Advanced Drug Delivery Reviews 158 (2020) 36–62

Contents lists available at ScienceDirect

Advanced Drug Delivery Reviews

journal homepage: www.elsevier.com/locate/addr

Physical triggering strategies for drug delivery

Tao Sun [a,b,c,1], Anshuman Dasgupta [d,1], Zongmin Zhao [a,b,1], Md Nurunnabi [e,1], Samir Mitragotri [a,b,*]

[a] John A. Paulson School of Engineering and Applied Sciences, Harvard University, Cambridge, MA 02138, USA
[b] Wyss Institute for Biologically Inspired Engineering, Harvard University, Boston, MA 02115, USA
[c] Department of Radiology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA 02115, USA
[d] Department of Nanomedicine and Theranostics, Institute for Experimental Molecular Imaging, RWTH Aachen University, Aachen, Germany
[e] Department of Pharmaceutical Sciences, School of Pharmacy, University of Texas at El Paso, TX 79902, USA

A R T I C L E I N F O

Article history:
Received 27 April 2020
Received in revised form 6 June 2020
Accepted 10 June 2020
Available online 24 June 2020

Keywords:
Drug delivery
Controlled release
Physical triggers
Ultrasound
Light
Electric field
Magnetic field

A B S T R A C T

Physically triggered systems hold promise for improving drug delivery by enhancing the controllability of drug accumulation and release, lowering non-specific toxicity, and facilitating clinical translation. Several external physical stimuli including ultrasound, light, electric fields and magnetic fields have been used to control drug delivery and they share some common features such as spatial targeting, spatiotemporal control, and minimal invasiveness. At the same time, they possess several distinctive features in terms of interactions with biological entities and/or the extent of stimulus response. Here, we review the key advances of such systems with a focus on discussing their physical mechanisms, the design rationales, and translational challenges.

Contents

* Corresponding author at: John A. Paulson School of Engineering and Applied Sciences, Harvard University, Cambridge, MA 02138, USA.
E-mail address: mitragotri@seas.harvard.edu (S. Mitragotri).
[1]Authors contributed equally to this work.

https://doi.org/10.1016/j.addr.2020.06.010

1. Introduction

Drug delivery systems triggered by physical sources offer several advantages due to their unique abilities of spatial targeting, spatiotemporal control, and minimal invasiveness [1,2]. These features may be desirable in enhancing the therapeutic efficacy of drug delivery where the on-demand control release is needed. In addition, designing targeted delivery systems based on the intrinsic biophysical properties of the disease site can be challenging due to the heterogenous nature of the vasculature or other physiological factors [2]. Adding spatial targeting of physical triggering can greatly simplify the design of drug carriers without compromising the targeting ability [1].

Physically triggered systems could allow a broad range of drug release patterns, depending on the adopted energy source, physiological properties of targeted cell/organ, physical and biochemical properties of the drug carriers and the site of administration. Although various reviews have been published focusing on each physical triggering system itself and/or its stimuli-responsive materials [3–6], the drug delivery field currently lacks an up-to-date review covering both recently reported preclinical efforts and clinical progress. Additionally, a high-level comparison across different physical triggers for drug delivery applications is needed for the research community to select, design and optimize drug delivery system for specific application.

In this review, we discuss four main physical triggering strategies that have been actively used in drug delivery – ultrasound, light, electric and magnetic fields. We describe the governing physical mechanisms of each triggering system, offer representative systems developed, and extend the discussion to the clinical needs and translational challenges. In addition, we highlight the growing efforts in multi-modality, multi-functional theranostic systems. Finally, we discuss the advantages and limitations for each trigger in different applications, and provide an outlook for the field.

2. Ultrasound

As mechanical longitudinal waves, ultrasound (US) waves produce compression/rarefaction and the pressure change when traveling through a medium. US can be transmitted as continuous sinusoidal waves, or in the pulsed mode as repetitive sinusoidal bursts with predefined length and repetition [7]. In the context of medical applications, US has been widely used as a non-invasive imaging modality in the clinic [8–10]. Such imaging applications primarily employ frequency ranging from 2 MHz and beyond. Over the decades, application of US in the range of 20 KHz–2 MHz has gained significant attention for therapeutic applications. These include tumor or neurological ablation, sonodynamic therapy, thrombolysis, osteoporosis, angioplasty, lipoplasty, hemostasis, pain palliation of metastatic bone cancer, and healing skin wounds, bone fractures and damaged nerves, among others [10–12].

Apart from the above-mentioned direct therapeutic effects, US has also been used as a physical trigger to facilitate drug and gene delivery across biological barriers. Several mechanisms including thermal and mechanical effects have been postulated to contribute to the enhancement of drug transport [10,13]. Propagating ultrasonic waves result in tissue displacements. With each ultrasonic cycle, a portion of sound energy is absorbed by the tissue, leading to local thermal deposition. The degree of energy absorption is dependent on not only the acoustic properties of the tissue, but also on the US frequency [14]. This local heating can ultimately be used to release drugs from heat activatable vehicles to targeted areas. Another family of US drug delivery relies on the mechanical effects arising from the US itself, or more popularly from biologically inert and pre-administrated acoustic enhancers (typically but not limited to microbubbles) [13,14]. These approaches benefit from the enhanced mechanical effects induced by cavitation inside the blood vessels. In addition to the direct “pushing” and “pulling” forces exerted onto the vessels during bubble oscillations, cavitating microspheres near a boundary can also induce radiation force, shear-related acoustic streaming, or even microjetting once bubble collapses [10]. These effects may be beneficial in delivering agents across the biological barriers.

In this section, we discuss these mechanisms and focus on the advances made in US-mediated drug delivery, namely (i) sonophoresis, (ii) sonopermeation and (iii) hyperthermia.

2.1. Sonophoresis

Sonophoresis refers to the application of US (20 kHz–1 MHz) in permeabilizing skin for improving transdermal drug delivery [15,16]. This is typically performed in the absence of acoustically responsive agents. Several key mechanisms have been known to contribute to US-mediated transdermal drug delivery. These include cavitation and acoustic streaming as a result of bubble oscillation, both of which are known to temporarily permeabilize the membranes of stratum corneum and enhance the convective transport of drugs (Fig. 1A) [15,16].

Sonophoresis was initially employed with higher US frequencies ranging between 20 kHz and 16 MHz, however since 1990s, several studies highlighted that low frequency US, i.e. 20–100 kHz, can be more effective in delivering drugs across the skin [16]. These initial findings formed the basis for several preclinical studies to enhance the delivery of several small and large size therapeutics including lidocaine, tetraphenylporphyrin, gemcitabine, cisplatin, methotrexate, insulin, interferon gamma, erythropoietin, heparin and tetanus toxoid across different skin models [17–22]. Recently, sonophoresis has been used to improve the skin penetration of nanomedicine, such as gold nanoparticles and Doxil-like liposomes in pig skin models [23,24]. Taking a step forward, sonophoresis has been combined with other physical permeation enhancers, such as iontophoresis and microneedle to achieve much greater skin permeabilization and drug penetration [25–27]. In the case of former, Park et al. reported a new device that was capable of performing both iontophoresis and sonophoresis simultaneously. They reported that the simultaneous application was superior to iontophoresis or sonophoresis treatment alone and demonstrated enhanced skin penetration of various cosmeceuticals including niacinamide, arbutin, caffeine, glutamic acid, retinol, alpa-bisabolol and minoxidil [25]. Another study used surface-enhanced Raman spectroscopy to

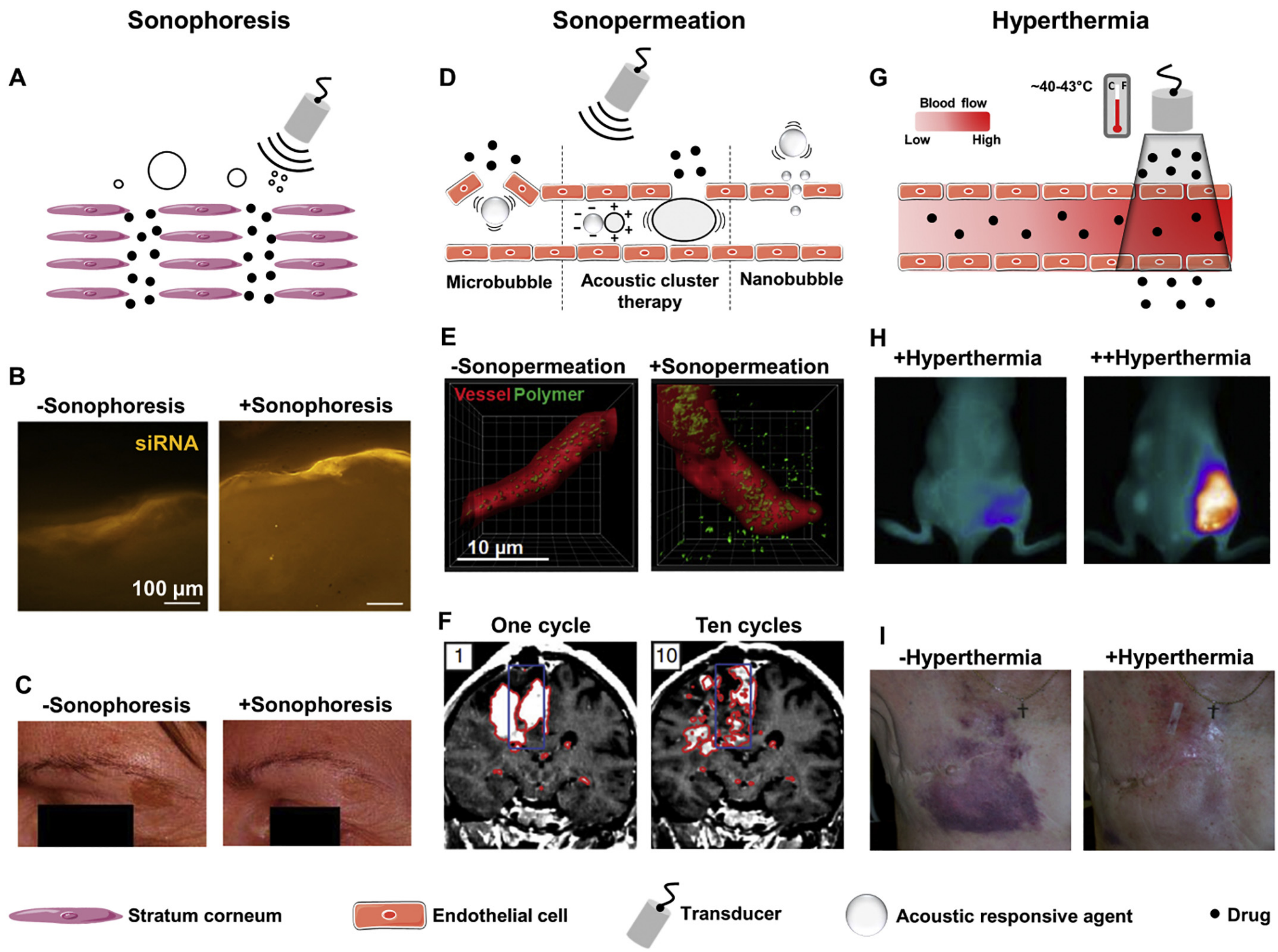

Fig. 1. Ultrasound-mediated drug delivery. Sonophoresis: (A) Low frequency ultrasound induces cavitation and acoustic streaming which can disrupt the stratum corneum of the skin and enhance transdermal drug delivery. (B) Microneedle application enhanced the skin penetration of fluorophore-labelled siRNA (left panel) and that penetration can be further amplified by a combination treatment of microneedle and sonophoresis (right panel). (C) A patient suffering from solar lentigo as shown by the dark spots (left panel) underwent sonophoresis in conjunction with depigmenting emulsion to achieve lightening of the skin (right panel). Sonopermeation: (D) Combination of ultrasound and acoustic responsive agent can result in a number of effects including push/pull, microstreaming, acoustic radiation force, microjets and together these can result in transient opening of blood vessels and improved drug delivery. (E) Intravenously administered polymeric nanocarriers did not cross the blood-brain barrier (left panel), however upon microbubble-mediated sonopermeation these nanocarriers extravasated and penetrated into deep compartments of the brain (right panel). (F) A patient with glioblastoma multiforme undergoing multiple sonopermeation and carboplatin treatments resulted in tumor volume reduction in the sonicated spots. Hyperthermia: (G) Ultrasound induces local rise in tumor temperature which can result in vasodilation, improved blood flow and drug delivery. (H) Repetitive hyperthermia treatment facilitates triggered release of Hycamtin® from temperature sensitive liposomes in mice bearing tumors. (I) A patient with chest wall recurrence of breast cancer (left panel) goes on to achieve partial response after two cycles of ThermoDox® administration followed by hyperthermia treatment (right panel). (Adapted and taken permission from [26,30,65,68,106,116,135].)

demonstrate the superiority of synergistic effect of iontophoresis and sonophoresis in transdermal delivery of oxaprozin [27]. In the case of the latter, Fig. 1B shows that fluorophore-labelled siRNA penetrated into the skin upon microneedle application (left panel), and that skin penetration levels were further enhanced by using a synergistic treatment of microneedle and sonophoresis (right panel) [26]. Apart from combining with physical permeation enhancers, sonophoresis has been employed with cavitation seeds to also achieve higher levels of skin permeability. In this regard, perfluorohexane core was adapted as a cavitation seed so that due to gravity it would concentrate on the skin surface and upon US activation the liquid core would convert into gas cavity thereby inducing biophysical effects that can enhance skin permeability. Indeed, by employing this technique, the authors reported an enhanced skin penetration of FITC-dextran by several folds [28]. Such combination approaches may increase the degree of complexity for ease of translation. However, it holds promise in delivering large size therapeutics to deeper layers of skin. One limitation in the above-mentioned preclinical setups is the need for duty cycles and fluid replacement to minimize the temperature rise in the coupling fluid when it is exposed to US. To overcome this issue, Robertson et al. devised a circulating thermoelectric system that was able to maintain the temperature of the coupling fluid between 10 °C and 16 °C when exposed to US, and at the same time, also enhanced the transdermal transport of drugs [29]. Since such setups do not require duty cycle and manual replacement of the coupling fluid, they end up saving time and hence can be useful in running multiple sets of repetition experiments for reliability.

In addition to the vast number of preclinical studies, efforts have also been made to advance and implement sonophoresis into the clinics. For instance, in the case of cosmetic skin disorders, sonophoresis enhanced the therapeutic responses of pharmaceutical intervention in patients with alopecia areata, melasma or solar lentigo [30]. Fig. 1C shows a patient suffering from solar lentigo with a patch of darkened skin (left panel), while the application of sonophoresis in conjunction with depigmenting emulsion resulted in enhanced lightening of the skin (right panel) [30]. Another anti-aging study in Poland assessing the efficacy of retinol and sonophoresis suggested that the combination therapy improved the overall skin condition with increased moisture level, less wrinkling and corrected skin discoloration [31]. Low frequency sonophoresis has also been used in patients for alleviating pain. These clinical setups used SonoPrep®, a proprietary US device of Echo Therapeutics Inc., at frequencies of 53–56 kHz. In the first study, skin was pretreated with US followed by eutectic mixture of local anesthetics (EMLA) cream, a co-formulation of lidocaine and prilocaine. Overall, the treatment was well tolerated and resulted in reduced pain as compared to the placebo arm, which was examined by pricking the skin site using a 20-gauge needle [32]. Similarly, Becker et al. also showed that pretreating the skin with US followed by 4% liposomal lidocaine cream can dramatically reduce pain perception in patients [33]. Apart from applications in cosmetic skin disorders and analgesia, sonophoresis has also shown promise in the treatment of malignant pleural effusion. A study that recruited 110 patients suffering from malignant pleural effusion was performed to test whether sonophoresis could enhance the delivery of interleukin-2 (IL-2). It was found that the patients receiving sonophoresis and IL-2 treatment had a higher objective remission rate and an improved quality of life compared to patients receiving the IL-2 administration alone [34]. The same team also demonstrated the safety and efficacy of sonophoresis in treating patients with refractory metastatic malignant bowel obstruction [35].

Overall, sonophoresis offers painless (without the use of injections) form of administration by enhancing topical delivery of a wide range of therapeutics. A large body of studies has demonstrated the safety and efficacy of sonophoresis in many animal models and clinical trials.

2.2. Sonopermeation

Contrary to sonophoresis, sonopermeation (also known as sonopermeabilization) typically applies US in the higher frequency range, i.e. 200 KHz–1 MHz [10]. Additionally, sonopermeation normally utilizes acoustically responsive agents for enhancing the acoustic effects locally to the targeted areas [36]. For the majority of sonopermeation applications, US can be delivered using focused ultrasound (FUS) transducers to achieve spatial targeting. The beam focusing can be achieved using curved transducers, plane transducers with acoustic lenses, or phase arrays with electronic focusing [7,37]. Transmitted sound waves induce a time-varying sinusoidal pressure perturbation on to these acoustic responsive agents, leading to the cavitation behavior that is either gentle, repetitive oscillation or violent, transient motion [38]. Cavitation is thus normally classified as either stable or inertial cavitation. Both stable and inertial cavitation can trigger aforementioned biophysical effects such as microstreaming, acoustic radiation force, microjettings and free radical formation, which have been confirmed to temporarily open up cellular membranes and enhance the delivery of drugs, genes and nanomedicine formulations (Fig. 1D) [10,39,40]. Based on the type of acoustic responsive agents, sonopermeation can be employed either using (i) microbubble, (ii) acoustic cluster therapy or (iii) nanobubble and nanodroplet.

2.2.1. Microbubbles

Microbubbles (MB) are routinely used as US contrast agents in the clinic. They are 1–10 μm hollow gas-filled particles whose outer shell is made of lipids, proteins or polymers. Commercially available MB include Definity®, SonoVue® and Optison™ and their shell is made of lipids or proteins, while house-made MB are generally made of lipids or polymers. Additionally, their outer shell can be functionalized with drugs, targeting ligands or nanoparticles [41,42]. MB were introduced into therapeutic US due to their well-accepted acoustic enhancing ability and safety profile. Due to their relatively large size, intravenously administered MB are typically confined to blood vessels. Therefore, the oscillating MB activated by US causes the nearby endothelial cells to transiently permeabilize thereby improving drug delivery across vascular barriers (Fig. 1D) [39].

One of the most studied applications in MB-based sonopermeation is the blood-brain barrier (BBB) opening for drug delivery to the brain [7,37,39,43,44]. MB-mediated sonopermeation has been widely confirmed to transiently, locally, and reversibly open the BBB through paracellular and/or transcellular trafficking [45–48]. Fluorophores such as Trypan Blue or Evans Blue, and gadolinium-based MR contrast agents were commonly used for visualizing sonopermeation-assisted drug delivery across the BBB [36,49,50]. Several therapeutic molecules including antibodies [51–53], viruses [54,55], neurotrophic factors [56], neurotransmitter [57], chemotherapeutics [58,59], nanotherapeutics [60,61], and other therapeutic particles [62–64] have also been delivered across the BBB for the treatment of brain cancer and neurodegenerative disorders. As an example, Fig. 1E shows that intravenously injected polymeric nanocarriers did not cross the BBB (left panel), while upon sonopermeation, these nanocarriers extravasated and penetrated deep into the brain (right panel) [65]. Other than disrupting the BBB, sonopermeation has also shown to selectively permeabilize and transfect brain endothelium without detectable signs of BBB disruption and extravascular transfection. This was achieved by using a very low peak negative pressure, 0.1 MPa, resulting in sonoselective transfection of brain endothelium without any detectable signs of inflammatory responses. However, increasing the pressure resulted in BBB opening and extravascular transfection. This novel approach may be useful in certain indications where BBB disruption may be contraindicated [66].

