2009) 325102.
[208] X. Wang, S. Li, Z. Wan, Z. Quan, Q. Tan, Investigation of thermo-sensitive amphiphilic micelles as drug carriers for chemotherapy in cholangiocarcinoma in vitro and in vivo, Int. J. Pharm. 463 (2014) 81–88.
[209] S. Cammas, K. Suzuki, C. Sone, Y. Sakurai, K. Kataoka, T. Okano, Thermo-responsive polymer nanoparticles with a core-shell micelle structure as site-specific drug carriers, J. Control. Release 48 (1997) 157–164.
[210] J.E. Chung, M. Yokoyama, M. Yamato, T. Aoyagi, Y. Sakurai, T. Okano, Thermo-responsive drug delivery from polymeric micelles constructed using block

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copolymers of poly(N-isopropylacrylamide) and poly(butylmethacrylate), J. Control. Release 62 (1999) 115–127.
[211] K. Kono, A. Henmi, H. Yamashita, H. Hayashi, T. Takagishi, Improvement of temperature-sensitivity of poly(N-isopropylacrylamide)-modified liposomes, J. Control. Release 59 (1999) 63–75.
[212] K. Kono, T. Ozawa, T. Yoshida, F. Ozaki, Y. Ishizaka, K. Maruyama, C. Kojima, A. Harada, S. Aoshima, Highly temperature-sensitive liposomes based on a thermosensitive block copolymer for tumor-specific chemotherapy, Biomaterials 31 (2010) 7096–7105.
[213] K. Kono, Thermosensitive polymer-modified liposomes, Adv. Drug Deliv. Rev. 53 (2001) 307–319.
[214] Z. Al-Ahmady, K. Kostarelos, Chemical components for the design of temperature-responsive vesicles as cancer therapeutics, Chem. Rev. 116 (2016) 3883–3918.
[215] P. Pradhan, J. Giri, F. Rieken, C. Koch, O. Mykhaylyk, M. Doblinger, R. Banerjee, D. Bahadur, C. Plank, Targeted temperature sensitive magnetic liposomes for thermo-chemotherapy, J. Control. Release 142 (2010) 108–121.
[216] Y. Chen, A. Bose, G.D. Bothun, Controlled release from bilayer-decorated magnetoliposomes via electromagnetic heating, ACS Nano 4 (2010) 3215–3221.
[217] L. Paasonen, T. Laaksonen, C. Johans, M. Yliperttula, K. Kontturi, A. Urtti, Gold nanoparticles enable selective light-induced contents release from liposomes, J. Control. Release 122 (2007) 86–93.
[218] L. Paasonen, T. Sipila, A. Subrizi, P. Laurinmaki, S.J. Butcher, M. Rappolt, A. Yaghmur, A. Urtti, M. Yliperttula, Gold-embedded photosensitive liposomes for drug delivery: triggering mechanism and intracellular release, J. Control. Release 147 (2010) 136–143.
[219] G.H. Wu, A. Milkhailovsky, H.A. Khant, C. Fu, W. Chiu, J.A. Zasadzinski, Remotely triggered liposome release by near-infrared light absorption via hollow gold nanoshells, J. Am. Chem. Soc. 130 (2008)(8175±).
[220] J. You, P. Zhang, F. Hu, Y. Du, H. Yuan, J. Zhu, Z. Wang, J. Zhou, C. Li, Near-infrared light-sensitive liposomes for the enhanced photothermal tumor treatment by the combination with chemotherapy, Pharm. Res. 31 (2014) 554–565.
[221] A. Gasselhuber, M.R. Dreher, F. Rattay, B.J. Wood, D. Haemmerich, Comparison of conventional chemotherapy, stealth liposomes and temperature-sensitive liposomes in a mathematical model, PLoS One 7 (2012), e47453.
[222] M.B. Yatvin, J.N. Weinstein, W.H. Dennis, R. Blumenthal, Design of liposomes for enhanced local release of drugs by hyperthermia, Science 202 (1978) 1290–1293.
[223] J.N. Weinstein, R.L. Magin, M.B. Yatvin, D.S. Zaharko, Liposomes and local hyperthermia: selective delivery of methotrexate to heated tumors, Science 204 (1979) 188–191.