Such promising preclinical outcomes have also advanced to multiple clinical trials for BBB opening using both implantable and external FUS transducer. A Phase I clinical trial was recently performed in France using an implanted FUS device, SonoCloud, to open the BBB in recurrent glioblastoma multiforme (GBM) patients. Upon intravenous administration of SonoVue® and FUS application under MRI guidance, carboplatin was non-invasively delivered to the brain tumor without any evidence of acute hemorrhage, ischemia or edema. Overall, the treatment was found to be safe and well tolerated in patients [67]. The same group extended these efforts to assess the efficacy of the treatment. Results showed that repeated sonication led to a reduction in tumor volume in the sonicated area (Fig. 1F), although the sonication volume was insufficient to cover the entire tumor. Furthermore, it was found that patients showing clear signs of BBB opening had relatively higher response rates with a median progression-free survival (PFS) and median overall survival (OS) of 4.11 and 12.94 months respectively; while patients with no evidence of BBB opening had PFS and OS of 2.73 and 8.64 months respectively [68]. These promising findings highlight the potential of MB and SonoCloud for the treatment of GBM patients. More recently, two BBB sonopermeation trials based on an incision-free and external FUS setup were initiated by Hynynen and colleagues. In the first trial, five patients suffering from high-grade glioma underwent MRI-guided FUS along with systemic administration of Definity® and Temozolomide or Doxil. The treatment was well tolerated and no signs of adverse events were reported. T1-weighted MRI did confirm BBB opening in sonicated spots and furthermore biochemical analysis also supported chemotherapy localization in these spots [69]. In another trial, the same group also demonstrated the safety and feasibility of MRI guided BBB sonopermeation in the motor cortex of amyotrophic lateral sclerosis patients [70]. These preliminary findings by Hynynen and colleagues demonstrate that sonopermeation can be used as an effective tool to safely permeabilize BBB in patients, and its efficacy results are awaited.

Sonopermeation has also made remarkable advances in improving drug delivery to pancreatic cancer, which is a highly stromal tumor with high degrees of vessel compression, poor tumor perfusion and ineffective drug delivery [71]. For example, it has been shown that sonopermeation treatment enhanced the accumulation and penetration of fluorophore-labelled liposomes to a BxPC-3 pancreatic tumor model [72]. In a more recent study using the same model, intravenously administered Abraxane® in conjunction with sonopermeation treatment significantly inhibited tumor growth [73].

Sonopermeation treating pancreatic cancer has also been implemented in the clinics. Dimcevski and colleagues initiated a phase I clinical trial using gemcitabine and SonoVue® microbubbles. Sonopermeation resulted in doubling of the median survival when compared to a historical control of gemcitabine alone treatment. This antitumor response can be explained by the cavitation effects of SonoVue®, causing the previously collapsed vessels to decompress and thus improving the perfusion of gemcitabine into pancreatic tumors [74].

Similarly, in the case of other tumor types e.g. breast cancer, colorectal cancer, hepatocellular carcinoma, sonopermeation has also shown to enhance therapeutic efficacy at preclinical stages [75–77]. However, no clinical trials have yet been initiated and efforts need to be invested in order to validate the feasibility, safety and efficacy of the treatment in such tumor types.

Apart from improving drug delivery and efficacy in brain and several tumor types, sonopermeation has also attracted attention in treatment of other indications. For example, Kohane and colleagues showed that high frequency US in conjunction with MB can deliver tetrodotoxin (a site 1 sodium channel blocker) to enhance nerve blockade [78,79]. In the case of urinary tract infection, it was shown that US activation of MB-liposome conjugate at the apical surface of the bladder significantly enhanced the delivery of gentamicin into urothelial cells in a human urothelial organoid model [80]. In the context of inner ear drug delivery, Liao et al. showed that filling the tympanic bulla with MB and exposing US transcanally and transcranially could enhance the delivery of biotin-FITC, a model drug, and gentamicin into cochlear and vestibular hair cells in guinea pigs [81]. These preliminary findings will form the basis of follow-up experiments that will be needed to assess the potential of sonopermeation in the treatment of medical indications other than brain disorders and tumors.

2.2.2. Acoustic cluster therapy

Acoustic cluster therapy (ACT) refers to a co-formulation produced by the electrostatic attraction of negatively charged MB and positively charged microdroplet. Exposing US to these intravenously administered clusters enable vaporization of the liquid in the microdroplet core into gas phase. Consequently, the ACT gas bubbles expand in size and thus reducing the distance between the ACT bubble and vessel wall. Further US application causes the ACT bubble to oscillate and collapse resulting in enhanced vessel permeability and improved drug delivery (Fig. 1D). Since ACT bubbles are relatively closer to the vessel wall than MB, they can be particularly useful in permeabilizing large vessels [82,83].

These concepts laid the basis for several preclinical studies. For instance, Davies and colleagues showed that ACT treatment in a human prostate adenocarcinoma mouse model resulted in liquid-to-gas phase shift, thus localizing 20–30 μm size bubbles in the vasculature. Further US treatment confirmed the feasibility of ACT in improving the delivery of a near infrared fluorophore, which was used as a model drug [84]. The same research group also showed that ACT treatment can greatly enhance the therapeutic efficacy of paclitaxel and Abraxane® in the same prostate cancer mouse model [85]. Using similar setups, studies have also shown to enhance the efficacy of irinotecan and Doxil® in different tumor models [86,87]. Other than enhancing tumor drug delivery, ACT has also shown to enhance BBB permeability in healthy rats and as expected this resulted in an increased extravasation of MRI contrast agent gadodiamide and fluorophore labelled polymer [88].

These encouraging preclinical findings were followed up by a first-in-human phase I trial (NCT04021277) which will recruit up to 37 patients suffering from liver metastasis in order to study the safety and feasibility of ACT in delivering standard of care chemotherapy. However, unlike MB, ACT bubbles are not commercially available and thus additional regulatory steps may be required to approve and implement the treatment protocol in the clinics. Nonetheless, it will be exciting to see if these initial clinical efforts can demonstrate safety and efficacy of ACT in a large patient cohort.

2.2.3. Nanobubbles and nanodroplets

In contrast to MB and ACT bubbles, which are confined to intravascular compartment thus permeabilizing blood vessels, nanobubbles (NB) and nanodroplets (ND) have primarily been used to permeabilize extravascular cells, e.g. tumor cells. NB are 50–300 nm sized air-filled particles whose outermost shell is made of lipids or polymers. The nanosize dimension allows NB to accumulate in tumors and other inflammatory lesions by Enhanced Permeability and Retention (EPR)-mediated passive targeting [89]. Consequently, NB accumulation in tumors can increase the permeability of the surrounding stromal and tumor cells when exposed to US. Furthermore, drugs can also be encapsulated into the NB, thus facilitating triggered drug release upon US exposure. Together, these notions have led to several preclinical studies and have shown that the combined use of US and NB can facilitate the delivery of chemotherapeutics and siRNA into tumor cells in vivo [90–92], revert hypoxia programming to enhance chemotherapy [93] and mediate the FUS-induced BBB opening [94]. However, unlike MB and ACT bubbles, NB are very small in size and encapsulate very little air volume, rendering inefficient imaging contrast, oscillation and permeabilization [89].

To address this shortcoming, ND have been employed in sonopermeation [89]. ND are nanosize material whose core contains perfluorocarbon liquid, and upon intravenous administration ND can also passively accumulate at tumors due to the EPR effect. As a result of ND accumulation, US activation can cause the liquid in the ND core to vaporize into gas and form micron-sized gas bubbles in the tumor, also known as acoustic droplet vaporization (Fig. 1D). Furthermore, these bubbles can oscillate and collapse into fragments in an US field, thus releasing the therapeutic payload and improving drug delivery into tumor cells [95]. In this regard, pioneering work has been done by Rapoport et al. where they synthesized a polymeric micelle co-encapsulating perfluoropentane and doxorubicin and showed that application of US caused the nanodroplets to vaporize into large bubbles. Additionally, the authors demonstrated that this technique could efficiently deliver doxorubicin and inhibit tumor growth in a breast cancer xenograft model [96]. Several follow-up studies have also demonstrated promising findings in delivering various therapeutics including doxorubicin, curcumin and siRNA into cells [97–99]. ND has also been used to mediate the targeted delivery of anesthetics into the brain [100].

Despite the advances made at the preclinical level, no NB and ND-mediated sonopermeation have been investigated in the clinic. In future, it will be vital to assess the feasibility, safety and efficacy of these treatment methods in a large cohort of patients.

In summary, sonopermeation has been employed either using MB, ACT bubbles, NB or ND. MB-based sonopermeation and ACT have been vastly used to permeabilize blood vessels and improve drug delivery across brain and tumors. On the contrary, NB and ND-based sonopermeation have been employed to permeabilize tumor cells and enhance drug uptake. In terms of clinical translation, MB-based sonopermeation are arguably easier to translate and implement in the clinic due to the availability of off-the shelf MB, their clinically acceptable acoustic properties and their promising clinical findings for the treatment of cancer and other brain diseases.

2.3. Hyperthermia

In comparison to sonophoresis and sonopermeation, hyperthermia uses high frequency US, typically in the range of 1–5 MHz [10]. Hyperthermia is based on thermal effects and is widely used as an anticancer treatment. With each propagating ultrasonic cycle, a portion of sound energy is absorbed by the tissue, leading to local thermal deposition. The degree of energy absorption is dependent on not only the acoustic properties of tissue, but also the ultrasound frequency. This local heating can induce a local rise in tumor temperature ~ 43 °C which results in vasodilation, enhanced tumor perfusion and improved drug delivery from within heat activatable vehicles to targeted area (Fig. 1G) [101].

Several studies have demonstrated the improved efficacy of various nanomedicine formulations upon US-mediated mild hyperthermia. For instance, Centelles and colleagues used a fluorophore-labelled Herceptin®, an antibody that blocks HER2 signaling in breast cancer, to non-invasively image biodistribution and tumor accumulation after US-assisted mild hyperthermia. The treatment protocol induced a rise in tumor temperature to 42 °C leading to enhanced accumulation of Herceptin® [102]. Similarly, Wu et al. used FUS-induced hyperthermia to improve the delivery of larger nanomedicine formulation, i.e. 100 nm sized Doxil®, across brain metastasis of breast cancer [103].

Another important application of US induced mild hyperthermia is the use of temperature sensitive liposomes (TSL). TSL are made of a temperature sensitive lipid bilayer which melts above its phase transition temperature (Tm) thereby releasing the encapsulated drug. This is particularly used in cancer therapy where the lesion is treated to hyperthermic conditions above the transition temperature, triggering drug release from TSL either in the intravascular or extravascular tumor compartment [104]. Wood and co-workers demonstrated that hyperthermia triggered the release of 50% doxorubicin from TSL whereas no doxorubicin could be detected from the control group. The higher tumor accumulation observed in treated group was considered to result from the rapid release of small molecular weight drug doxorubicin after hyperthermia-triggered release. On the other hand, the lower tumor accumulation of the NTSL (non-TSL) was likely due to the limited extravasation of the 100 nm intact liposomal doxorubicin [105]. In another study, it was shown that hyperthermia triggered the release of Hycamtin® from TSL in tumors and that second hyperthermia application 60 mins later further enhanced Hycamtin® release in tumors (Fig. 1H) [106]. Similarly, other studies have also highlighted the potential of hyperthermia treatment for TSL delivery to and into tumors [107–109].

Recently, hyperthermia-mediated TSL delivery has also been used in combination with immunotherapy for tumor therapy. In a pioneering study, intravenously administered TSL was activated by US to trigger the release of doxorubicin and this led to immunogenic cell death and cross-presentation of tumor antigen. Furthermore, when TLR9 agonist and PD-1 immunotherapy were administered for 1 week followed by hyperthermia-mediated TSL delivery in three different tumor models, the combination treatment resulted in the highest response rate than other treatment protocols. This strategy shows the potential of chemo-immunotherapy in improving anticancer treatments [110].

Hyperthermia is generally integrated with MRI as it helps in treatment monitoring by providing anatomical information of target tissues and temperature mapping in real time. Moreover, it also enables real time monitoring and quantification of in-vivo drug release from TSL. This was shown by Grüll and colleagues, where they monitored local doxorubicin delivery from TSL under MR image guidance in tumor bearing rats. Specifically, the TSL were co-encapsulated with doxorubicin and an MRI contrast agent [Gd(HPDO$_3$A)(H$_2$O)], which were released at the tumor site upon US mediated hyperthermia treatment. MRI enabled real time monitoring of local temperature rise as well as visualization of the released doxorubicin in tumors by co-relating it to the T1 mapping of the released MRI contrast agent [111]. Similar studies have been performed to image, monitor and improve drug targeting to tumors in various animal models [112,113].

Recently, high intensity focused ultrasound (HIFU) and TSL have also been used in combination treatment with ablation. This is especially useful in tumor therapy where ultrasound ablation at the tumor core can potentially destroy necrotic areas which are either less vascularized or poorly perfused, while the induced local hyperthermia in the vascularized tumor regions can be treated with TSL. An example of this combination treatment regime was shown by Ferrara and colleagues, where they first insonified the tumor to 42 °C prior to intravenous administration of doxorubicin encapsulated TSL, subsequently followed by a second treatment of tumor ablation to temperatures greater than 65 °C under MRI guidance. Peripheral tumor accumulation was confirmed by PET-CT imaging upon labelling the liposomes with ^{64}Cu. The combination treatment of hyperthermia with TSL and ablation significantly suppressed tumor growth and improved survival rates as compared to other groups in both NDL and 4 T1 tumor models [114]. Similar findings have been reported in rats bearing tumors where the combination treatment of hyperthermia and TSL followed by ablation showed the most promising therapeutic outcome, while free doxorubicin and Caelyx, a non-thermosensitive liposome, showed only modest efficacy with or without hyperthermia treatment [115].

Apart from pre-clinical findings, clinical progresses have also been made in hyperthermia-based treatments in combination with ThermoDox®, a clinical grade TSL formulation marketed by Celsion Corporation. For instance, in a phase I clinical trial, 29 women with chest wall recurrences of breast cancer were treated with six cycles of ThermoDox® followed by hyperthermia. Fig. 1I clearly shows a patient with tumor margins prior to the treatment (left panel), while after two cycles of treatment the patient had achieved partial response (right panel). The combination treatment led to an overall response rate of 48% with 5 patients achieving complete responses and 9 having partial responses [116]. Recently, targeted doxorubicin study was initiated with an aim to assess the feasibility, safety and therapeutic efficacy of US-mediated hyperthermia for delivery of ThermoDox® to solid liver tumors. In a phase I cohort of 10 participants, it was demonstrated that without using real time thermometry, US models guided by B-mode imaging can be feasible for planning hyperthermia treatments and for facilitating triggered drug release in a safe and efficient way [117].

Taken together, US has been used as a physical trigger to induce cavitation and thermal effects in tissues. These effects have primarily contributed to the enhanced delivery of drugs, genes, nanomedicines and other therapeutics across hard-to-reach biological barriers such as skin, brain and various tumor types.

2.4. Clinical challenges

Despite the large number of clinical trials implemented in US-mediated drug delivery (see Table 2), several limitations and challenges exist for expanding and improving the clinical translation of this technique. Firstly, there is a lack of clinically established online treatment monitoring tool for nonthermal applications. This is particularly vital for (1) brain applications where vascular damage is less tolerable [7], (2) nonthermal cavitation-based systems where heat cannot be monitored through MRI [118], and (3) other applications that fast monitoring tools, such as diagnostic US, are not available or compatible. Recently, there are growing efforts in developing passive cavitation imaging [7,119–124] and cavitation-based feed-back controlling approaches [118,125–134] to address this issue. We envision these US-based monitoring techniques, together with the established MR- and CT-based treatment guidance tools, will expedite the translation of US-mediated drug delivery and advance the technical development in the whole field. Secondly, even though preclinical systems such as NB, ND and ACT may offer several advantages, it needs to undergo additional regulatory procedures before clinical applications. In this front, it may be more pragmatic to employ off-the shelf systems such as Definity®, Optison®, SonoVue™ and ThermoDox® for fostering clinical translation. Finally, a clearer understanding of the biophysical effects involved in US-mediated drug delivery (i.e. disrupting cellular membranes vs disrupting intercellular junctions) may help scientists in designing US protocols for specific applications.

3. Light

Light is another form of physical trigger that has been extensively applied in therapeutic interventions. As a form of electromagnetic radiation, light is typically described by its amplitude and wavelength. The unique nature of light is often known as the wave-particle duality, which describes light as a collection of particles known as photons behaving like waves. A light-interacting molecule can absorb quantized energy from photons. The excessive energy absorption may sometimes cause molecules dissociation through breakage of weaker bonds. Light can generate heat, degenerate/degrade light sensitive molecules or change their chemical structures, bleach a light sensitive fluorescence dye, and induce luminescence [136–138]. These unique properties have been extensively utilized in biomedical research for disease diagnosis and treatment [139–141]. With superior targeting precision but typically shallow penetration, light-mediated therapeutic strategies have recently emerged as a promising tool for topical therapy to precisely treat skin diseases such as psoriasis, acne vulgaris, eczema, wound healing and cancer [142,143]. The therapeutic spectrum of light significantly depends on the absorption wavelength. Studies have shown that ultraviolet and visible light can only penetrate the epidermis and upper dermis, whereas the near infrared light has displayed advantages in deep penetration toward the lower dermis layer of skin [144]. Near infrared light has several advantages over ultraviolet and visible light that include minimal photodamage and deep tissue penetration [145–147].

Light can directly affect the tissue as a direct therapeutic intervention or through photosensitive agents for enhanced therapeutic effects. Based on the availability of the photosensitive mediators, light-based drug delivery can be classified into two groups: direct light triggering systems and light triggered systems via photosensitizing particles. Direct light triggering systems include photocleavage and photoisomerization, whereas upconversion, photodynamic, photothermal and photoacoustic approaches are within the group of photosensitizer mediated drug delivery systems.

3.1. Direct light triggering systems

3.1.1. Photocleavage

Photocleavage refers to light-induced disassembly or cleavage of molecules for biomedical applications [148,149]. For example, vascular endothelial growth factor (VEGF) plays a vital role in tumor vasculature growth. Tumor growth can be inhibited by killing the tumor cells through inhibiting the binding of adenosine triphosphate with VEGFR-2, a main receptor function in tumor angiogenesis mediating almost all of the known cellular responses to VEGF [149]. Compounds with oxazole and porphyrins like structures have shown effectiveness in cleaving the VEGFR-2 gene in the presence of light that interferes with binding between the gene and ATP.

The photocleavage technique has been utilized in drug delivery through breaking down the covalent bonds directly or by photochemical reactions [150]. The carrier molecule undergoes dissociation via absorption of sufficient amount of energy from the light. The dissociation of the carrier then results in an enhanced release of the drug payload. This technique has been utilized for designing a formulation for on-demand drug release as well. The absorption of sufficient light energy facilitates breaking the covalent bonds to release doxorubicin [151]. In addition to covalent bonds, otro-nitrobenzyl groups, coumarin, and pyrene derivatives that contain esters bond also have the potential as photocleavage molecules [152–154]. Ester bonds readily undergo cleavage even in the presence of ultraviolet light irradiation. As an alternative to ultraviolet light, two-photon absorption [155], triplet-triplet annihilation [156], second harmonic generation [157], and near infrared photosensitizers [158] have also been used for photocleavage in drug delivery systems (Fig. 2A). For example, Sodano et al. reported a novel polymeric platform that enhances the release of an anticancer drug (doxorubicin) and nitric oxide to improve cancer therapy [159]. The polymeric carrier was designed in combination of nitric oxide photo donor and amphiphilic block-copolymer that enhances the release of nitric oxide as well as doxorubicin in presence of light. The photo-released doxorubicin and nitric oxide synergistically enhanced the therapeutic effect for treating lung, intestine and skin cancers observed in cell lines [159–161]. Light mediated drug delivery systems remain as one of the most popular methods that disrupt the lysosomal bilayer stability and facilitate drug release [162]. The incorporation of photosensitizers such as gold, graphene, and pheophorbide within the formulation triggers drug release upon irradiation with light [163–165].

3.1.2. Photoisomerization

Light is known to induce cis-trans isomerization, a phenomenon known as photoisomerization [166]. A series of thorough reviews on photoisomerization-based drug delivery has been reported by Kamaly et al. [166], Karimi et al. [167], Rwei et al. [168], and Zhou et al. [169]. Photoisomerization of molecules is reversible. For example, azobenzene transforms from an apolar trans to a polar cis isomeric form when irradiated by UV light and vice versa (Fig. 2B) [170]. The transition upon UV light irradiation of azobenzene results in a change in hydrophilicity and facilitates disintegration of the carrier that triggers the release of encapsulated drug molecules [171]. In another study, spiropyran and 2-diazo-1,2-naphthoquinone molecules that can transform from hydrophobic to hydrophilic, have also been utilized for drug delivery [172]. Though the photoisomerization strategy shows promise in improving drug delivery controlled by light, their clinical applications are limited due to the lack of tissue penetration ability and possibility of significant toxicity generated from absorption of the UV light by the biological molecules [173].

Additionally, light mediated isomerization of polymeric vehicle has potential for biologic delivery. For example, β-Cyclodextran has been used for siRNA delivery through hot-guest interaction that can lead to complex formation. The incorporation of azobenzene with β-Cyclodextran facilitated a strong interaction and entrapment of the siRNA [170]. However, upon near-infrared irradiation the trans-azobenzene complex transforms into a cis-azobenzene complex that results in changes in polarity and steric hindrance. The polarity changes facilitate destabilization of the interaction and up to 85% of the loaded siRNA can be released within 20 min of irradiation [170].

3.2. Photosensitizer mediated drug delivery

3.2.1. Upconversion

Upconversion nanoparticles are a comparatively new class of light triggered materials that have shown potential in drug delivery [174–176]. The materials absorb two or more relatively low energy photons and upconvert to emit a single but relatively higher energy photon. Upconverting nanoparticles have been widely investigated for photo-triggered and photo-controlled release of therapeutics and diagnostics [174]. Upconverting nanoparticles have also been utilized for prodrug delivery. As an example, a hybrid formulation composed of adamantane-modified camptothecin, adamantane-modified photosensitizer and cyclodextrin-hyaluronic acid was tested in breast cancer bearing mice [177]. Upon light activation, the photosensitizer generates reactive oxygen species, which facilitate the breakage of the thio-ketal linker and trigger the release of free camptothecin within the tumor. The upconversion based pro-drug delivery systems were found to be safe and have demonstrated significant potential for controlled drug delivery. Mesoporous silica shell ($mSiO_2$)a highly biocompatible carrier, has been widely used for drug delivery [178,179] (Fig. 2C). Upconversion $mSiO_2$ nanoparticles can be utilized for light triggered on-demand drug release, resulting in 78% doxorubicin release from $mSiO_2$ upconversion nanoparticles [180]. Near infrared light responsive upconversion nanoparticles can be easily functionalized with therapeutic reagents/biomolecules to improve cancer treatments through synergistic effect of chemotherapy and phototherapy [181,182]. Near infrared

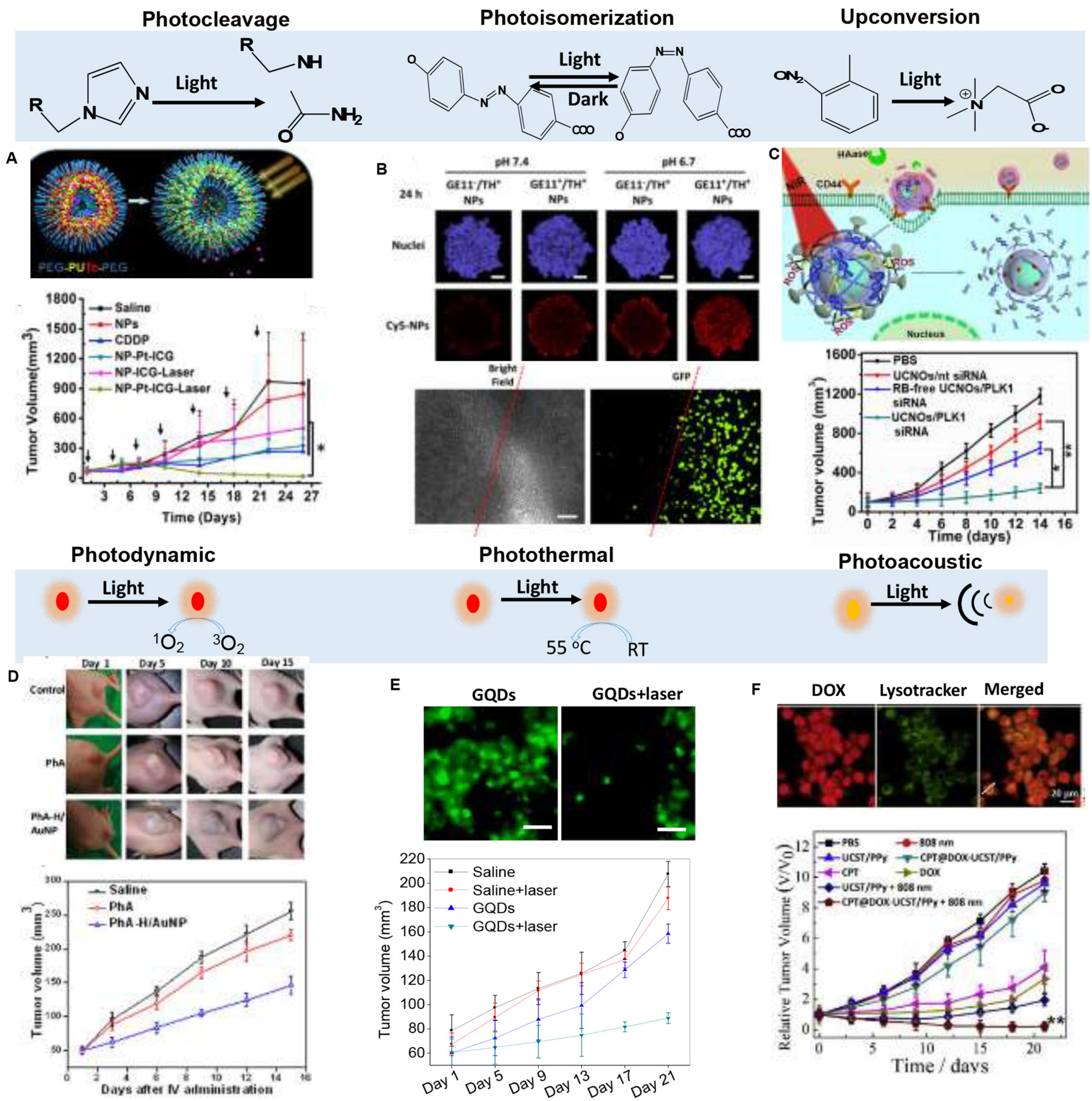

Fig. 2. Light-mediated drug delivery. Light has a dynamical application in drug delivery via donating energy to the carrier molecules through, (A) cleavage of PEG-PUTe-PEG based carrier that facilitates the release of therapeutic molecules for efficient tumor therapy [237], (B) by isomerization of the carrier molecules that enhance deep tissue penetration of the therapeutic molecule to silencing the gene expression, Adapted with permission from [170], and (C) by upconversion of the carrier molecules that enhances siRNA delivery to the nucleus for enhanced cancer therapy in vivo [158]. A photosensitize materials can be used for (D) photodynamic therapy for treating cancer by generating toxic oxygen [190], (E) by photothermal therapy that can produce enough heat to kill the tumor cell through photoablation [165], and (F) by photoacoustic therapy upon laser irradiation with a specific light source applied exogenously [238]. Adapted with permission from Elsevier and American Chemical Society.

regions can also absorb photoenergy, increasing the temperatures in the surroundings which triggers the rapid release of the drug molecules. For example, Evans et al have reported a photo-activated NO releasing moiety and co-delivered it with Nd^{3+}-doped upconverting nanoparticles by loading into PLGA microparticles [183]. Near infrared light triggered NO release was observed within a 3D tumor spheroid, suggesting the potential application of this upconversion nanoparticle as therapeutics and diagnostics.

3.2.2. Photodynamic

Photodynamic therapy is one of the four clinical modalities that are currently used for cancer treatment along with surgery, radiotherapy, and chemotherapy [184]. Photodynamic therapy involves a mechanism that generates cytotoxic reactive oxygen (Singlet oxygen or $^1O_2$) species, derived from ozone oxygen (triplet oxygen or $^3O_2$). Unlike triplet oxygen, a singlet oxygen is toxic enough to kill a cancerous cell [185–188]. Photosensitizers such as porphyrin, phthalocyanines, fluoresce graphene, and bacteriochlorin derivatives have been widely considered as photodynamic therapeutic agents over the decades. Photofrin, Temoporfin, Motexafin, Palladium, Purlytin, Verteporfin, Talaporfin are some of the examples of photodynamic agents that are currently being used in the clinic or are currently undergoing clinical trials [189].

Hybrid nanostructures composed of gold nanoparticles are also a promising photodynamic agent for cancer treatment. Hybridization of the photodynamic agent pheophorbide A with gold nanoparticles has shown to trigger a therapeutic effect in tumor bearing mice [190] (Fig. 2D). Masking the hybrid particle with a polysaccharide has been shown to further improve stability, non-specific toxicity and aqueous solubility. The same group has further improved the formulation with the incorporation of magnetic particles and superparamagnetic iron oxide nanoparticles, for bimodal imaging and therapy of cancer in vivo [191]. Recently, Wang et al. has designed a photodyanamic nanosystem that consists of perfluorohexane for simultaneous tumor imaging and therapy. The upconversion particles with Rose Bengal and perfluorohexane promote generation of singlet oxygen under low intensity focused ultrasound and laser irradiation which led to ovarian cancer treatment and imaging non-invasively. According to the record from ClinicalTrials.gov, more than 250 trials have been completed and nearly 70 clinical trials are in active/recruiting/enrolling status for various photodynamic modalities (see Table 2 for selected clinical studies). Among several photodynamic therapeutic agents, aminolevulinic acid and its derivatives have shown great potentials for clinical translation and there are more than 20 undergoing clinical trials according to ClinicalTrial.Gov. Aminolevulinic acid has been used for the treatment of oral cancer, acne, Crohn's disease, brain tumor, brain neoplasms, and glioblastoma [192–194].

3.2.3. Photothermal

In the photothermal therapy, a photosensitizer converts the photo energy to thermal energy and produces adequate heat to kill the surrounding tissues [195–198]. Therefore, the materials that have photothermal properties hold promise in therapeutic applications for various cancer types, such as melanoma, skin, head, neck, and breast cancers [195]. Among various inorganic materials, gold nanomaterials have shown the capability to absorb light in near infrared region and convert the absorbed energy to heat. Various delivery systems have been designed, such as liposomes, mesoporous silica shells, and red blood cells, based on the properties of gold nanomaterials that can absorb light and produce photothermal conversion [142]. Apart from photothermal therapy, photothermal materials have also been shown to improve controlled drug delivery by destabilizing the vehicles. The destabilization of the carriers greatly influences on-demand drug release [199,200]. Hybridization of photothermal strategy with chemo-phototherapy [201] and immune-phototherapy has shown improved therapeutic effects in vivo [202]. Gold nanoparticles can be modified with thermosensitive polymers which can absorb near infrared light and produce photothermal conversion. Gold nanoparticles and gold nanostars have been used for delivery of immunomodulators for enhanced therapeutic effects [142]. The combination of photothermal materials with immunotherapy significantly enhances therapeutic effect by the synergy of cellular uptake induction and cellular death through photoablation [143]. The immune-phototherapy also prevents tumor recurrence and inhibits previously reported metastasis [203–206]. Among several clinical studies with gold-based photothermal formulations [207], Rastinehad and his colleagues have investigated the therapeutic feasibility of silica-coated gold nanoparticles in 16 prostate cancer patients [208]. Implementation of high precision laser ablation, to silica-coated gold nanoparticle infused patients, resulted in the reduction of prostate volume from 49 cm^2 to 42 cm^2 at 3 months of post treatment, measured by multi-parametric magnetic resonance imaging. This finding provides significant information toward clinical translation of laser ablation device and photothermal therapeutic materials. Apart from inorganic nanomaterials, various 2D nanomaterials, including graphene oxide [165,209], boron nitride [210,211] and molybdenum sulfide [212,213] have showed potential as photothermal therapeutic agents [214,215] (Fig. 2E). These 2D nanomaterials have shown promising photothermal effects and feasibility as a cancer therapeutic agent in rodent models [216–218]. Further development with hybrid nanocomposites, including 2D nanomaterials with gold, silver and iron oxide, demonstrated the enhanced photothermal effects [214,215]. Given the progress in preclinical and clinical studies, photothermal therapeutic modality shows great potential in cancer treatment and holds significant promise in clinical translation.

3.2.4. Photoacoustic

Serving traditionally as a unique imaging modality, photoacoustic technology has also shown potential in drug delivery applications [219–221]. Photoacoustics is defined as the formation of an acoustic wave in media upon absorption of light [222]. Photoacoustic technology incorporated with photoacoustic contrast agents facilitates the transformation of energy within light, heat and sound (Fig. 2F). Upon light irradiation, the photoacoustic contrast agents trigger the thermoelastic expansion of tissues to enhance drug penetration and transportation [223–225]. More importantly, photoacoustic approach significantly improves the penetration depth of traditional light-based techniques. The biophysical effects can be delivered with a penetration depth up to 6 cm in tissue, unlike other light-mediated modalities that can only penetrate tissue up to a few millimeters [226].

There are a range of materials from both inorganic (Au and Pd) and organic (WS_2, and TiS_2) groups that were found to have photoacoustic properties. The recent thorough review has summarized potentials and perspectives of photoacoustic modality in drug delivery [227,228]. Meanwhile, a formulation comprised with perfluorocarbon droplets and gold nanorods was well utilized for photoacoustic mediated drug delivery [229]. The release of loaded paclitaxel controlled upon laser implementation showed significant suppression of tumor growth in vivo. In addition to organic and inorganic metal particles, porphyrin containing polymeric nanoparticles have also shown photoacoustic properties. The self-assembled porphyrin bilayer nano-vesicle shows photothermal properties together with the photoacoustic properties that undergo biodegradation, and release the payload within the biological system upon laser irradiation [230].

Photoacoustic drug delivery systems bear intrinsic theranostic nature. Therefore, in addition to the improvement in drug delivery, photoacoustic technique has also been used for controlling the drug release from the carrier and real-time monitoring [230]. Moon et al. have coloaded hydrophilic organic dyes, Methylene blue/Rhodamine 6 g, with 1-tetradecanol and monitored the release profile of the dye at 38 °C, a temperature that facilitates 1-tetradecanol melting. Zhang et al. recently reported on synthesis of a hybrid hollow microsphere that has potential for photoacoustic imaging and treating tumor through chemo-photothermal ablation, when being exposed to 808 nm wavelength near infrared laser [231]. Upon transformation of the light to heat deposition, the carrier molecule starts to melt, triggering the release of the loaded chemotherapeutics. It is suggested that those hybrid formulations may enhance therapeutic efficacy due to bimodal properties, such as photoacoustic-photothermal and photoacoustic-photodynamic approaches.

3.3. Clinical challenges

Despite having significant progress in the clinical translation of various light mediated drug delivery applications, several toxicity related issues still hinder the wide availability of many highly effective systems clinically. A common tradeoff is the phytotoxicity, penetration depth and chemical effects of the light source. Some low energy systems, such as near-infrared systems, have potential of deep tissue penetration and are able to reach the critical organs located inside body such as liver, pancreases, kidney etc. However, the chemical effects of near-infrared light on molecules are limited [232]. The UV light typically has desirable chemical effects, but can be difficult to be applied deeply in a noninvasive fashion due to the poor tissue penetration ability [232]. The clinical translation of the visible light sensitive systems is hindered because of a higher risk of light toxicity. There are various biological pigments in human body that also absorbs the visible light and cause inflammation, irritation and cell damage in severe cases [233,234]. Another clinical challenge of some light sensitive materials is the lack of biocompatibility and biodegradability properties. Hydrophobic properties of many of the light sensitive materials also significantly limit their bioavailability [235,236]. However, various strategies have been implied to improve the biocompatibility using micelles, liposomal and particle-based formulations.

4. Electric field

As another important physically based approach, electrically based drug delivery has been widely investigated in the both pre-clinical and clinical settings [239,240]. Over the decades, several electrically based technologies including iontophoresis and electroporation have been developed for enhancing drug delivery across multiple biological barriers [241–244]. These technologies have particularly found great utility in transdermal and ocular drug delivery, with applications being extended to other areas such as oral drug delivery [245–247]. Along the same line, being another important category of electrically based drug delivery approaches, materials that are responsive to electrical triggers are being extensively explored to navigate the transport of drugs and to control the release of drug payloads at target sites [1,248]. Here, we introduce the fundamental mechanisms underlying electrically based drug delivery, discuss different electrically based drug delivery technologies, highlight the recent advances and summarize the translational concerns.