[224] M.B. Yatvin, H. Muhlensiepen, W. Porschen, J.N. Weinstein, L.E. Feinendegen, Selective delivery of liposome-associated cis-dichlorodiammineplatinum(II) by heat and its influence on tumor drug uptake and growth, Cancer Res. 41 (1981) 1602–1607.
[225] K. Iga, N. Hamaguchi, Y. Igari, Y. Ogawa, K. Gotoh, K. Ootsu, H. Toguchi, T. Shimamoto, Enhanced antitumor activity in mice after administration of thermosensitive liposome encapsulating cisplatin with hyperthermia, J. Pharmacol. Exp. Ther. 257 (1991) 1203–1207.
[226] T. Lu, T.L.M. Ten Hagen, Inhomogeneous crystal grain formation in DPPC-DSPC based thermosensitive liposomes determines content release kinetics, J. Control. Release 247 (2017) 64–72.
[227] M.H. Gaber, K. Hong, S.K. Huang, D. Papahadjopoulos, Thermosensitive sterically stabilized liposomes: formulation and in vitro studies on mechanism of doxorubicin release by bovine serum and human plasma, Pharm. Res. 12 (1995) 1407–1416.
[228] C.D. Landon, J.Y. Park, D. Needham, M.W. Dewhirst, Nanoscale drug delivery and hyperthermia: the materials design and preclinical and clinical testing of low temperature-sensitive liposomes used in combination with mild hyperthermia in the treatment of local cancer, Open Nanomed. J. 3 (2011) 38–64.
[229] Q. Chen, A. Krol, A. Wright, D. Needham, M.W. Dewhirst, F. Yuan, Tumor microvascular permeability is a key determinant for antivascular effects of doxorubicin encapsulated in a temperature sensitive liposome, Int. J. Hyperth. 24 (2008) 475–482.
[230] Q. Chen, S. Tong, M.W. Dewhirst, F. Yuan, Targeting tumor microvessels using doxorubicin encapsulated in a novel thermosensitive liposome, Mol. Cancer Ther. 3 (2004) 1311–1317.
[231] D. Needham, G. Anyarambhatla, G. Kong, M.W. Dewhirst, A new temperature-sensitive liposome for use with mild hyperthermia: characterization and testing in a human tumor xenograft model, Cancer Res. 60 (2000) 1197–1201.
[232] B.J. Wood, R.T. Poon, J.K. Locklin, M.R. Dreher, K.K. Ng, M. Eugeni, G. Seidel, S. Dromi, Z. Neeman, M. Kolf, C.D. Black, R. Prabhakar, S.K. Libutti, Phase I study of heat-deployed liposomal doxorubicin during radiofrequency ablation for hepatic malignancies, J. Vasc. Interv. Radiol. 23 (2012) 248–255e247.
[233] T.M. Zagar, Z. Vujaskovic, S. Formenti, H. Rugo, F. Muggia, B. O'Connor, R. Myerson, P. Stauffer, I.C. Hsu, C. Diederich, W. Straube, M.K. Boss, A. Boico, O. Craciunescu, P. Maccarini, D. Needham, N. Borys, K.L. Blackwell, M.W. Dewhirst, Two phase I dose-escalation/pharmacokinetics studies of low temperature liposomal doxorubicin (LTLD) and mild local hyperthermia in heavily pretreated patients with local regionally recurrent breast cancer, Int. J. Hyperth. 30 (2014) 285–294.
[234] U. Salati, A. Barry, F.Y. Chou, R. Ma, D.M. Liu, State of the ablation nation: a review of ablative therapies for cure in the treatment of hepatocellular carcinoma, Future Oncol. 13 (2017) 1437–1448.
[235] D.J. Holzwanger, D.C. Madoff, Role of interventional radiology in the management of hepatocellular carcinoma: current status, Chin. Clin. Oncol. 7 (2018) 49.
[236] R. Lencioni, L. Crocetti, Local-regional treatment of hepatocellular carcinoma, Radiology 262 (2012) 43–58.
[237] C. Rossmann, M.A. McCrackin, K.E. Armeson, D. Haemmerich, Temperature sensitive liposomes combined with thermal ablation: effects of duration and timing of heating in mathematical models and in vivo, PLoS One 12 (2017), e0179131.