4.1. Iontophoresis

Iontophoresis is a non-invasive technique that applies small electric current to enhance the transport of ionic and charged molecules into the tissue [243,247,249]. Iontophoresis follows the basic principle of physics – "like poles repel and unlike poles attract". When an electric current is applied to an electrolytic solution, positive ions are attracted to the negative electrode while negative ions move toward the positive electrode [250]. Therefore, the mechanism of iontophoresis relies on the "Nernst-Planck effect" that ionized molecules are transported into the target tissue by electro-repulsion (Fig. 3A) [251]. Positively charged drugs are driven into the tissue at the anode while negatively charged molecules are transported at the cathode. The delivery of neutral molecules can also be enhanced by iontophoresis and the mechanism underlying this is the "electroosmotic flow" [240,252]. The bulk flow of the solvents

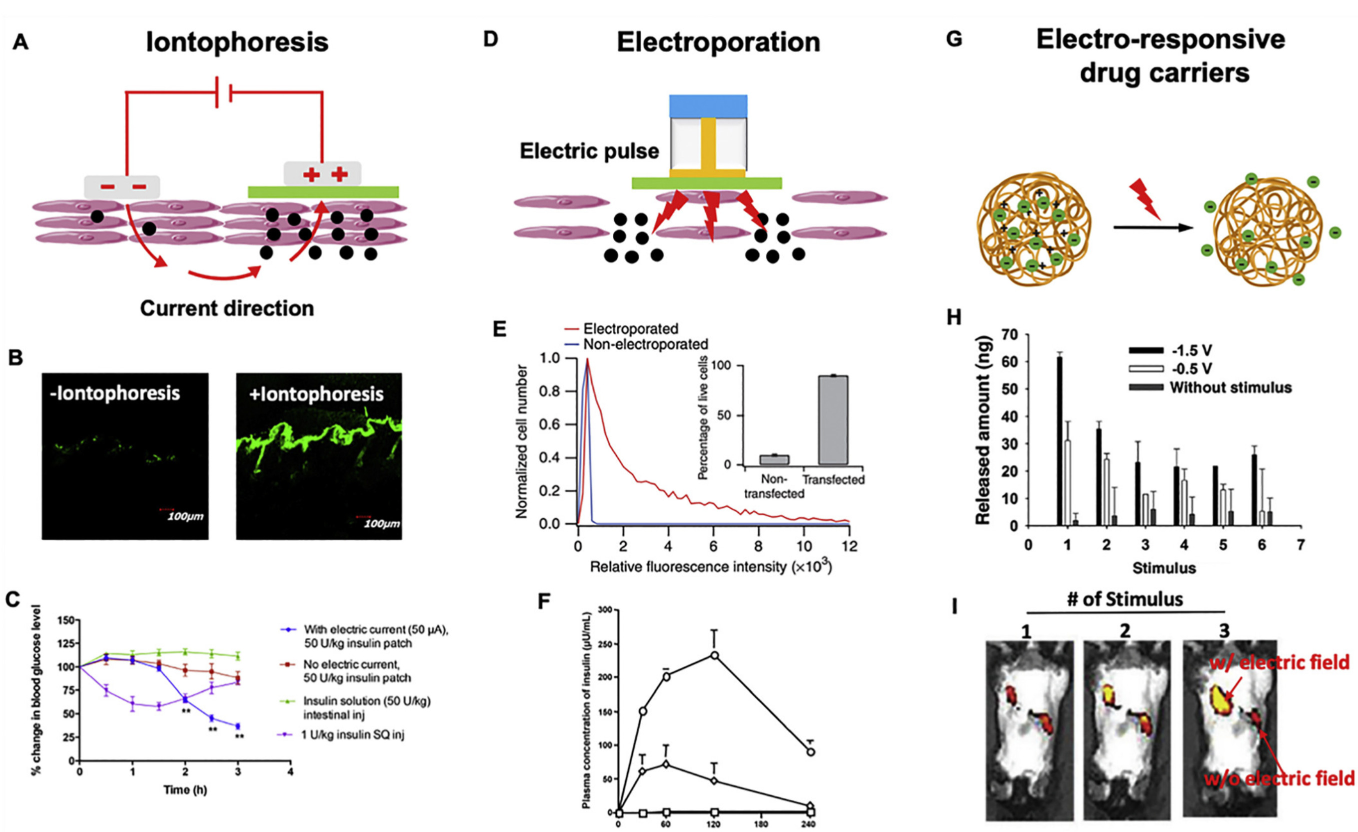

Fig. 3. Electrically based drug delivery. (A-C) Iontophoresis based drug delivery. (A) Mechanism of iontophoresis for drug delivery. Adapted with permission from [135]. (B) Iontophoresis enhanced the transdermal delivery of indomethacin-loaded PLGA nanoparticles as indicted by the green fluorescence. Adapted with permission from [269]. (C) Iontophoresis improved the oral delivery of insulin from a mucoadhensive patch and led to better control of blood glucose control. Adapted with permission from [245]. (D-F) Electroporation based drug delivery. (D) Mechanism of electrophoresis for drug delivery. Adapted with permission from [135]. (E) A high-throughput suspended-drop electroporation method significantly improved the delivery of dextran-fluorescein into hard-to-transfect HL-60 cells. Adapted with permission from [279]. (F) Electroporation, in combination with iontophoresis significantly improved the plasma insulin concentration following transdermal administration. Adapted with permission from [290]. (G-I) Electrically responsive carriers for drug delivery. (G) Mechanism of drug release from electrically responsive nanocarriers. (H—I) Release of fluorescein from an electro-responsive nanoparticle, polypyrrole nanoparticle, can be controlled by electric stimulus in vitro (H) and in vivo (I). Adapted with permission from [307].

occurring when a voltage difference is generated drives the neutral molecules into the tissue. Moreover, "damage effect" of an electric current that causes increase of tissue permeability is another mechanism to enhance drug penetration into the target tissues [242,249].

Due to its ease of implementation, iontophoresis has been widely studied for drug delivery across the skin [242,249,251]. Transdermal drug delivery provides a non-invasive way to deliver therapeutics locally or systemically and thus has been regarded as a promising approach for better patient compliance [253]. Iontophoresis has been developed as an important approach for transdermal drug delivery. Iontophoresis was first explored for transdermal delivery of small molecules, including agents for pain management, agents for dermatological conditions and skin cancer, antiviral agents, cardiovascular agents, steroids, and many others [243]. As an example, Mannem et al. studied iontophoresis mediated transdermal delivery of amoxicillin and cefuroxime, two oral antibiotics for treatment of skin bacterial infections [254]. Iontophoresis was performed using constant currents of different densities for 60 min in a rabbit model. They found that iontophoresis enhanced the delivery of these antibiotics to the skin and achieved therapeutically effective skin concentrations when using a high current density [254]. Transport efficiency of transdermal iontophoresis has shown to be associated with the applied current density. Delgado-Charro et al. studied the effect of current density on iontophoresis delivery of nafarelin [255]. They found that the transport flux was enhanced with the increase of current density. Particularly, out of all the tested current densities (0.16, 0.31, 0.47, and 0.63 mA/cm^2), the highest current density led to a ~ 4-fold enhancement as compared to the lowest density [255]. Similarly, Lopez-Castellano and co-workers found that a higher current density (0.50 mA/cm^2) resulted in a significantly increased iontophoresis influx (2.4-fold) of sumatriptan compared to a lower density (0.25 mA/cm^2) [256]. Iontophoresis can be used with other transdermal techniques for synergistically delivering drugs across the skin [257]. Murthy and co-workers investigated the feasibility of transdermal delivery of propofol phosphate via iontophoresis assisted with chemical permeation enhancers [257]. Their in vitro experiments on rat skins suggested that cathodal iontophoresis in combination with 0.1% sodium dodecyl sulfate (SDS) significantly improved the transport flux of the drug. Their in vivo study in a rat model further validated that the combination of iontophoresis and SDS significantly improved the plasma concentration of the drug which was within the therapeutically relevant levels [257]. As another example, Hellmann et al. investigated transdermal delivery of treprostinil, a prostacyline analog for healing of microvascular skin ulcers, in healthy and diabetic patients [258]. They observed that transdermal iontophoresis of 250 uM treprostinil improved the microvascular blood flux in the malleolus area of healthy and diabetic patients. In addition, no systemic or local side effect was observed, suggesting treprostinil iontophoresis could be a promising local therapy for treating diabetic ulcers [258].

Apart from small molecules, iontophoresis has also been explored for transdermal delivery of large molecules (peptides and proteins), including insulin, human hormone, LHRH analogs, somatostatin analogs, vasopressin analogs, and somatorelin analogs [243,251]. Peptide/protein molecules with a molecular weight of ~10–15 kDa are ideal for iontophoresis delivery. In addition, because the skin has a negatively charged surface, anodal iontophoresis can be more effective than cathodal iontophoresis for peptide/protein delivery [251]. Moreover, molecules with a high isoelectric point generally achieve higher delivery by iontophoresis because they are positively charged in the formulation and can avoid precipitation of the molecules in the skin [251]. Furthermore, iontophoretic delivery of peptides/proteins is more challenging than that of small molecules due to their high degrees of molecular and structural complexities. Pillai et al. performed serial studies on fundamental understanding of iontophoretic delivery of insulin [259–263]. In their first few studies, they found that the delivery efficiency of insulin is largely affected by electrode selection, electronic parameters (current, duration, and mode of applications), and formulation properties (formulation pH, peptide concentration, buffer type and concentration) [259–261]. In their following studies, they further demonstrated that iontophoresis mediated transdermal delivery of insulin can be enhanced by combination with the use of permeation enhancers [262,263]. Particularly, they found that permeation enhancers that act on intercellular lipids such as ethanol, dimethyl acetamide, and ethyl acetate could synergistically enhance the delivery efficiency of insulin by iontophoresis [263]. As another example, Medi et al. studied the effect of iontophoresis on transdermal delivery of human parathyroid hormone on a porcine skin model. They investigated the transport flux of the hormone through porcine skin at different iontophoresis current (0.2–0.5 mA/cm^2). They found that delivery flux of the hormone was enhanced by ~3-fold when using a higher current of 0.5 mA/cm^2 [264].

In recent decades, researchers have started to investigate the potential of iontophoresis for transdermal delivery of nanoparticles such as polymeric nanoparticles, liposomes, lipid nanoparticles and gold nanoparticles [265–268]. Tomoda et al. demonstrated that iontophoresis improved the delivery of indomethacin loaded PLGA nanoparticles through the mouse skin in vivo when iontophoresis was conducted at 0.05 mA/cm^2. This enhanced delivery of PLGA nanoparticles improved the indomethacin drug concentrations in the muscle and plasma (Fig. 3B) [269]. Labala et al. investigated the transdermal delivery of gold nanoparticles carrying a chemotherapeutic drug (imatinib) and anti-STAT3 siRNA for melanoma treatment. Payload-carrying gold nanoparticles were prepared by layer-by-layer assembly. They demonstrated that iontophoresis significantly improved the accumulation of nanoparticles in the melanoma tumor. Meanwhile, they found that iontophoresis mediated delivery of nanoparticles led to a significant tumor volume reduction and the efficacy was comparable to intratumoral administration [270]. As another example, Bernardi et al. studied iontophoresis enhanced transdermal delivery of antigen nanoparticles for transcutaneous immunization. They showed that cathodal iontophoresis significantly improved the penetration of antigen-loaded liposomes and silver nanoparticles by 92-fold, which subsequently induced potent antibody production and differentiation of immune-competent cells in vivo [271].

In parallel to transdermal drug delivery, applying the similar mechanism, iontophoresis has also been studied for overcoming the ocular barrier for local as well as systemic delivery of various drugs [247,272]. Recently, new research directions have been proposed to extend the application of iontophoresis to other drug delivery areas beyond transdermal and ocular delivery. One such area is oral drug delivery. In a recent study, Banerjee et al. applied the iontophoresis technology to tackle the intestinal barrier. Specifically, they investigated whether iontophoresis across the intestine could be used to improve oral delivery of insulin. They found that iontophoresis led to opening of tight intestinal junctions and improved the paracellular transport of insulin by 3-fold in vitro. They further demonstrated that iontophoresis resulted in significant hypoglycemia (Fig. 3C) without causing detectable damages to the intestinal tissue when using an insulin-loaded mucoadhensive patch, highlighting the promise of iontophoresis for oral drug delivery [245].

Due to its outstanding advantages (Table 1), including non-invasiveness, versatility and adaptability to cargo molecules, and easy control over the delivered dose and rate, iontophoresis has been investigated in the clinic, particularly for topical/transdermal and ocular drug delivery (Table 2). Currently, several transdermal/topical iontophoresis products have been approved by FDA, including Ionsys® (transdermal fentanyl), Zecuity® (transdermal sumatriptan), and Lidosite® (transdermal lidocaine and epinephrine). More than 50 clinical trials have been completed or are ongoing for iontophoresis mediated drug delivery that covers a range of indications (representative examples shown in Table 2). For example, iontophoretic delivery of treprostinil has been investigated for promoting wound healing in diabetic foot skin ulcers (NCT03654989) and systemic sclerosis digital ulcers (NCT03120533). In addition, iontophoresis is being tested for ocular

Table 1
Physical triggers for drug delivery: advantages, limitations, and the corresponding applications.

Physical trigger	Advantages	Limitations	Application
Ultrasound	• High spatiotemporal targeting precision facilitating drug delivery at desired location and time • Deep tissue penetration • Clinically established image--guided drug delivery: Ultrasound and/or MRI guidance • Clinically established ultrasound responsive agents: Definity®, Optison™, SonoVue®, ThermoDox®	• Drug delivery to lungs remain an obstacle due to mismatch in acoustic impedance. • Tissue necrosis and edema at high ultrasound power • Online treatment monitoring during cavitation-based systems remains challenging	• Increased permeability of stratum corneum, vascular endothelium and extravascular cells for drug delivery across biological barriers such as the blood-brain barrier • Enhanced tumor perfusion • Triggered drug release • Enhanced drug accumulation and penetration through augmented extracellular agent trafficking
Light	• Very high spatiotemporal targeting precision • Many light sensitive materials can be used both as therapeutic and diagnostic agents • Clinically established light sensitive agents: Photofrin®, Foscan®, Purlytin®, Laserphysin®	• Shallow tissue penetration • Absorption of UV and short wavelength light may cause unavoidable damage in tissue • Some photosensitizing materials may induce toxicity due to non-biocompatibility and non-biodegradability • Biological applications of some hydrophobic materials are inconvenient	• Photodegradable materials have potential as vehicle/-carrier for light-controlled drug release and delivery. • Photosensitizing materials can be used as therapeutic mediators themselves for photothermal and photodynamic therapies.
Electric fields	• High temporal control over the administered drug dose and the delivery rate of drugs • Versatility and adaptability to cargo molecules • Clinically established products: Ionsys®, Zecuity®, Lidosite®, NanoKnife® (for research purpose)	• Safety concern: potential damage to target tissue and cells. Cutaneous adverse events are sometimes associated with iontophoresis and electroporation. • Some systems are not truly non-invasive due to the involvement of implanted devices • Low cost-effectiveness: relatively expensive compared to non-device-based formulations	• Iontophoresis for transdermal, topical, ocular delivery of therapeutics • Electroporation for intracellular delivery of therapeutics • Electroporation for transdermal delivery of therapeutics • Electro-responsive materials for programmed drug release
Magnetic fields	• High spatiotemporal targeting precision can be achieved • Deep tissue penetration • Clinically established magnetically responsive agents: ferumoxytol	• Although magnetic triggering itself is considered safe clinically, the safety profile of SPIONs or other MRPs are in debate. Many of the previous FDA-approved SPIONs used in medical imaging are discontinued (except for ferumoxytol). • Customized magnetic device design can be complicated	• Enhanced magnetic hyperthermia • Triggered drug release • Magnetically control the cell/tissue mechanobiology via SPIONs-seeded cells • MRI monitoring capability for theranostic and/or multi--stimuli responsive systems

delivery of dexamethasone and analogs for eye indications such as dry eye (NCT01129856) and uveitis (NCT00694135).

4.2. Electroporation

Electroporation is another electrically based strategy for overcoming biological barriers for effective drug delivery [246,273]. Electroporation involves the physical rearrangement of cellular membranes under electric pulse. The kT energy associated with fundamental thermal fluctuations and electrical energy associated with elevated transmembrane voltage lead to the stochastic creation of microscopic pores [274]. As such, the fundamental mechanism of electroporation mediated drug delivery involves the transient, reversible formation of aqueous pores across biological barriers such as cell membrane and stratum corneum of the skin when a short duration of a high voltage electric pulse is applied (Fig. 3D) [244]. The creation of aqueous pores facilitates the transport of molecules by various mechanisms depending on the properties of the delivered molecules such as size, charge, and hydrophobicity. While small molecules typically reply on simple diffusion across the pores, transport of large molecules involves additional mechanisms such as electrophoretic driven movements [241,273].

Overcoming the cellular membrane barrier is a significant application which electroporation has found great utility in [244,273]. Conventional electroporation for intracellular delivery involves the use of a bulk electroporation setup. This electroporation process is typically done in a cuvette-style parallel plate setup. In this setup, molecules of interest and cell suspension are mixed in a conducting buffer solution between two electrodes [273]. Despite having advantages such as ease of operation and excellent versatility, bulk electroporation suffers from two distinguished drawbacks including uncontrollable cell membrane disruption and difficulty in controlling delivered cargo dose [244,273]. In recent two decades, advances in the field of macro−/nano-fabrication have driven the design of the new generation of electroporation setups. Particularly, the emerging concept of micro−/nano-electroporation and microfluidic-based electroporation are being explored with potential to solve the challenges faced by bulk electroporation [273]. Electroporation was first invented for DNA transfer into cells [275]. Early attempts were focused on small molecules, DNA, proteins, and mRNA [273]. For example, small molecules such as ascorbic acid and mannitol could be efficiently delivered into human erythrocytes by electroporation [276]. As another example, electroporation has been proven to be a powerful strategy for intracellular delivery of protein antigens or antigen-encoding mRNAs into dendritic cells, which have found great utilities in developing dendritic cell based vaccines for cancer and other diseases [277,278]. With the rapid development of cell-engineering molecules, electroporation is being investigated for intracellular delivery of these novel molecules. Representative categories of these novel molecules include siRNA, genome editing agents, molecular probes, and even nanoparticles [273]. Meyer and co-workers designed a high-throughput suspended-drop electroporation (SDE) method for intracellular delivery of siRNA into hard-to-transfect cells [279]. This electroporation device consisted of an array of 96 suspended electrode pairs. Samples of small volume were top-loaded, electroporated, and bottom-ejected into a 96-well plate. They demonstrated that siRNA could be delivered into a hard-to-transfect cell (differentiated HL-60 cell) by this method (Fig. 3E) to knock down the expression of lamin A/C (a nuclear envelop protein) with a high efficiency of ~70% [279]. In a recent study by Roth et al., the authors reported an electroporation-mediated intracellular delivery of a designed CRISPR-Cas9 genome-targeting system into primary human T cells [280]. This strategy allowed efficient, site-specific

Table 2
Clinical progress of physically triggered drug delivery systems.