[238] A. Gasselhuber, M.R. Dreher, A. Negussie, B.J. Wood, F. Rattay, D. Haemmerich, Mathematical spatio-temporal model of drug delivery from low temperature sensitive liposomes during radiofrequency tumour ablation, Int. J. Hyperth. 26 (2010) 499–513.
[239] C.E. Swenson, D. Haemmerich, D.H. Maul, B. Knox, N. Ehrhart, R.A. Reed, Increased duration of heating boosts local drug deposition during radiofrequency ablation in combination with thermally sensitive liposomes (ThermoDox) in a porcine model, PLoS One 10 (2015), e0139752.
[240] W.Y. Tak, S.M. Lin, Y. Wang, J. Zheng, A. Vecchione, S.Y. Park, M.H. Chen, S. Wong, R. Xu, C.Y. Peng, Y.Y. Chiou, G.T. Huang, J. Cai, B.J.J. Abdullah, J.S. Lee, J.Y. Lee, J.Y. Choi, J. Gopez-Cervantes, M. Sherman, R.S. Finn, M. Omata, M. O'Neal, L. Makris, N. Borys, R. Poon, R. Lencioni, Phase III HEAT study adding Lyso-thermosensitive liposomal doxorubicin to radiofrequency ablation in patients with unresectable hepatocellular carcinoma lesions, Clin. Cancer Res. 24 (2018) 73–83.
[241] Y. Dou, K. Hynynen, C. Allen, To heat or not to heat: challenges with clinical translation of thermosensitive liposomes, J. Control. Release 249 (2017) 63–73.
[242] T. Nakashima, M. Kojiro, Y. Kawano, F. Shirai, N. Takemoto, Y. Tomimatsu, H. Kawasaki, K. Okuda, Histologic growth pattern of hepatocellular carcinoma: relationship to orcein (hepatitis B surface antigen)-positive cells in cancer tissue, Hum. Pathol. 13 (1982) 563–568.
[243] G.G. Van den Eynden, A.W. Majeed, M. Illemann, P.B. Vermeulen, N.C. Bird, G. Hoyer-Hansen, R.L. Eefsen, A.R. Reynolds, P. Brodt, The multifaceted role of the microenvironment in liver metastasis: biology and clinical implications, Cancer Res. 73 (2013) 2031–2043.
[244] Study of ThermoDox With Standardized Radiofrequency Ablation (RFA) for Treatment of Hepatocellular Carcinoma (HCC) (OPTIMA), https://clinicaltrials.gov/ct2/show/NCT02112656 2018.
[245] Celsion Reports Unanimous Independent Data Monitoring Committee Recommendation to Continue the Phase III OPTIMA Study of ThermoDox® in Primary Liver Cancer, http://investor.celsion.com/news-releases/news-release-details/celsion-reports-unanimous-independent-data-monitoring-committee 2019.
[246] M.D. Gray, P.C. Lyon, C. Mannaris, L.K. Folkes, M. Stratford, L. Campo, D.Y.F. Chung, S. Scott, M. Anderson, R. Goldin, R. Carlisle, F. Wu, M.R. Middleton, F.V. Gleeson, C.C. Coussios, Focused ultrasound hyperthermia for targeted drug release from thermosensitive liposomes: results from a phase I trial, Radiology 291 (2019) 232–238.
[247] R.M. Staruch, M. Ganguly, I.F. Tannock, K. Hynynen, R. Chopra, Enhanced drug delivery in rabbit VX2 tumours using thermosensitive liposomes and MRI-controlled focused ultrasound hyperthermia, Int. J. Hyperth. 28 (2012) 776–787.
[248] D. Haemmerich, Non-invasive image-guided targeted drug delivery, Lancet Oncol. 19 (2018) 1000–1001.
[249] B. Banno, L.M. Ickenstein, G.N. Chiu, M.B. Bally, J. Thewalt, E. Brief, E.K. Wasan, The functional roles of poly(ethylene glycol)-lipid and lysolipid in the drug retention and release from lysolipid-containing thermosensitive liposomes in vitro and in vivo, J. Pharm. Sci. 99 (2010) 2295–2308.
[250] M.C. Sandstrom, L.M. Ickenstein, L.D. Mayer, K. Edwards, Effects of lipid segregation and lysolipid dissociation on drug release from thermosensitive liposomes, J. Control. Release 107 (2005) 131–142.