Physical trigger	Drug delivery systems	Disease indication	ClinicalTrials.gov Identifier	Status
Ultrasound	*Sonophoresis:*			
	Lidocaine 4% *w*/w and SonoPrep	Pain	NCT00126932 NCT00126919	Phase 4
	Methylprednisolone or cyclosporine	Alopecia areata	N/A (Ref [30])	
	Depigmenting emulsion	Melasma, Solar lentigo		
	Retinol	Anti-aging therapy	N/A (Ref [31])	
	Herbal gel formulation	Malignant pleural effusion	N/A (Ref [34])	
	Hydrogel	Refractory metastatic malignant bowel obstruction	N/A (Ref [35])	
	Sonopermeation:			
	SonoVue® and chemotherapy	Colorectal cancer Hepatic metastases	NCT03458975	Phase 2
	SonoVue® and chemotherapy	Colorectal neoplasms Breast neoplasms	NCT03477019	Phase 1 Phase 2
	SonoVue® and FOLFIRINOX	Pancreatic ductal carcinoma	NCT04146441	Phase 2
	Blood-Brain Barrier (BBB) opening using FUS and Definity®	Low grade brain glioma	NCT04063514	Not applicable
		Alzheimer's disease	NCT04118764	Not applicable
	BBB opening using FUS and SonoVue®	Glioblastoma	NCT03626896	Not applicable
	BBB opening using implantable FUS devive and SonoVue®	Alzheimer's disease	NCT03119961	Phase 1/2
	Primary Motor Cortex BBB opening using FUS and Definity®	Amyotrophic lateral sclerosis	NCT03321487	Not applicable
	BBB opening using FUS and Definity® with standard chemo-radiation with temozolomide	Glioblastoma	NCT03616860	Not applicable
	BBB opening using FUS and Definity® with temozolomide	Glioma/Glioblastoma Glioblastoma	NCT03551249 NCT03712293	Not applicable
	SonoVue® and recombinant tissue plasminogen factor	Cerebrovascular stroke	NCT01678495	Phase 2
	ACT and FOLFOX/FOLFIRI	Solid tumor, colorectal cancer	NCT04021277	Phase 1
	ACT and Gemcitabine/Abraxane®	Pancreatic cancer		
	Hyperthermia:			
	ThermoDox®	Liver tumors	NCT02181075	Phase 1
	ThermoDox® and cyclophosphamide	Breast cancer	NCT03749850	Phase 1
Light	*Photodynamic:*			
	Hexaminolevulinate	Bladder cancer	NCT02660645	Not applicable
		Basal cell carcinoma	NCT02367547	Phase 1/2
		High-risk Bladder Cancer	NCT01303991	Phase 1
	Aminolevulinic Acid	Antinic Keratoses	NCT01459393	Phase 3
		Oral Leukoplakia	NCT00571558	Phase 1
		Acne Vulgaris	NCT00706433	Phase 2
		Lentigo Maligna	NCT02685592	Phase 4
		Superficial Basal Cell Carcinoma	NCT01491711	Phase 4
		Non-melanomatous Skin Cancer	NCT00747903	Phase 2
	Vismodegib	Basal cell carcinoma	NCT02639117	Phase 1
	5-fluorouracil	Actinic Keratoses	NCT01525329	Phase 3
		Bowen's Disease	NCT03909646	Phase 4
	Ameluz/Protoporphyrin	Actinic keratoses	NCT04319159	Phase 1
		Non-melanomatous Skin Cancer	NCT00663910	Phase 1
	Porfimer sodium for treating	Head & Neck Cancer	NCT00453336	Phase 2
		Non-Small Cell Lung Carcinoma	NCT03678350	Phase 1
		Cholangiocarcinoma	NCT00540735	Phase 3
		Pancreatic cancer	NCT01770132	Phase 1
		Recurrent brain Tumor	NCT01966809	Phase 2
		Extrahepatic Bile Duct Cancer	NCT00003923	Phase 2
	Methylene blue for treating Chronic	Periodontitis	NCT03262077	Not applicable
		Oral Mucositis	NCT02555501	Phase 3
		Abscess	NCT02240498	Phase 1
		Onychomycosis of Toenail	NCT03098342	Not applicable
		Lichen Amyloidosis	NCT03068208	Not applicable
		Diabetic Lower Limb Ulcer	NCT03222544	Not applicable
	LUZ11	Head and neck cancer	NCT02070432	Phase 1/2
	Lemuteporfin	Prostatic hyperplasia	NCT00116571	Phase 2
		Acne	NCT01490736	Phase 1/2
	Clobetasol propionate	Vulvar lichen sclerosus	NCT02416531	Not applicable
	Verteporfin	Central Serous Chorioretinopathy	NCT00211445	Phase 2
		Pancreatic cancer	NCT00211445	Phase 2
		Metastasis breast cancer	NCT03033225	Phase 2
		Recurrent Prostate cancer	NCT02939274	Phase 2
			NCT03067051	Phase 1
	Imiquimod	Actinic keratoses treatment	NCT04219358	Phase 2/3
		Lentigo Maligna	NCT02394132	Phase 3
	Photothermal:			
	Silica-gold NP	Atherosclerosis	NCT01270139	Not applicable
	Gold Nanoparticles	Coronary Artery Disease	NCT01436123	Phase 1

Table 2 (*continued*)

Physical trigger	Drug delivery systems	Disease indication	ClinicalTrials.gov Identifier	Status
Electric fields	*Iontophoresis*:			
	Ionsys® (Iontophoresis transdermal fentanyl)			FDA approved
	Zecuity® (Iontophoresis transdermal sumatriptan)			FDA approved
	Lidosite® (Iontophoresis transdermal lidocaine and epinephrine)			FDA approved
	Dermadry (Iontophoresis for hyperhidrosis)			FDA approved
	Iontophoresis dexamethasone	Pediatric knee apophysitis	NCT03606980	Phase 2
	Ocular iontophoresis dexamethasone phosphate	Dry eye	NCT01129856	Phase 3
	Iontophoresis lidocaine	Juvenile idiopathic arthritis	NCT00465504	Phase 3
	Iontophoresis treprostinil to enhance wound healing	Diabetic foot skin ulcers	NCT03654989	Phase 1/2
	Ocular iontophoresis dexamethasone phosphate	Anterior uveitis	NCT00694135	Phase 2
	Iontophoresis urotensin-II and soluble epoxide hydrolase inhibitors for skin microvessel toning	Heart Failure	NCT00654966	Phase 2
	Iontophoresis treprostinil for systemic sclecrosis digital ulceration	Systemic scleroderma	NCT03120533	Phase 1
	Electroporation:			
	Electroporation of HPV DNA vaccine (VGX-300)	HIV-positive high-grade anal lesions	NCT03603808	Phase 2
	Electroporation of tavokinogene telseplasmid in combination with perbrolizumab for treating	Unresectable head and neck cancer	NCT03823131	Phase 2
		Locally advanced or metastatic triple negative breast cancer	NCT03567720	Phase 2
		Stage III/IV melanoma	NCT03132675	Phase 2
	Irreversible electroporation and gemcitabine	Locally Advanced Pancreatic Adenocarcinoma	NCT03673137	Phase 2/3
	Medpulser Electroporation System with bleomycin	Head and neck cancer	NCT00198263	Phase 4
	Electroporation of VGX-3100	Cervical High Grade Squamous	NCT03185013	Phase 3
		Intraepithelial Lesion	NCT03721978	Phase 3
	In vivo electroporation-mediated plasmid DNA vaccine therapy and IL-12 gene for treating	Merkel cell cancer	NCT01440816	Phase 2
		Malignant melanoma	NCT01502293	Phase 2
	Electroporation of INO-5401 and INO-9012 in combination with Cemiplimab	Newly diagnosed glioblastoma	NCT03491683	Phase 1/2
Magnetic fields	Ferrofluid with noncovalently adsorbed epirubicin	Various	N/A (Ref [355])	Phase 1/2
	Doxorubicin adsorbed to magnetic beads	Liver cancer	NCT00041808	Phase 1/2
			NCT00054951	Phase 1/2
			NCT00034333	Phase 2/3
	SPIONs-enhanced magnetic thermoablation	Prostate cancer	NCT02033447	Early Phase 1 (Phase 0)
	SPIONs-enhanced neoadjuvant chemotherapy	Osteosarcoma	NCT04316091	Phase 1
	Magnetically guided photothermal therapy via hybrid nanostructures of silica, gold, and iron-bearing nanoparticles that are loaded in microbubbles and internalized into stem cells	Coronary atherosclerosis	NCT01270139	Not applicable

insertion of large DNA sequences in the genome and preserved the cell viability and function in the meantime. They demonstrated that this strategy could be successfully applied to replace endogenous T cell receptor locus with a new TCR that enabled T cells to recognize a cancer antigen. The engineered T cells were able to specifically recognize tumor antigens and led to strong T cell mediated anti-cancer responses in vitro and in vivo [280]. Espinosa and co-workers designed a nanofountain probe electroporation setup that was able to deliver a molecule probe (molecule beacons) into single cells for detecting the intracellular expression levels of proteins and mRNAs [281]. They demonstrated that this electroporation method could efficiently deliver a DNA-based beacon for detecting glyceraldehyde 3-phosphate dehydrogenase and an RNA-based beacon for detecting a sequence cloned on GFP mRNA [281]. Electroporation mediated intracellular delivery are quickly evolving as an important tool in many biomedical applications. Especially, electroporation enabled intracellular delivery is being and will continuously be a key player in gene therapy, adoptive cell therapy, and single cell analysis.

Apart from intracellular delivery, transdermal drug delivery is another field which electroporation has played a significant role in [241,246]. Transdermal electroporation usually involves the use of a higher voltage (>50 V) of electric pulse than intracellular electroporation, because the stratum corneum of the skin is regarded as a thicker barrier than cell membrane [135]. Extensive studies have demonstrated that electroporation could enhance the transdermal delivery of a diverse spectrum of molecules ranging from small molecules (such as mannitol, metoprolol, fentanyl) to macromolecules (such as heparin, DNA, and protein antigens) [246,282–286]. Particularly, electroporation can achieve orders of enhancement in delivery efficiency and its potency depends on the parameters of the electric pulse and the physicochemical properties of the drug. Although electroporation by it alone has demonstrated potential for transdermal delivery, the electroporation field has moved toward its combination with other transdermal delivery technologies for achieving better delivery efficiency [246]. For example, its combination with chemical enhancers has shown promise in further improving the efficiency. Literature evidence suggested that chemicals that can stabilize the transient disruption of the skin barrier generated by electroporation can improve the delivery efficiency of transdermal electroporation [246,287]. Such chemicals include phospholipids, sodium thiosulfate, dextran, heparin, among others [288,289]. In addition, the combination of electroporation with iontophoresis has shown to be another combination strategy to enhance the efficacy of electroporation [290]. For example, Sugibayashi and co-workers demonstrated that the combined use of iontophoresis and electroporation significantly increased the plasm concentration of transdermally delivered insulin in a rat model compared to the use of electroporation alone (Fig. 3F) [290]. Moreover, apart from chemical enhancers and iontophoresis, other transdermal technologies, including laser ablation, ultrasound and microneedles, have been reported to have synergy with electroporation [135,291].

Electroporation has many outstanding advantages that make them a clinically viable drug delivery approach. Electroporation are usually easy to operate. In addition, its adaptability to drug types render it a versatile drug delivery strategy (Table 1) [244]. Electroporation has been extensively investigated for drug delivery in the clinic (representative examples shown in Table 2). More than 50 clinical trials have been performed or are ongoing for electroporation mediated drug delivery. Most of the trials are focused on DNA delivery to tumors for cancer treatment. For example, electroporation mediated delivery of tavokinogene telseplasmid in combination with perbrolizumab are being tested in phase 2 trials for the treatment of multiple types of cancer, such as unresectable head and neck cancer (NCT03823131), locally advanced or metastatic triple negative breast cancer (NCT03567720), and stage III/IV melanoma (NCT03132675). In addition, irreversible electroporation in combination with gemcitabine is also being tested for the treatment of locally advanced pancreatic cancer (NCT03673137).

4.3. Electrically responsive drug carriers

Electrically responsive drug carriers that allow controlled release of drugs are another strategy to achieve electrically based drug delivery. Such carriers are usually made from polyelectrolyte or conductive polymers. Electric field induced redox reactions or ionization, which leads to the bond cleavage or drug carrier deformation, is the major mechanism for responsive drug release from such carriers [1]. Many electrically responsive drug carriers have been investigated over the past decades. These carriers fall into three major categories including bulk carriers, responsive films, and dispersed nanoparticle carriers [1,292,293].

Bulk electrically responsive carriers, such as bulk conductive polymer materials and polyelectrolyte hydrogels, are first investigated for controlled drug release [292–294]. Polyelectrolyte hydrogels undergo electro-triggered structural changes including swelling, shrinking, or erosion in an electric field [295]. Drug release from electrically responsive polyelectrolyte hydrogels can be attributed to one or combination of the following mechanisms: gradient-dependent drug diffusion, drug ejection with synereses out of the fluid phase, electrophoresis of the drug toward an oppositely charged electrode, and drug liberation with the erosion of the gel [294,295]. As a seminar example, Kagatani et al. designed a poly(dimethylami- nopropylacrylamide) (PDMAPAA) gel system for electro-responsive delivery of insulin [284]. The insulin-loaded PDMAPAA gel was injected subcutaneously in a rat model. The authors demonstrated that this electro-responsive insulin gel could lead to programmed insulin release and thus controlled plasma glucose decrease in vivo [284]. Bulk electrically responsive carriers suffer from several challenges including poor responsiveness and limited drug adaptability [292]. To solve these challenges, electro-responsive films have been investigated for drug delivery. Various types of electro-responsive films incorporating different features have been devised [292]. For example, ultrathin films can be fabricated on a bulk substrate by the layer-by-layer assembly replying on the electrostatic interactions between charged drugs and an oppositely charged substrate. The loaded drug can be released from the film in a controlled manner due to the disassembly of the film in an electric field [1,296,297]. Apart from this, many other types of electro-responsive films having nano-engineered features are also being investigated for controlled drug delivery, such as nano-textured films, nano-porous films [298,299], and nano-composite films [292,300–302]. As an example, Svirskis and *co*-workers reported a polypyrrole nano-porous film for electrically controlled release of risperidone [299]. The nano-porous film was fabricated by electropolymerization of polypyrrole via the interstitial voids of a colloidal crystal template followed by chemical etching of the template. They demonstrated that the nano-porous film can be actuated by an electrical stimulus which in turn modified the drug release profile [299].

Electrically responsive nanocarriers have also been investigated in recent years for controlled drug delivery [303,304]. These nanocarriers are made from conductive polymers such as polypyrrole [303,305,306]. The polymers are reduced to a neutral state when being exposed to an electric potential. This usually leads to a reduced affinity between the drugs and carriers, which induces the drug release (Fig. 3G) [1]. For example, Zare and *co*-workers designed an electrically responsive polypyrrole nanoparticle (~150 nm) for the delivery of therapeutic pharmaceutics in a mouse model. They demonstrated that the release of two model drugs, fluorescein and daunorubicin, could be controlled by applying a direct current electric field in vitro (Fig. 3H). In addition, they also proved that the release of drugs could be controlled by an electric field when the nanoparticles were administered subcutaneously with the help of a hydrogel (Fig. 3I) [307]. Apart from nanoparticles, other types of electrically responsive nanocarriers have also been investigated for drug delivery, such as micelles and vesicular structures [292,308,309].

4.4. Clinical challenges

Various clinical experiences in iontophoresis- and electroporation-mediated drug delivery raised several concerns (Table 1) [239]. Tissue damage and related local adverse events are a major concern [310–312]. Tissue irritation can be associated with normal iontophoresis/electroporation and tissue injury may be caused by disoperation of devices. In addition, depending on the device needed, iontophoresis/electroporation may be less cost-effective than the respective non-device based formulations [239]. However, with the advances in the technical level, iontophoresis and electroporation is moving to more diverse and flexible setups that could allow better control of the treatment process. This will help solve critical issues faced by conventional approaches such as irreversible damage.

Despite having distinguished advantages such as minimal-invasiveness and spatial-temporal control over the delivery process [248], electrically responsive carrier mediated drug delivery is still in its early stage of development. Most of the current developed systems are in preclinical investigations and have not advanced to the clinic. Future work needs to address several urgent challenges to further their preclinical and clinical applications. Most of the work so far has focused on evaluating the electrical responsiveness of the materials in vitro. Future studies need to more focus on the in vivo feasibility and responsiveness of electrically responsive carriers. In addition, release of delivered drugs is also to be better controlled though materials design in future studies. Moreover, many of the current electrically responsive carriers have sophisticated structures. Reducing the complexity while maintaining the responsiveness of the carriers will accelerate their clinical translation. Furthermore, safety and biocompatibility of electrically responsive carriers should be more extensively studied to assess their feasibility for clinical use.

5. Magnetic field

Magnetic field is another form of external trigger that has been explored in drug delivery applications. Magnetic fields also offer deep tissue penetration with confirmed safety profile clinically [1,313]. Compared to other forms of physical stimuli, the most unique nature of the magnetic triggering is that biological tissue is typically magnetically inert. Therefore, unlike light and ultrasound, the magnetic forces normally would not be attenuated as much by affected tissue, which is beneficial for preventing the excessive energy deposition in healthy tissue in the active magnetic field. Unlike all the aforementioned physical triggers, this distinct physical feature also suggests that magnetic fields do not typically act on biological barriers directly by itself. Magnetic drug delivery systems may heavily rely on drug vehicles that possess a strong magnetic moment for enhanced accumulation and controlled release by magnetic fields.

Magnetic fields generally either trigger heat deposition (temperature increase) from magnetically responsive particles (MRPs) in the alternating magnetic fields (AMF) or mechanical deformation of the drug-carrying agents/cells for drug release. In this section, we will first review and discuss the most recent advancements in these two areas. In addition, we highlight the emerging and growing efforts on developing theranostic and multi-stimuli responsive capabilities of magnetic drug delivery systems. Lastly, advances and challenges in the clinical setting of this field are discussed.

5.1. Heat-mediated magnetic drug delivery

One of the most widely adopted approach in magnetic drug delivery is through thermal effects from MRPs in the AMF. High-frequency AMF (>10 kHz) [1] can heat MRPs via Néel (reorientation of the magnetization) and/or Brownian (physical motion of the particles) relaxations [314]. Recent study suggested that this local heating mechanism may be dominated by Néel relaxation for silica-encapsulated MRPs [315]. Based on this local heating effect, many metal oxides based MRPs were developed for localized hyperthermia treatment and/or thermally sensitive nanocomplex for drug delivery. Here, we specifically focus on the drug delivery applications in this subsection.

Over the years, magnetically manipulated on-demand drug delivery has been attracting significant attention. Earlier works using superparamagnetic iron oxide nanoparticles (SPIONs) showed enhanced accumulation and drug release via temperature or pH change [4]. Classic SPIONs typically have two structures (1) a core made of iron oxides that are magnetically responsive with a drug-loaded polymeric coating or (2) a porous structures with drugs and SPIONs precipitated inside the pores [4]. These systems have been designed to deliver peptides, DNA molecules, and chemotherapeutics [4,316]. In addition to those polymers, typical forms of MRPs also include magnetoliposomes. These particles have a typical structure with a magnetic iron oxide core surrounded by lipid bilayer coating [317,318]. In the magnetic liposomes, one can encapsulate the drug into the liposomes and decorate the liposomes for biologically specific targeting, aiming for an integrated concept of biological and physical drug targeting for magnetically triggered drug release and hyperthermia.

Recently, growing efforts have been made in overcoming challenges encountered by classic drug delivery systems with poor controllability in drug release, low magnetization and limited applications outside the intravascular system.

To improve the controllability of the MRNs in response to the external stimulus in a more precise manner, many new designs of MRPs have been developed. Katahiri et al. developed a unique magnetically responsive hybrid liposome that can release the encapsulated drug on-demand without significant perturbation of lipid bilayer structure [319]. In their system, hydrophobized Fe_3O_4 nanoparticles were embedded into liposomal membranes rather than being encapsulated inside. Local heating effects could thus be directed to the thermosensitive segment of the copolymer for creating gaps to release drugs without liposomal rupture. The release rate could be controllable by changing the amount of Fe_3O_4 nanoparticles and/or by re-designing the block copolymer. In another report, to control the sustained and on-off drug release, Hoare et al. designed a smart system with nanocomposite membranes composed of thermoresponsive nanogels and SPIONs (Fig. 4C) for drug release upon the application of AMF (Fig. 4A) [320]. It was found that the dose of drug delivered across the membrane in their system can be tailored by changing the loading density of nanogels in the membrane, and even simply changing the membrane thickness (Fig. 4B), allowing for over at least 2 orders of magnitude in drug delivery. This design enabled the precise control of drug dosing based on both the physical properties and compositions of the membrane and the duration of the magnetic field.

More recently, several works further investigated the spatiotemporal drug release profile in response to external magnetic stimulus for their optimized systems. Fuller et al. designed a thermo-labile drug conjugate encapsulating iron oxide MRPs, and achieved the spatially controlled drug release using alternating magnetic field generated via a 1.27 T/m magnetic field gradient. Their MRPs consist of a hydrophobic core of SPIONs that release heat in response to magnetic stimuli and a thermoresponsive polymer that releases a molecular cargo through the breakage of thermally labile Diels—Alder bonds [321]. In another report, Chen et al. realized the spatial, temporal, and dose control of drug release using a monodispersed manganese- and cobalt-doped iron oxide ($MnFe_2O_4$@$CoFe_2O_4$) nanoparticles with a thermal-responsive gatekeeper [322]. This work demonstrated that the amount of drug released could be controlled by the exposure time of the magnetic field. Step-wise and sequential release was thus accomplished by applying multiple sequential exposures of the external trigger.

In addition to new designs on MRPs with delicate drug release mechanisms, improving the spatial controllability can also be achieved by optimizing the applied magnetic fields. As mentioned before, a significant body of work utilizes the AMF to induce local heating and drug release. However, the targeting specificity of AMF-induced drug release from thermally sensitive carriers is restricted by the spatial resolution of the AMF due to the intrinsic frequency-dependent diffraction limit [323]. As SPIONs are typically more responsive to frequencies in the 100–500 kHz range [323–325], focusing of the AMF normally bears the spatial resolution of around 1 m, which is way too large compared to the scale of human cells and tissue. Liu et al. developed a device that superimposes a strong static field containing a sharp zero point onto an AMF to threshold the MRP response to AMF [323]. Their system induced drug release from thermally sensitive liposomes within a 3.2 mm radius target. Additional advantage of this novel system is that the size and location of the targeted region can be independently controlled.