[251] N. Sadeghi, R. Deckers, B. Ozbakir, S. Akthar, R.J. Kok, T. Lammers, G. Storm, Influence of cholesterol inclusion on the doxorubicin release characteristics of lysolipid-based thermosensitive liposomes, Int. J. Pharm. 548 (2018) 778–782.
[252] Phase 3 Study of ThermoDox With Radiofrequency Ablation (RFA) in Treatment of Hepatocellular Carcinoma (HCC), https://clinicaltrials.gov/ct2/show/NCT00617981 2017.
[253] A.L. Bredlau, A. Motamarry, C. Chen, M.A. McCrackin, K. Helke, K.E. Armeson, K. Bynum, A.M. Broome, D. Haemmerich, Localized delivery of therapeutic doxorubicin dose across the canine blood-brain barrier with hyperthermia and temperature sensitive liposomes, Drug Deliv. 25 (2018) 973–984.
[254] L.H. Lindner, M.E. Eichhorn, H. Eibl, N. Teichert, M. Schmitt-Sody, R.D. Issels, M. Dellian, Novel temperature-sensitive liposomes with prolonged circulation time, Clin. Cancer Res. 10 (2004) 2168–2178.
[255] M. Hossann, M. Wiggenhorn, A. Schwerdt, K. Wachholz, N. Teichert, H. Eibl, R.D. Issels, L.H. Lindner, In vitro stability and content release properties of phosphatidylglyceroglycerol containing thermosensitive liposomes, Biochim. Biophys. Acta 1768 (2007) 2491–2499.
[256] K. Zimmermann, M. Hossann, J. Hirschberger, K. Troedson, M. Peller, M. Schneider, A. Bruhschwein, A. Meyer-Lindenberg, G. Wess, M. Wergin, R. Dorfelt, T. Knosel, M. Schwaiger, C. Baumgartner, J. Brandl, S. Schwamberger, L.H. Lindner, A pilot trial of doxorubicin containing phosphatidyldiglycerol based thermosensitive liposomes in spontaneous feline soft tissue sarcoma, Int. J. Hyperth. 33 (2017) 178–190.
[257] G. Kong, G. Anyarambhatla, W.P. Petros, R.D. Braun, O.M. Colvin, D. Needham, M.W. Dewhirst, Efficacy of liposomes and hyperthermia in a human tumor xenograft model: importance of triggered drug release, Cancer Res. 60 (2000) 6950–6957.
[258] W.J. Lokerse, E.C. Kneepkens, T.L. ten Hagen, A.M. Eggermont, H. Grull, G.A. Koning, In depth study on thermosensitive liposomes: optimizing formulations for tumor specific therapy and in vitro to in vivo relations, Biomaterials 82 (2016) 138–150.
[259] D.S. Dizon, J. Schwartz, N. Kemeny, Regional chemotherapy: a focus on hepatic artery infusion for colorectal cancer liver metastases, Surg. Oncol. Clin. N. Am. 17 (2008) 759–771viii.
[260] A. Haeri, L.R. Pedrosa, T.L. Ten Hagen, S. Dadashzadeh, G.A. Koning, A novel combined approach of short-chain sphingolipids and thermosensitive liposomes for improved drug delivery to tumor cells, J. Biomed. Nanotechnol. 12 (2016) 630–644.

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[261] M. van Lummel, W.J. van Blitterswijk, S.R. Vink, R.J. Veldman, M.A. van der Valk, D. Schipper, B.M. Dicheva, A.M. Eggermont, T.L. ten Hagen, M. Verheij, G.A. Koning, Enriching lipid nanovesicles with short-chain glucosylceramide improves doxorubicin delivery and efficacy in solid tumors, FASEB J. 25 (2011) 280–289.
[262] A. Yudina, M. de Smet, M. Lepetit-Coiffe, S. Langereis, L. Van Ruijssevelt, P. Smirnov, V. Bouchaud, P. Voisin, H. Grull, C.T. Moonen, Ultrasound-mediated intracellular drug delivery using microbubbles and temperature-sensitive liposomes, J. Control. Release 155 (2011) 442–448.
[263] L. Li, T.L. ten Hagen, A. Haeri, T. Soullie, C. Scholten, A.L. Seynhaeve, A.M. Eggermont, G.A. Koning, A novel two-step mild hyperthermia for advanced liposomal chemotherapy, J. Control. Release 174 (2014) 202–208.
[264] T. Ojha, V. Pathak, Y. Shi, W.E. Hennink, C.T.W. Moonen, G. Storm, F. Kiessling, T. Lammers, Pharmacological and physical vessel modulation strategies to improve EPR-mediated drug targeting to tumors, Adv. Drug Deliv. Rev. 119 (2017) 44–60.
[265] L. Li, T.L. Ten Hagen, A. Haeri, T. Soullie, C. Scholten, A.L. Seynhaeve, A.M. Eggermont, G.A. Koning, A novel two-step mild hyperthermia for advanced liposomal chemotherapy, J. Control. Release (2014) 202–208.
[266] J.M. Cha, D.G. You, E.J. Choi, S.J. Park, W. Um, J. Jeon, K. Kim, I.C. Kwon, J.C. Park, H.R. Kim, J.H. Park, Improvement of antitumor efficacy by combination of thermosensitive liposome with high-intensity focused ultrasound, J. Biomed. Nanotechnol. 12 (2016) 1724–1733.
[267] A.A. Gabizon, O. Lyass, G.J. Berry, M. Wildgust, Cardiac safety of pegylated liposomal doxorubicin (Doxil/Caelyx) demonstrated by endomyocardial biopsy in patients with advanced malignancies, Cancer Investig. 22 (2004) 663–669.
[268] O. Lyass, A. Hubert, A.A. Gabizon, Phase I study of doxil-cisplatin combination chemotherapy in patients with advanced malignancies, Clin. Cancer Res. 7 (2001) 3040–3046.
[269] A.A. Gabizon, Stealth liposomes and tumor targeting: one step further in the quest for the magic bullet, Clin. Cancer Res. 7 (2001) 223–225.
[270] M. Lotem, A. Hubert, O. Lyass, M.A. Goldenhersh, A. Ingber, T. Peretz, A. Gabizon, Skin toxic effects of polyethylene glycol-coated liposomal doxorubicin, Arch. Dermatol. 136 (2000) 1475–1480.
[271] T. Safra, F. Muggia, S. Jeffers, D.D. Tsao-Wei, S. Groshen, O. Lyass, R. Henderson, G. Berry, A. Gabizon, Pegylated liposomal doxorubicin (doxil): reduced clinical cardiotoxicity in patients reaching or exceeding cumulative doses of 500 mg/m2, Ann. Oncol. 11 (2000) 1029–1033.
[272] O. Lyass, B. Uziely, R. Ben-Yosef, D. Tzemach, N.I. Heshing, M. Lotem, G. Brufman, A. Gabizon, Correlation of toxicity with pharmacokinetics of pegylated liposomal doxorubicin (Doxil) in metastatic breast carcinoma, Cancer 89 (2000) 1037–1047.
[273] A. Cabanes, D. Tzemach, D. Goren, A.T. Horowitz, A. Gabizon, Comparative study of the antitumor activity of free doxorubicin and polyethylene glycol-coated liposomal doxorubicin in a mouse lymphoma model, Clin. Cancer Res. 4 (1998) 499–505.
[274] L. Zheng, C. Li, X. Huang, X. Lin, W. Lin, F. Yang, T. Chen, Thermosensitive hydrogels for sustained-release of sorafenib and selenium nanoparticles for localized synergistic chemoradiotherapy, Biomaterials 216 (2019) 119220.
[275] X. Wu, Y. Wu, H. Ye, S. Yu, C. He, X. Chen, Interleukin-15 and cisplatin co-encapsulated thermosensitive polypeptide hydrogels for combined immunochemotherapy, J. Control. Release 255 (2017) 81–93.
[276] L. Bezu, L.C. Gomes-de-Silva, H. Dewitte, K. Breckpot, J. Fucikova, R. Spisek, L. Galluzzi, O. Kepp, G. Kroemer, Combinatorial strategies for the induction of immunogenic cell death, Front. Immunol. 6 (2015) 187.
[277] L. Galluzzi, A. Buque, O. Kepp, L. Zitvogel, G. Kroemer, Immunogenic cell death in cancer and infectious disease, Nat. Rev. Immunol. 17 (2017) 97–111.
[278] G. Kroemer, L. Galluzzi, O. Kepp, L. Zitvogel, Immunogenic cell death in cancer therapy, Annu. Rev. Immunol. 31 (2013) 51–72.

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