Another major issue using SPIONs for drug delivery is that the individual particles do not typically display high magnetization, challenging the guidance and accumulation via external magnetic triggers. A way to overcome this problem is using techniques of nanoparticle clustering or assembly to increase the overall magnetism [326]. In order to enhance the magnetization of the drug delivery system, multi-layer design has been explored. Yang et al. fabricated a nanosized system in which the SPIONs with the grafted poly(styrene)-*b*-poly(acrylicacid) (PS-*b*-PAA) block copolymer were self-assembled into the membranes [327]. The thickness of the magneto-vesicles was found to be well controlled from 9.8 to 93.2 nm via changing the weight ratio of SPIONs to PS-*b*-PAA, which further triggered the self-assembly behavior from monolayer to multi-layer particles with the ability to pack high load of SPOINs. The team incorporated doxorubicin in the hollow cavity of the particles and demonstrated the enhanced tumor drug accumulation and growth inhibition, as well as the drastic MR contrast enhancement.

In addition, most of the magnetic hyperthermia and/or heat-mediated drug release systems are designed for intravenous administration, limiting the applications in diseases of the gastrointestinal tract. To address this issue, Che Rose et al. proposed a drug delivery system for use in the gastrointestinal tract that can release its payload on demand in response to localized magnetic hyperthermia trigger [328]. The system was based on a SPIONs/wax composite capsule coating, which was synthesized using a simple dip-coating process from pharmaceutically approved materials. In vitro tests show that the coating is completely melted within 2 min at the triggering of magnetic fields under biologically-relevant conditions. In a follow-up study, the same group also demonstrated the drug release for theranostic applications of the system [329]. This method has potential for magnetic hyperthermia-controlled drug release in the gastrointestinal tract, for diseases such as Crohn's disease, colitis ulcerosa, and cancer.

5.2. Non-thermal magnetic drug delivery

Although the heat-mediated approaches dominate the drug delivery efforts via MRPs, some studies showed that low-frequency or static fields can trigger drug release non-thermally. One mechanism of the

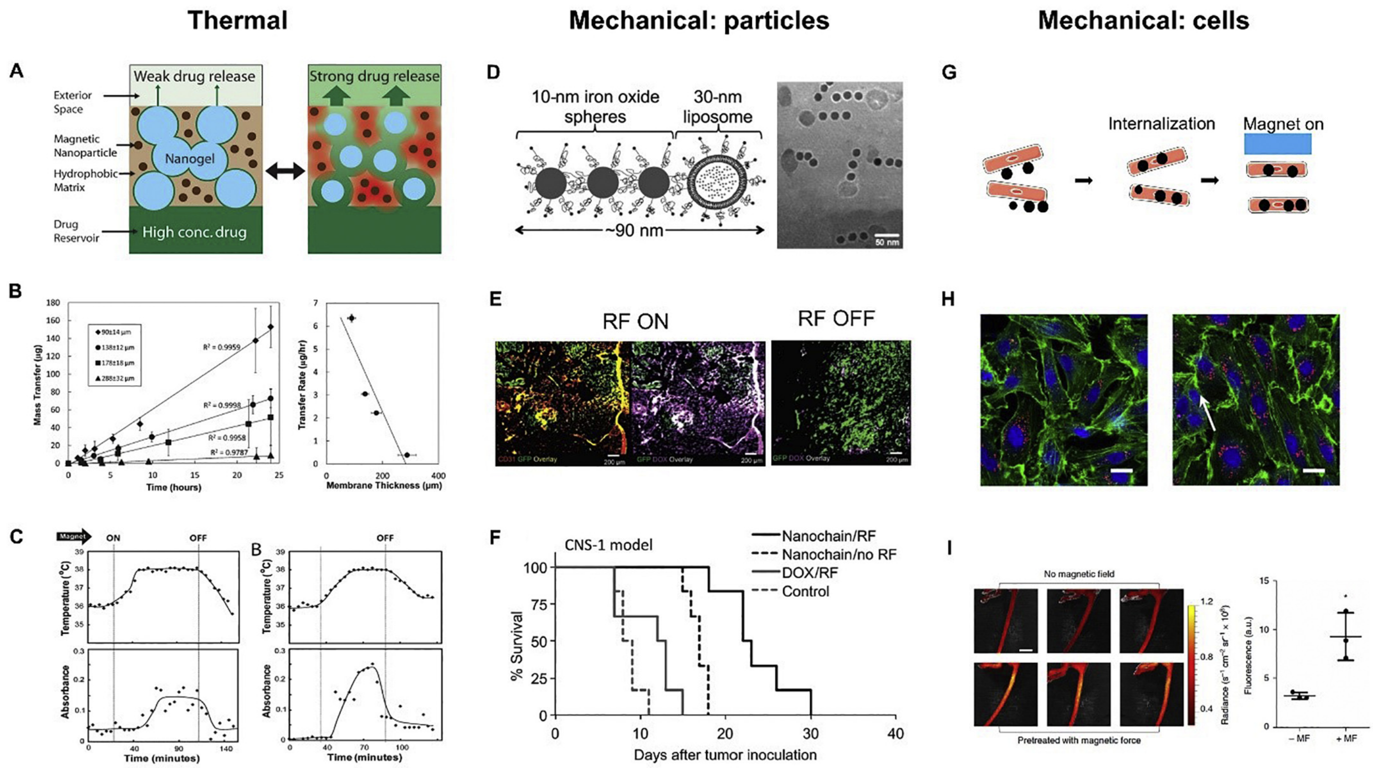

Fig. 4. Magnetic drug delivery. (A-C) Heat-mediated magnetic drug delivery. Adapted with permission from [320]. (A) Mechanism of one heat-mediated magnetic drug delivery system. Upon application of the alternating magnetic field, the SPIONs release heat (red) and reversibly shrink the nanogel, enabling release of a drug (green) from a reservoir contained by the membrane. (B) Membrane thickness regulates sodium fluorescein flux. Left: Mass transfer of sodium fluorescein as a function of "on" triggering time for membranes with different thicknesses. Right: Rate of mass transfer as a function of membrane thickness for data represented in the left panel. (C) Magnetic on-off triggering of membranes. (D-F) Magnetic drug release through the nanochain particles and its therapeutic effect on brain tumors. Adapted with permission from [332]. (D) Left: schematics of a linear nanochain particle composed of three iron oxide nanospheres and one drug-loaded liposome. Right: TEM image of nanochain particles. (E) The distribution of doxorubicin molecules is shown with (left) or without (right) external RF stimulus with respect to the location of cancer cells. DOX refers to doxorubicin. (F) The survival profiles of CNS-1 tumor-bearing animals are shown after treatment with saline (untreated control), doxorubicin followed by RF, nanochains (no RF), and nanochains followed by RF. (G-I) Nonthermal Magnetic enhancement of vascular permeability. Adapted with permission from [333]. (G) Mechanism of non-thermal magnetic drug delivery via internalized SPOINs to cells. (H) Left: the stress fibers (green) of endothelial cells have a random orientation after internalizing MNPs (red). Right: after exposed to external magnetic force, stress fibers appear to align with the force (the arrow indicates the direction of magnetic force). Scale bar, 20 mm. (I) Magnetic enhancement of vascular permeability in vivo.

nonthermal delivery is due to the mechanical deformation of the MRP itself. A classic example used a low-frequency field (13.3 Hz) to release insulin from subcutaneously implanted polymer matrices and embedded magnets [330]. This effect of drug releasing from the polymer matrix was considered to result from the magnetic motion directly. Another more recent work designed multicomponent nanochains with three magnetic nanospheres and one doxorubicin-loaded liposome (Fig. 4D) [331]. This design takes advantage of the magnetic nanosphere chain as a secondary mechanical transducer to amplify the mechanical effects to the drug-loaded liposomes. The disruption of the liposomal walls resulted in the release of chemotherapeutics, which triggered a widespread cytotoxic effect throughout the entire tumor. More recently, the same group applied this technique into the treatment of rodent glioma models and demonstrated the enhanced site-specific drug delivery (Fig. 4E) and improved survival (Fig. 4F) [332].

Another way of concentrating and amplifying the mechanical effects to targeted cells/tissue is to seed the SPIONs directly to the biological entities. Qiu et al. demonstrated that the permeability of vascular endothelium can be enhanced using internalized SPIONs and external magnetic field (Fig. 4G) [333]. Tested in endothelialized microfluidic channels in vitro (Fig. 4H) and in vivo experiments with a mouse lateral tail vein model (Fig. 4I), magnetic forces enabled temporarily disruption of endothelial adherens junctions, activating the paracellular transport pathway and facilitating the local extravasation of circulating substances. This work suggested to control the magnetic physical triggering by harnessing the biology of endothelial adherens junction, which may be promising to shift the paradigm of the magnetic particle-based drug delivery.

5.3. Theranostic and multi-stimuli responsive systems

Theranostic systems are, without doubt, intriguing for triggered drug delivery systems, where online treatment monitoring is expected for a precise control. In addition, with MRI, ultrasound and light-based imaging techniques have been widely used in the clinics and preclinical settings, construction of multi-stimuli responsive systems/probes would have broad applications, such as achieving more precise targeting, synergistic therapeutic effects, and/or lowering agent administration dose.

Typically for combing magnetic and optical responsive agents together, mesoporous silica-related nanostructures are widely used. Das et al. demonstrated a theranostic system with magnetic gadolinium oxide—iron oxide core, mesoporous silica shell gated with boronic acid functionalized highly luminescent carbon quantum dot for delivering chemotherapeutics [334]. The porous silica shell served as the drug reservoir for anticancer drug 5-fluorouracil, whereas the quantum dot controls the drug transport under simulated intracellular environment, which signals the fluorescence switch-on response enabling the fluorescence imaging for monitoring the treatment. Site-specific drug delivery with fluorescence and MR imaging were therefore achieved. Other recent works using magnetic gold nanoparticles can also achieve similar goal. Das et al. highlighted recent advances in the development of multifunctional gold nanohybrids with magnetic and optical properties for multimodal theranostic in a review paper [335].

Other forms to link SPIONs with photosensitizers were also reported. To combine magnetic drug targeting with photodynamic therapy, SPIONs can be coated with dextran to prevent them from aggregation and to achieve the linkage of hypericine (a photosensitizer) to its hydroxyl groups [336]. Unterweger et al. demonstrated this technique aiming for lowering the side effects of photodynamic therapy, as the therapeutic effect can only occur in the combined foci of magnetic fields and laser irradiation.

In addition, magnetic drug delivery systems were also re-designed as magnetic bubbles for enhanced ultrasound response. Magnetic microbubbles were shown to be used as a dual-modality imaging contrast agents [337], and were considered to have unique potential in drug/gene delivery as the natures of ultrasound-based and magnetic drug delivery systems are complementary [338–341]. Magnetic microbubbles have been envisioned to be accumulated to targeted areas (for example tumor vasculature) by the magnetic guidance, monitored by real-time ultrasonography for treatment planning, and activated by FUS to trigger the drug release. However, traditional synthesis methods of magnetic bubbles can normally change the acoustic behaviors of microbubbles by reducing the stiffness, leading to poor ultrasound sensitivity. Chertok and Langer performed a comprehensive study to [342] develop magnetic microbubbles that exhibit strong magnetic and acoustic behaviors while also preserving circulation stability in the circulation system. The authors demonstrated that their bubbles could evade lung entrapment, possibly due to the preserved bubble compressibility and surface protection with stealth heparin.

5.4. Clinical challenges and advances

Despite the in-depth preclinical exploration in this field, clinical adoptions using magnetic drug delivery systems are still very limited. One of the main challenges of its clinical translation is the safety concern of the MRPs [343]. SPIONs are currently the only clinically approved metal oxide MRPs [344]. From 1996, after the first SPION-derived MRI contrast agent (ferumoxides) was approved by the FDA, several other products were FDA cleared (e.g., ferumoxytol, ferucarbotran, ferristene, ferumoxsil and ferumoxtran-10) [345]. However, most of them were discontinued due to safety issues reported in the clinical trials [346] and/or negative market attraction [345]. The potential toxicity issues of SPIONs include the impaired mitochondrial membrane function, DNA damage and oxidative stress on cells [344]. Currently, the only FDA-approved product is ferumoxytol, which is used in the clinics to treat iron-deficiency anemia in patients with chronic kidney disease. Ferumoxytol is also off-label used as an MR angiography agent in patients with renal failure who cannot be given gadolinium and in trials for diagnostic usages including the characterization of metastatic lymph nodes [346].

Although truly magnetically triggered drug delivery systems have not been widely assessed clinically, some clinical trials based on SPIONs were performed for enhancing MRI. Clinical studies have been performed to assess the feasibility of macrophage imaging using ferumoxytol in the cerebral aneurysmal wall [347]. SPIONs were also applied to MR-based lymph node imaging aiming for enhancing the detection accuracy clinically. The combination of SPIONs and diffusion-weighted magnetic resonance imaging facilitated the detection of metastases in normal-sized pelvic lymph nodes of patients with bladder and prostate cancer in a short reading time [348]. Sentinel lymph node biopsy using SPIONs has shown promising results in clinical trials in Europe [349–352] and Japan [353]. These trials were mostly aiming to compare this new approach to the “gold standard” of localizing the sentinel node using radioactive tracers. These clinical results suggested that the adopted SPIONs were non-inferior to the radiotracer and safe in performing sentinel lymph node biopsy. More recently, Taruno et al. developed a new handheld and cordless magnetic probe for this type of application [353]. More clinical results for SPIONs-enhanced imaging applications were reviewed elsewhere [343,354].

Despite the commercialization and FDA clearance/approval of SPION based probes for enhancing MRI, reports of clinical trials of magnetic drug delivery are still very limited compared to other physically triggering drug delivery systems (see Table 2). One of the early reported clinical results was a trial using a ferrofluid with noncovalently adsorbed epirubicin to treat various advanced and unsuccessfully pretreated cancers or sarcomas [355]. The result of the Phase I trial showed that the ferrofluid could be successfully directed to the tumors in about half of the patients. Based on MRI, pharmacokinetics and histology assessments, the treatment seemed to be safe, with limited or unknown efficacy [355]. In another series of clinical trials (see Table 2 for details), FeRx Inc. introduced magnetic beads that carried doxorubicin to treating hepatocellular carcinomas (a type of liver cancer). From their published report in a conference abstract [356], the Phase I/II results showed that no clinically significant toxicities were observed in either single or multiple treatment cycles. However, in April 2004, FeRx halted its clinical trial after Phase III, as the statistical evidence of the treatment efficacy was insufficiently strong [354].

6. Discussion and outlook

In this review, we highlighted four main physical triggering strategies that have been actively used in drug delivery, with a focus on associating the physical mechanisms and clinical needs to the design and optimization of the drug delivery system. With numerous ways and systems having been used to physically trigger drug delivery events, the selection of a particular trigger will depend on many factors. However, understanding how the biological effects are triggered by the physical stimuli would therefore be vital to select, design and optimize the drug delivery system for specific scenario.

To provide a high-level comparison across different physical triggers for drug delivery applications, we summarize the advantages, limitations and corresponding applications for each trigger in Table 1. In addition, we listed the past and current clinical studies for overviewing the clinical progress of these triggering systems in Table 2. Some of the highlights of each triggering system include:

- Ultrasound may be particularly useful in drug delivery to the brain due to the overall balanced capability of deep penetration, spatial targeting specificity and tunability to achieve noninvasive and reversible BBB opening. Compared to ultrasound, electrically and light triggered systems may need to rely on implantable devices for brain drug delivery. However, drug delivery to tissue with a gassy environment (such as lungs) through ultrasound remains very challenging.
- There exist many light sensitive materials that can be used both as therapeutic and diagnostic agents, suggesting a potential wide range of combinational design for light-based drug delivery systems.
- Electrically triggered drug delivery systems are normally considered to carry a less ideal safety profile with potential damage to targeted tissue and/or cutaneous adverse events. However, this may not be a big challenge for some of the cancer treatment during which the damage would be caused directly on the cancerous tissue. Therefore, many clinical progresses are being made.
- Less clinical progress has been made for magnetic drug delivery systems generally. The main reason could be due to the safety concerns raised from previous clinical assessments using SPIONs for enhancing imaging. In addition, we believe optimization of the current magnetic devices for producing a deeper and more precise particle manipulation would be important as well.

Taken together, some generalized features can be identified:

- Transdermal applications – All triggering systems except for magnetic field have extensive transdermal applications. This is possibly due to the easy accessibility of triggering device and drug/sensitizer-carrying agents to the skin.
- Physical input window – In almost all triggering systems, the stimulus itself can be harmful when higher energies are delivered. Awareness of the safe parameter sets of the energy source is thus important. Additionally, it is particularly vital to calibrate the *therapeutic window* for drug delivery applications, which defines the range of energy input where drug can be delivered in a therapeutically effective range without severe damage to the biological entities. When comparing the performance of different triggering systems, ones with wider input window stand out due to their better control in modulating the delivery efficiency.
- Deposition of energy – The efficacy and safety of the triggered drug delivery depends on the local accumulation of the sensitizer/vehicles, as well as the deposition and diffusion of the energy. Ideal systems would apply the focal point (area with the peak intensity of specific energy form) to the target of interest, while leaving the healthy tissue away from the high intensity focal area. Therefore, achieving a fine focal point is normally preferable for precise spatial targeting. However, controlling a tight focus is typically accomplished by high frequency waves and/or the combination of multiple sources (for example, the multi-element phased array). High frequency waves may lead to shallow penetration, and multi-source approaches can result in a complicated system design to avoid undesirable energy deposition along the beam path. In addition, one may need to make sure that the sensitizer/vehicles outside the targeted area but inside the beam path remain inactivated. Delicate calibration of the deposition and diffusion map of the triggering energy would thus be necessary to make sure the energy intensity at the unwanted locales is below the activation threshold of the drug/sensitizer particles. Additional calibration can focus on characterizing the physical property changes before and after the application of sensitizers, drug vehicles or other modalities, which may offer insights on possible variations of the triggering mechanism.
- Possible side effects after barrier disruption – Apart from the aforementioned evident vascular or tissue damage, some possible adverse effects as a result of enhanced permeation of delivered drug across tissue barriers may include higher trafficking of toxins or unfavorable immune cells. Although many biophysiological aspects of this concern remain unidentified, it is believed that reversible opening or disruption of the biological barriers are preferred. However, typically for cancer therapy, clinicians may still adopt irreversible disrupting techniques based on the benefit to risk ratio of specific scenario. Another possible side effect is that the physical techniques may promote cancer metastasis via enhanced circulating tumor cells. However, this concern has not been well confirmed by preclinical [357] or clinical data. With growing preclinical and clinical studies underway, it is envisioned that more biological details about these possible side effects will be discovered in the near future.

Although each type of physical trigger varies in many technical aspects, there are some common goals in future efforts for this field:

Combination of multiple triggers – As mentioned in the above sections, multi-stimuli responsive systems are particularly interesting to achieve therapeutic synergy and simultaneous diagnostic capability, as the advantages of different physical triggers can be complementary. For example, light has the most confined focus for precise targeting, but holds the worst ability to penetrate tissue. Ultrasound can be easily monitored in real-time with better tissue penetrating ability, and a relatively tight focal area for targeted drug delivery. However, it is challenging to pass the air-filled locations such as the lung. A better understanding of these physical properties can facilitate the development of more effective combinational physical targeting strategies for specific drug delivery issue. In addition, the important role of therapeutic window in drug delivery systems also highlights the need for developing theranostic systems for online treatment monitoring using advanced imaging technologies.

Combination of immunotherapy – More and more preclinical and clinical evidence show that current immunotherapeutic approaches, largely dominated by but not limited to checkpoint-inhibitor therapy, may be challenged by severe issues in drug delivery. This could result from not only the limited drug access to the diseased tissue due to the biological barriers, but also the limited immune effectors in the abnormal immune microenvironment. With a growing interest to develop the combination immunotherapies with physically triggered drug delivery, we need to understand more about how those physical triggers affect the landscape of the immune microenvironment. Specifically, how physical triggers can help to release antigen, recruit immune effectors, and destruct the immune suppressors. In addition, it is also important to understand if those local therapies can trigger systematic effects, as most physically triggered drug delivery systems are local therapies. There are a growing number of studies working on understanding these effects, yet many more remain unclear.

Combination of cell-based drug delivery – Though still in its early-stage of development, cell-based drug delivery strategies are well accepted as one of the most exciting and promising emerging techniques over traditional drug delivery approaches due to its natural targeting specificity and versatility. With growing efforts in engineering cells for various artificial functions, we believe making “living drug carriers and therapeutics” to be more physically responsive can be favorable in drug delivery, and may potentially shift the paradigm of the current drug delivery technologies.

In summary, growing efforts in designing drug delivery systems using physical triggers have been made both preclinically and clinically. It is suggested to choose the ideal triggering systems based on the biophysical properties of the targeted tissue and if it is simple to deliver both the energy and drug carrying agents. To optimize the treatment efficacy and safety, one may particularly consider assessing the treatment window of each triggering system. It is also envisioned that the combinations of multi-stimuli systems, immunotherapies and cell-based approaches will potentially open new doors for next-generation drug delivery technologies.

Acknowledgements

Authors acknowledge support from John A. Paulson School of Engineering & Applied Sciences and Wyss Institute at Harvard University. Image templates made freely available by Servier Medical Art (https://smart.servier.com/) or BioRender were used for some of the illustrations shown in figures.

References

[1] Y. Wang, D.S. Kohane, External triggering and triggered targeting strategies for drug delivery, Nat Rev Mater. 2 (2017), 17020. https://doi.org/10.1038/natrevmats.2017.20.

[2] S. Mura, J. Nicolas, P. Couvreur, Stimuli-responsive nanocarriers for drug delivery, Nat. Mater. 12 (2013) 991–1003, https://doi.org/10.1038/Nmat3776.

[3] S.R. Sirsi, M.A. Borden, State-of-the-art materials for ultrasound-triggered drug delivery, Adv. Drug Deliv. Rev. 72 (2014) 3–14, https://doi.org/10.1016/j.addr.2013.12.010.

[4] M. Mahmoudi, S. Sant, B. Wang, S. Laurent, T. Sen, Superparamagnetic iron oxide nanoparticles (SPIONs): development, surface modification and applications in chemotherapy, Adv. Drug Deliv. Rev. 63 (2011) 24–46, https://doi.org/10.1016/j.addr.2010.05.006.

[5] J. Kolosnjaj-Tabi, L. Gibot, I. Fourquaux, M. Golzio, M.-P. Rols, Electric field-responsive nanoparticles and electric fields: physical, chemical, biological mechanisms and therapeutic prospects, Adv. Drug Deliv. Rev. 138 (2019) 56–67, https://doi.org/10.1016/j.addr.2018.10.017.

[6] G. Shim, S. Ko, D. Kim, Q.-V. Le, G.T. Park, J. Lee, T. Kwon, H.-G. Choi, Y.B. Kim, Y.-K. Oh, Light-switchable systems for remotely controlled drug delivery, J. Control. Release 267 (2017) 67–79, https://doi.org/10.1016/j.jconrel.2017.09.009.

[7] T. Sun, Cavitation Control and Imaging for Focused Ultrasound Brain Therapy, Ph.D. Tufts University, 2018. http://search.proquest.com/pqdtglobal/docview/2109764235/abstract/A502B0B6D4B45BEPQ/1 accessed February 24, 2020.
[8] M. Baues, A. Dasgupta, J. Ehling, J. Prakash, P. Boor, F. Tacke, F. Kiessling, T. Lammers, Fibrosis imaging: current concepts and future directions, Adv. Drug Deliv. Rev. 121 (2017) 9–26, https://doi.org/10.1016/j.addr.2017.10.013.
[9] F. Kiessling, S. Fokong, J. Bzyl, W. Lederle, M. Palmowski, T. Lammers, Recent advances in molecular, multimodal and theranostic ultrasound imaging, Adv. Drug Deliv. Rev. 72 (2014) 15–27, https://doi.org/10.1016/j.addr.2013.11.013.
[10] S. Mitragotri, Healing sound: the use of ultrasound in drug delivery and other therapeutic applications, Nat. Rev. Drug Discov. 4 (2005) 255–260, https://doi.org/10.1038/nrd1662.
[11] S. Dababou, C. Marrocchio, R. Scipione, H.-P. Erasmus, P. Ghanouni, M. Anzidei, C. Catalano, A. Napoli, High-intensity focused ultrasound for pain management in patients with cancer, Radiographics 38 (2018) 603–623, https://doi.org/10.1148/rg.2018170129.
[12] K.-H. Choi, J.-H. Kim, Therapeutic applications of ultrasound in neurological diseases, J. Neurosonol. Neuroimag. 11 (2019) 62–72, https://doi.org/10.31728/jnn.2019.00046.
[13] C.C. Coussios, R.A. Roy, Applications of acoustics and cavitation to noninvasive therapy and drug delivery, Annu. Rev. Fluid Mech. 40 (2008) 395–420, https://doi.org/10.1146/annurev.fluid.40.111406.102116.
[14] K. Ferrara, R. Pollard, M. Borden, Ultrasound microbubble contrast agents: fundamentals and application to gene and drug delivery, Annu. Rev. Biomed. Eng. 9 (2007) 415–447, https://doi.org/10.1146/annurev.bioeng.8.061505.095852.
[15] S. Mitragotri, J. Kost, Low-frequency sonophoresis, Adv. Drug Deliv. Rev. 56 (2004) 589–601, https://doi.org/10.1016/j.addr.2003.10.024.
[16] M. Ogura, S. Paliwal, S. Mitragotri, Low-frequency sonophoresis: current status and future prospects, Adv. Drug Deliv. Rev. 60 (2008) 1218–1223, https://doi.org/10.1016/j.addr.2008.03.006.
[17] K.M.D. Tachibana, S.M.D. Tachibana, Use of ultrasound to enhance the local anesthetic effect of topically applied aqueous lidocaine, Anesthesiology 78 (1993) 1091–1096.
[18] S. Mitragotri, D. Blankschtein, R. Langer, Ultrasound-mediated transdermal protein delivery, Science 269 (1995) 850–853, https://doi.org/10.1126/science.7638603.
[19] S. Mitragotri, J. Kost, Transdermal Delivery of Heparin and Low-Molecular Weight Heparin Using Low-Frequency Ultrasound, Pharm. Res. 18 (2001) 1151–1156.
[20] N.B. Smith, S. Lee, E. Maione, R.B. Roy, S. McElligott, K.K. Shung, Ultrasound-mediated transdermal transport of insulin in vitro through human skin using novel transducer designs, Ultrasound Med. Biol. 29 (2003) 311–317, https://doi.org/10.1016/S0301-5629(02)00706-8.
[21] A. Tezel, S. Paliwal, Z. Shen, S. Mitragotri, Low-frequency ultrasound as a transcutaneous immunization adjuvant, Vaccine 23 (2005) 3800–3807, https://doi.org/10.1016/j.vaccine.2005.02.027.
[22] R.I.Y. Quiroz-Segoviano, M.A. García-Sánchez, N.L. Delgado-Buenrostro, Y.I. Chirino, S. Bernal-Chávez, M.G. Nava-Arzaluz, A. Ganem-Rondero, Tetraphenylporphyrin intended for use in photodynamic therapy: influence of sonophoresis and the formulation (solution or microemulsion) on percutaneous penetration, J. Drug Deliv. Scie. Technol. 53 (2019), 101145. https://doi.org/10.1016/j.jddst.2019.101145.
[23] W. Rangsimawong, P. Opanasopit, T. Rojanarata, S. Panomsuk, T. Ngawhirunpat, Influence of sonophoresis on transdermal drug delivery of hydrophilic compound-loaded lipid nanocarriers, Pharm. Dev. Technol. 22 (2017) 597–605, https://doi.org/10.1080/10837450.2016.1221428.
[24] Q. Xu, E. Jalilian, J.W. Fakhoury, R. Manwar, B. Michniak-Kohn, K.B. Elkin, K. Avanaki, Monitoring the topical delivery of ultrasmall gold nanoparticles using optical coherence tomography, Skin Res. Technol. 26 (2020) 263–268, https://doi.org/10.1111/srt.12789.
[25] J. Park, H. Lee, G.-S. Lim, N. Kim, D. Kim, Y.-C. Kim, Enhanced transdermal drug delivery by sonophoresis and simultaneous application of sonophoresis and iontophoresis, AAPS PharmSciTech 20 (2019), 96. https://doi.org/10.1208/s12249-019-1309-z.
[26] Y.C. Ryu, D.I. Kim, S.H. Kim, H.-M.D. Wang, B.H. Hwang, Synergistic transdermal delivery of biomacromolecules using sonophoresis after microneedle treatment, Biotechnol. Bioproc. Eng. 23 (2018) 286–292, https://doi.org/10.1007/s12257-018-0070-6.
[27] S. Liu, X. Bao, S. Zhang, H. Zhang, X. Lu, T. Li, Z. Chen, N. Chen, The study of ultrasound and iontophoresis on oxaprozin transdermal penetration using surface-enhanced Raman spectroscopy, Drug Deliv. and Transl. Res. 10 (2020) 83–92, https://doi.org/10.1007/s13346-019-00664-9.
[28] D. Park, J. Won, U. Shin, H. Park, G. Song, J. Jang, H. Park, C.-W. Kim, J.B. Seo, Transdermal drug delivery using a specialized cavitation seed for ultrasound, IEEE Trans. Ultrason. Ferroelect. Freq. Contr. 66 (2019) 1057–1064, https://doi.org/10.1109/TUFFC.2019.2907702.
[29] J. Robertson, M. Squire, S. Becker, A thermoelectric device for coupling fluid temperature regulation during continuous skin sonoporation or sonophoresis, AAPS PharmSciTech 20 (2019), 147. https://doi.org/10.1208/s12249-019-1357-4.
[30] P. SantoiannI, M. Nino, G. Calabro, Intradermal drug delivery by low frequency sonophoresis (25KHz), Dermatol. Online J. 10 (2004,). https://escholarship.org/uc/item/4pc7m5d9 accessed April 25, 2020).
[31] M. Zasada, Z. Drożdż, A. Erkiert-Polguj, E. Budzisz, A blinded study assessment of the efficacy of an original formula with retinol in combination with sonophoresis, Dermatol. Ther. 33 (2020) https://doi.org/10.1111/dth.13163.
[32] N.P. Katz, D.E. Shapiro, T.E. Herrmann, J. Kost, L.M. Custer, Rapid onset of cutaneous anesthesia with EMLA cream after pretreatment with a new ultrasound-emitting device, Anesth. Analg. (2004) 371–376, https://doi.org/10.1213/01.ANE.0000099716.02783.C4.
[33] B.M. Becker, Ultrasound with topical Anesthetic rapidly decreases pain of intravenous cannulation, Acad. Emerg. Med. 12 (2005) 289–295, https://doi.org/10.1197/j.aem.2004.11.019.
[34] A. Tian, Y. Yin, L. Yu, B. Yang, N. Li, J. Li, Z. Bian, S. Hu, C. Weng, L. Feng, Low-frequency sonophoresis of Chinese medicine formula improves efficacy of malignant pleural effusion treatment, Chin. J. Integr. Med. 26 (2020) 263–269, https://doi.org/10.1007/s11655-019-3167-7.
[35] A. Tian, Y. Yin, L. Yu, B. Yang, N. Li, J. Li, Z. Bian, S. Hu, C. Weng, L. Feng, Topical delivery of modified Da-Cheng-Qi decoction (加味大承气汤) using low-frequency ultrasound sonophoresis for refractory metastatic malignant bowel obstruction: an open-label single-arm clinical trial, Chin. J. Integr. Med. (2019) https://doi.org/10.1007/s11655-019-3041-7.
[36] T. Sun, G. Samiotaki, S. Wang, C. Acosta, C.C. Chen, E.E. Konofagou, Acoustic cavitation-based monitoring of the reversibility and permeability of ultrasound-induced blood-brain barrier opening, Phys. Med. Biol. 60 (2015) 9079–9094, https://doi.org/10.1088/0031-9155/60/23/9079.
[37] M.A. O'Reilly, Methods for Focused Ultrasound-Induced Blood-Brain Barrier Disruption, University of Eastern Finland, 2012.
[38] T. Leighton, The Acoustic Bubble, Academic Press, 2012.
[39] A. Dasgupta, M. Liu, T. Ojha, G. Storm, F. Kiessling, T. Lammers, Ultrasound-mediated drug delivery to the brain: principles, progress and prospects, Drug Discov. Today Technol. 20 (2016) 41–48, https://doi.org/10.1016/j.ddtec.2016.07.007.
[40] S. Snipstad, E. Sulheim, C. de Lange Davies, C. Moonen, G. Storm, F. Kiessling, R. Schmid, T. Lammers, Sonopermeation to improve drug delivery to tumors: from fundamental understanding to clinical translation, Expert Opin. Drug Deliv. 15 (2018) 1249–1261, https://doi.org/10.1080/17425247.2018.1547279.
[41] P. Koczera, L. Appold, Y. Shi, M. Liu, A. Dasgupta, V. Pathak, T. Ojha, S. Fokong, Z. Wu, M. van Zandvoort, O. Iranzo, A.J.C. Kuehne, A. Pich, F. Kiessling, T. Lammers, PBCA-based polymeric microbubbles for molecular imaging and drug delivery, J. Control. Release 259 (2017) 128–135, https://doi.org/10.1016/j.jconrel.2017.03.006.
[42] B.H.A. Lammertink, C. Bos, R. Deckers, G. Storm, C.T.W. Moonen, J.-M. Escoffre, Sonochemotherapy: from bench to bedside, Front. Pharmacol. 6 (2015) https://doi.org/10.3389/fphar.2015.00138.
[43] M. Aryal, C.D. Arvanitis, P.M. Alexander, N. McDannold, Ultrasound-mediated blood–brain barrier disruption for targeted drug delivery in the central nervous system, Adv. Drug Deliv. Rev. 72 (2014) 94–109, https://doi.org/10.1016/j.addr.2014.01.008.
[44] A. Bunevicius, N.J. McDannold, A.J. Golby, Focused ultrasound strategies for brain tumor therapy, Oper. Neurosurg. (2019) opz374, https://doi.org/10.1093/ons/opz374.
[45] I. Beekers, M. Vegter, K.R. Lattwein, F. Mastik, R. Beurskens, A.F.W. van der Steen, N. de Jong, M.D. Verweij, K. Kooiman, Opening of endothelial cell–cell contacts due to sonoporation, J. Control. Release 322 (2020) 426–438, https://doi.org/10.1016/j.jconrel.2020.03.038.
[46] I. Lentacker, I. De Cock, R. Deckers, S.C. De Smedt, C.T.W. Moonen, Understanding ultrasound induced sonoporation: definitions and underlying mechanisms, Adv. Drug Deliv. Rev. 72 (2014) 49–64, https://doi.org/10.1016/j.addr.2013.11.008.
[47] H. Chen, C.C. Chen, C. Acosta, S.-Y. Wu, T. Sun, E.E. Konofagou, A new brain drug delivery strategy: focused ultrasound-enhanced intranasal drug delivery, PLoS One 9 (2014), e108880. https://doi.org/10.1371/journal.pone.0108880.
[48] S. Wang, M.E. Karakatsani, C. Fung, T. Sun, C. Acosta, E. Konofagou, Direct brain infusion can be enhanced with focused ultrasound and microbubbles, J. Cereb. Blood Flow Metab. 37 (2017) 706–714, https://doi.org/10.1177/0271678X16637881.
[49] K. Hynynen, N. McDannold, N. Vykhodtseva, F.A. Jolesz, Noninvasive MR imaging–guided focal opening of the blood-brain barrier in rabbits, Radiology 220 (2001) 640–646, https://doi.org/10.1148/radiol.2202001804.
[50] P.-C. Chu, W.-Y. Chai, C.-H. Tsai, S.-T. Kang, C.-K. Yeh, H.-L. Liu, Focused ultrasound-induced blood-brain barrier opening: association with mechanical index and cavitation index analyzed by dynamic contrast-enhanced magnetic-resonance imaging, Sci. Rep. 6 (2016) https://doi.org/10.1038/srep33264.
[51] M. Kinoshita, N. McDannold, F.A. Jolesz, K. Hynynen, Targeted delivery of antibodies through the blood–brain barrier by MRI-guided focused ultrasound, Biochem. Biophys. Res. Commun. 340 (2006) 1085–1090, https://doi.org/10.1016/j.bbrc.2005.12.112.
[52] M. Kinoshita, N. McDannold, F.A. Jolesz, K. Hynynen, Noninvasive localized delivery of Herceptin to the mouse brain by MRI-guided focused ultrasound-induced blood-brain barrier disruption, Proc. Natl. Acad. Sci. 103 (2006) 11719–11723, https://doi.org/10.1073/pnas.0604318103.
[53] S.B. Raymond, L.H. Treat, J.D. Dewey, N.J. McDannold, K. Hynynen, B.J. Bacskai, Ultrasound enhanced delivery of molecular imaging and therapeutic agents in Alzheimer's disease mouse models, PLoS One 3 (2008), e2175. https://doi.org/10.1371/journal.pone.0002175.
[54] S. Wang, O.O. Olumolade, T. Sun, G. Samiotaki, E.E. Konofagou, Noninvasive, neuron-specific gene therapy can be facilitated by focused ultrasound and recombinant adeno-associated virus, Gene Ther. 22 (2015) 104–110, https://doi.org/10.1038/gt.2014.91.
[55] E. Thévenot, J.F. Jordão, M.A. O'Reilly, K. Markham, Y.-Q. Weng, K.D. Foust, B.K. Kaspar, K. Hynynen, I. Aubert, Targeted delivery of self-complementary adeno-associated virus serotype 9 to the brain, using magnetic resonance imaging-guided focused ultrasound, Hum. Gene Ther. 23 (2012) 1144–1155, https://doi.org/10.1089/hum.2012.013.
[56] M.E. Karakatsani, S. Wang, G. Samiotaki, T. Kugelman, O.O. Olumolade, C. Acosta, T. Sun, Y. Han, H.A.S. Kamimura, V. Jackson-Lewis, S. Przedborski, E. Konofagou, Amelioration of the nigrostriatal pathway facilitated by ultrasound-mediated

neurotrophic delivery in early Parkinson's disease, J. Control. Release 303 (2019) 289–301, https://doi.org/10.1016/j.jconrel.2019.03.030.

[57] N. McDannold, Y. Zhang, C. Power, C.D. Arvanitis, N. Vykhodtseva, M. Livingstone, Targeted, noninvasive blockade of cortical neuronal activity, Sci. Rep. 5 (2015) 1–7, https://doi.org/10.1038/srep16253.

[58] J. Park, Y. Zhang, N. Vykhodtseva, F.A. Jolesz, N.J. McDannold, The kinetics of blood brain barrier permeability and targeted doxorubicin delivery into brain induced by focused ultrasound, J. Control. Release 162 (2012) 134–142, https://doi.org/10.1016/j.jconrel.2012.06.012.

[59] H.-L. Liu, M.-Y. Hua, P.-Y. Chen, P.-C. Chu, C.-H. Pan, H.-W. Yang, C.-Y. Huang, J.-J. Wang, T.-C. Yen, K.-C. Wei, Blood-brain barrier disruption with focused ultrasound enhances delivery of chemotherapeutic drugs for glioblastoma treatment, Radiology 255 (2010) 415–425, https://doi.org/10.1148/radiol.10090699.

[60] M. Aryal, N. Vykhodtseva, Y.-Z. Zhang, J. Park, N. McDannold, Multiple treatments with liposomal doxorubicin and ultrasound-induced disruption of blood–tumor and blood–brain barriers improve outcomes in a rat glioma model, J. Control. Release 169 (2013) 103–111, https://doi.org/10.1016/j.jconrel.2013.04.007.

[61] L.H. Treat, N. McDannold, Y. Zhang, N. Vykhodtseva, K. Hynynen, Improved anti-tumor effect of liposomal doxorubicin after targeted blood-brain barrier disruption by MRI-guided focused ultrasound in rat glioma, Ultrasound Med. Biol. 38 (2012) 1716–1725, https://doi.org/10.1016/j.ultrasmedbio.2012.04.015.

[62] B.P. Mead, P. Mastorakos, J.S. Suk, A.L. Klibanov, J. Hanes, R.J. Price, Targeted gene transfer to the brain via the delivery of brain-penetrating DNA nanoparticles with focused ultrasound, J. Control. Release 223 (2016) 109–117, https://doi.org/10.1016/j.jconrel.2015.12.034.

[63] A. Burgess, Y. Huang, W. Querbes, D.W. Sah, K. Hynynen, Focused ultrasound for targeted delivery of siRNA and efficient knockdown of Htt expression, J. Control. Release 163 (2012) 125–129, https://doi.org/10.1016/j.jconrel.2012.08.012.

[64] T.-Y. Wang, J.W. Choe, K. Pu, R. Devulapally, S. Bachawal, S. Machtaler, S.M. Chowdhury, R. Luong, L. Tian, B. Khuri-Yakub, J. Rao, R. Paulmurugan, J.K. Willmann, Ultrasound-guided delivery of microRNA loaded nanoparticles into cancer, J. Control. Release 203 (2015) 99–108, https://doi.org/10.1016/j.jconrel.2015.02.018.

[65] J.-N. May, S.K. Golombek, M. Baues, A. Dasgupta, N. Drude, A. Rix, D. Rommel, S. von Stillfried, L. Appold, R. Pola, M. Pechar, L. van Bloois, G. Storm, A.J.C. Kuehne, F. Gremse, B. Theek, F. Kiessling, T. Lammers, Multimodal and multiscale optical imaging of nanomedicine delivery across the blood-brain barrier upon sonopermeation, Theranostics 10 (2020) 1948–1959, https://doi.org/10.7150/thno.41161.

[66] C.M. Gorick, A.S. Mathew, W.J. Garrison, E.A. Thim, D.G. Fisher, C.A. Copeland, J. Song, A.L. Klibanov, G.W. Miller, R.J. Price, Sonoselective transfection of cerebral vasculature without blood–brain barrier disruption, Proc. Natl. Acad. Sci. U. S. A. 117 (2020) 5644–5654, https://doi.org/10.1073/pnas.1914595117.

[67] A. Carpentier, M. Canney, A. Vignot, V. Reina, K. Beccaria, C. Horodyckid, C. Karachi, D. Leclercq, C. Lafon, J.-Y. Chapelon, L. Capelle, P. Cornu, M. Sanson, K. Hoang-Xuan, J.-Y. Delattre, A. Idbaih, Clinical trial of blood-brain barrier disruption by pulsed ultrasound, Sci. Transl. Med. 8 (2016) https://doi.org/10.1126/scitranslmed.aaf6086343re2.

[68] A. Idbaih, M. Canney, L. Belin, C. Desseaux, A. Vignot, G. Bouchoux, N. Asquier, B. Law-Ye, D. Leclercq, A. Bissery, Y. De Rycke, C. Trosch, L. Capelle, M. Sanson, K. Hoang-Xuan, C. Dehais, C. Houillier, F. Laigle-Donadey, B. Mathon, A. André, C. Lafon, J.-Y. Chapelon, J.-Y. Delattre, A. Carpentier, Safety and feasibility of repeated and transient blood–brain barrier disruption by pulsed ultrasound in patients with recurrent glioblastoma, Clin. Cancer Res. 25 (2019) 3793–3801, https://doi.org/10.1158/1078-0432.CCR-18-3643.

[69] T. Mainprize, N. Lipsman, Y. Huang, Y. Meng, A. Bethune, S. Ironside, C. Heyn, R. Alkins, M. Trudeau, A. Sahgal, J. Perry, K. Hynynen, Blood-brain barrier opening in primary brain tumors with non-invasive MR-guided focused ultrasound: a clinical safety and feasibility study, Sci. Rep. 9 (2019), 321. https://doi.org/10.1038/s41598-018-36340-0.

[70] A. Abrahao, Y. Meng, M. Llinas, Y. Huang, C. Hamani, T. Mainprize, I. Aubert, C. Heyn, S.E. Black, K. Hynynen, N. Lipsman, L. Zinman, First-in-human trial of blood–brain barrier opening in amyotrophic lateral sclerosis using MR-guided focused ultrasound, Nat. Commun. 10 (2019), 4373. https://doi.org/10.1038/s41467-019-12426-9.

[71] A. Dimou, K.N. Syrigos, M.W. Saif, Overcoming the stromal barrier: technologies to optimize drug delivery in pancreatic cancer, Ther. Adv. Med. Oncol. 4 (2012) 271–279, https://doi.org/10.1177/1758834012446008.

[72] B. Theek, M. Baues, T. Ojha, D. Möckel, S.K. Veettil, J. Steitz, L. van Bloois, G. Storm, F. Kiessling, T. Lammers, Sonoporation enhances liposome accumulation and penetration in tumors with low EPR, J. Control. Release 231 (2016) 77–85, https://doi.org/10.1016/j.jconrel.2016.02.021.

[73] D. Bressand, A. Novell, A. Girault, W. Raoul, G. Fromont-Hankard, J.-M. Escoffre, T. Lecomte, A. Bouakaz, Enhancing nab-paclitaxel delivery using microbubble-assisted ultrasound in a pancreatic cancer model, Mol. Pharm. 16 (2019) 3814–3822, https://doi.org/10.1021/acs.molpharmaceut.9b00416.

[74] G. Dimcevski, S. Kotopoulis, T. Bjånes, D. Hoem, J. Schjøtt, B.T. Gjertsen, M. Biermann, A. Molven, H. Sorbye, E. McCormack, M. Postema, O.H. Gilja, A human clinical trial using ultrasound and microbubbles to enhance gemcitabine treatment of inoperable pancreatic cancer, J. Control. Release 243 (2016) 172–181, https://doi.org/10.1016/j.jconrel.2016.10.007.

[75] M. Chen, X. Liang, C. Gao, R. Zhao, N. Zhang, S. Wang, W. Chen, B. Zhao, J. Wang, Z. Dai, Ultrasound triggered conversion of porphyrin/camptothecin-fluoroxyuridine triad microbubbles into nanoparticles overcomes multidrug resistance in colorectal cancer, ACS Nano 12 (2018) 7312–7326, https://doi.org/10.1021/acsnano.8b03674.

[76] S. Snipstad, S. Berg, Ý. Mørch, A. Bjørkøy, E. Sulheim, R. Hansen, I. Grimstad, A. van Wamel, A.F. Maaland, S.H. Torp, C. de L. Davies, Ultrasound improves the delivery and therapeutic effect of nanoparticle-stabilized microbubbles in breast cancer xenografts, Ultrasound Med. Biol. 43 (2017) 2651–2669, https://doi.org/10.1016/j.ultrasmedbio.2017.06.029.

[77] F. Zhu, Y. Jiang, F. Luo, P. Li, Effectiveness of localized ultrasound-targeted microbubble destruction with doxorubicin liposomes in H22 mouse hepatocellular carcinoma model, J. Drug Target. 23 (2015) 323–334, https://doi.org/10.3109/1061186X.2014.996759.

[78] K. Cullion, C.M. Santamaria, C. Zhan, D. Zurakowski, T. Sun, G.L. Pemberton, N.J. McDannold, D.S. Kohane, High-frequency, low-intensity ultrasound and microbubbles enhance nerve blockade, J. Control. Release 276 (2018) 150–156, https://doi.org/10.1016/j.jconrel.2018.02.027.

[79] K. Cullion, L.C. Petishnok, T. Sun, C.M. Santamaria, G.L. Pemberton, N.J. McDannold, D.S. Kohane, Local anesthesia enhanced with increasing high-frequency ultrasound intensity, Drug Deliv. Transl. Res. (2020) https://doi.org/10.1007/s13346-020-00760-1.

[80] H. Horsley, J. Owen, R. Browning, D. Carugo, J. Malone-Lee, E. Stride, J.L. Rohn, Ultrasound-activated microbubbles as a novel intracellular drug delivery system for urinary tract infection, J. Control. Release 301 (2019) 166–175, https://doi.org/10.1016/j.jconrel.2019.03.017.

[81] A.-H. Liao, C.-H. Wang, P.-Y. Weng, Y.-C. Lin, H. Wang, H.-K. Chen, H.-L. Liu, H.-C. Chuang, C.-P. Shih, Ultrasound-induced microbubble cavitation via a transcanal or transcranial approach facilitates inner ear drug delivery, JCI Insight 5 (2020), e132880. https://doi.org/10.1172/jci.insight.132880.

[82] A.J. Healey, P.C. Sontum, S. Kvåle, M. Eriksen, R. Bendiksen, A. Tornes, J. Østensen, Acoustic cluster therapy: in vitro and ex vivo measurement of activated bubble size distribution and temporal dynamics, Ultrasound Med. Biol. 42 (2016) 1145–1166, https://doi.org/10.1016/j.ultrasmedbio.2015.12.011.

[83] P. Sontum, S. Kvåle, A.J. Healey, R. Skurtveit, R. Watanabe, M. Matsumura, J. Østensen, Acoustic cluster therapy (ACT) – a novel concept for ultrasound mediated, targeted drug delivery, Int. J. Pharm. 495 (2015) 1019–1027, https://doi.org/10.1016/j.ijpharm.2015.09.047.

[84] A. van Wamel, A. Healey, P.C. Sontum, S. Kvåle, N. Bush, J. Bamber, C. de Lange Davies, Acoustic Cluster Therapy (ACT) — pre-clinical proof of principle for local drug delivery and enhanced uptake, J. Control. Release 224 (2016) 158–164, https://doi.org/10.1016/j.jconrel.2016.01.023.

[85] A. van Wamel, P.C. Sontum, A. Healey, S. Kvåle, N. Bush, J. Bamber, C. de Lange Davies, Acoustic cluster therapy (ACT) enhances the therapeutic efficacy of paclitaxel and Abraxane® for treatment of human prostate adenocarcinoma in mice, J. Control. Release 236 (2016) 15–21, https://doi.org/10.1016/j.jconrel.2016.06.018.

[86] N. Bush, A. Healey, A. Shah, G. Box, V. Kirkin, S. Kotopoulis, S. Kvåle, P.C. Sontum, J. Bamber, Therapeutic dose response of acoustic cluster therapy in combination with irinotecan for the treatment of human colon cancer in mice, Front. Pharmacol. 10 (2019) 1299, https://doi.org/10.3389/fphar.2019.01299.

[87] N. Bush, A. Healey, A. Shah, G. Box, V. Kirkin, S. Eccles, P.C. Sontum, S. Kotopoulis, S. Kvåle, A. van Wamel, C. de L. Davies, J. Bamber, Theranostic attributes of acoustic cluster therapy and its use for enhancing the effectiveness of liposomal doxorubicin treatment of human triple negative breast cancer in mice, Front. Pharmacol. 11 (2020) 75, https://doi.org/10.3389/fphar.2020.00075.

[88] A.K.O. Åslund, S. Snipstad, A. Healey, S. Kvåle, S.H. Torp, P.C. Sontum, C. de L. Davies, A. van Wamel, Efficient enhancement of blood-brain barrier permeability using acoustic cluster therapy (ACT), Theranostics 7 (2017) 23–30, https://doi.org/10.7150/thno.16577.

[89] L. Duan, L. Yang, J. Jin, F. Yang, D. Liu, K. Hu, Q. Wang, Y. Yue, N. Gu, Micro/nano-bubble-assisted ultrasound to enhance the EPR effect and potential theranostic applications, Theranostics 10 (2020) 462–483, https://doi.org/10.7150/thno.37593.

[90] 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. 108 (2019) 3091–3098, https://doi.org/10.1016/j.xphs.2019.05.004.

[91] T. Yin, P. Wang, J. Li, R. Zheng, B. Zheng, D. Cheng, R. Li, J. Lai, X. Shuai, Ultrasound-sensitive siRNA-loaded nanobubbles formed by hetero-assembly of polymeric micelles and liposomes and their therapeutic effect in gliomas, Biomaterials 34 (2013) 4532–4543, https://doi.org/10.1016/j.biomaterials.2013.02.067.

[92] S. Zhong, Z. Ling, Z. Zhou, J. He, H. Ran, Z. Wang, Q. Zhang, W. Song, Y. Zhang, J. Luo, Herceptin-decorated paclitaxel-loaded poly(lactide- *co* -glycolide) nanobubbles: ultrasound-facilitated release and targeted accumulation in breast cancers, Pharm. Dev. Technol. 25 (2020) 454–463, https://doi.org/10.1080/10837450.2019.1709500.

[93] P. Bhandari, G. Novikova, C.J. Goergen, J. Irudayaraj, Ultrasound beam steering of oxygen nanobubbles for enhanced bladder cancer therapy, Sci. Rep. 8 (2018), 3112. https://doi.org/10.1038/s41598-018-20363-8.

[94] C. Bing, Y. Hong, C. Hernandez, M. Rich, B. Cheng, I. Munaweera, D. Szczepanski, Y. Xi, M. Bolding, A. Exner, R. Chopra, Characterization of different bubble formulations for blood-brain barrier opening using a focused ultrasound system with acoustic feedback control, Sci. Rep. 8 (2018), 7986. https://doi.org/10.1038/s41598-018-26330-7.

[95] A. Prabhakar, R. Banerjee, Nanobubble Liposome Complexes for Diagnostic Imaging and Ultrasound-Triggered Drug Delivery in Cancers: A Theranostic Approach, ACS Omega 4 (2019) 15567–15580.

[96] N. Rapoport, Z. Gao, A. Kennedy, Multifunctional nanoparticles for combining ultrasonic tumor imaging and targeted chemotherapy, J. Nat. Cancer Inst. 99 (2007) 1095–1106, https://doi.org/10.1093/jnci/djm043.

[97] F. Baghbani, M. Chegeni, F. Moztarzadeh, S. Hadian-Ghazvini, M. Raz, Novel ultrasound-responsive chitosan/perfluorohexane nanodroplets for image-guided

smart delivery of an anticancer agent: curcumin, Mater. Sci. Eng. C 74 (2017) 186–193, https://doi.org/10.1016/j.msec.2016.11.107.
[98] Y. Cao, Y. Chen, T. Yu, Y. Guo, F. Liu, Y. Yao, P. Li, D. Wang, Z. Wang, Y. Chen, H. Ran, Drug release from phase-changeable nanodroplets triggered by low-intensity focused ultrasound, Theranostics 8 (2018) 1327–1339, https://doi.org/10.7150/thno.21492.
[99] J.Y. Lee, C. Crake, B. Teo, D. Carugo, M. de Saint Victor, A. Seth, E. Stride, Ultrasound-enhanced siRNA delivery using magnetic nanoparticle-loaded chitosan-deoxycholic acid nanodroplets, Adv. Healthcare Mater. 6 (2017), 1601246. https://doi.org/10.1002/adhm.201601246.
[100] H. Lea-Banks, M.A. O'Reilly, C. Hamani, K. Hynynen, Localized anesthesia of a specific brain region using ultrasound-responsive barbiturate nanodroplets, Theranostics 10 (2020) 2849–2858, https://doi.org/10.7150/thno.41566.
[101] 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, https://doi.org/10.1016/j.addr.2017.07.007.
[102] M.N. Centelles, M. Wright, W. Gedroyc, M. Thanou, Focused ultrasound induced hyperthermia accelerates and increases the uptake of anti-HER-2 antibodies in a xenograft model, Pharmacol. Res. 114 (2016) 144–151, https://doi.org/10.1016/j.phrs.2016.10.017.
[103] S.-K. Wu, C.-F. Chiang, Y.-H. Hsu, H.-C. Liou, W.-M. Fu, W.-L. Lin, Pulsed-wave low-dose ultrasound hyperthermia selectively enhances nanodrug delivery and improves antitumor efficacy for brain metastasis of breast cancer, Ultrason. Sonochem. 36 (2017) 198–205, https://doi.org/10.1016/j.ultsonch.2016.11.033.
[104] H. Grüll, S. Langereis, Hyperthermia-triggered drug delivery from temperature-sensitive liposomes using MRI-guided high intensity focused ultrasound, J. Control. Release 161 (2012) 317–327, https://doi.org/10.1016/j.jconrel.2012.04.041.
[105] S. Dromi, V. Frenkel, A. Luk, B. Traughber, M. Angstadt, M. Bur, J. Poff, J. Xie, S.K. Libutti, K.C.P. Li, B.J. Wood, Pulsed-high intensity focused ultrasound and low temperature sensitive liposomes for enhanced targeted drug delivery and antitumor effect, Clin. Cancer Res. 13 (2007) 2722–2727, https://doi.org/10.1158/1078-0432.CCR-06-2443.
[106] M.N. Centelles, M. Wright, P.-W. So, M. Amrahli, X.Y. Xu, J. Stebbing, A.D. Miller, W. Gedroyc, M. Thanou, Image-guided thermosensitive liposomes for focused ultrasound drug delivery: using NIRF-labelled lipids and topotecan to visualise the effects of hyperthermia in tumours, J. Control. Release 280 (2018) 87–98, https://doi.org/10.1016/j.jconrel.2018.04.047.
[107] 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 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, https://doi.org/10.1016/j.jconrel.2011.12.011.
[108] M.A. Santos, D.E. Goertz, K. Hynynen, Focused ultrasound hyperthermia mediated drug delivery using thermosensitive liposomes and visualized with *in vivo* two-photon microscopy, Theranostics 7 (2017) 2718–2731, https://doi.org/10.7150/thno.19662.
[109] S.T. Tucci, A. Kheirolomoom, E.S. Ingham, L.M. Mahakian, S.M. Tam, J. Foiret, N.E. Hubbard, A.D. Borowsky, M. Baikoghli, R.H. Cheng, K.W. Ferrara, Tumor-specific delivery of gemcitabine with activatable liposomes, J. Control. Release 309 (2019) 277–288, https://doi.org/10.1016/j.jconrel.2019.07.014.
[110] A. Kheirolomoom, M.T. Silvestrini, E.S. Ingham, L.M. Mahakian, S.M. Tam, S.K. Tumbale, J. Foiret, N.E. Hubbard, A.D. Borowsky, K.W. Ferrara, Combining activatable nanodelivery with immunotherapy in a murine breast cancer model, J. Control. Release 303 (2019) 42–54, https://doi.org/10.1016/j.jconrel.2019.04.008.
[111] M. de Smet, E. Heijman, S. Langereis, N.M. Hijnen, H. Grüll, Magnetic resonance imaging of high intensity focused ultrasound mediated drug delivery from temperature-sensitive liposomes: an in vivo proof-of-concept study, J. Control. Release 150 (2011) 102–110, https://doi.org/10.1016/j.jconrel.2010.10.036.
[112] N. Farr, Y.-N. Wang, S. D'Andrea, F. Starr, A. Partanen, K.M. Gravelle, J.S. McCune, L.J. Risler, S.G. Whang, A. Chang, S.R. Hingorani, D. Lee, J.H. Hwang, Hyperthermia-enhanced targeted drug delivery using magnetic resonance-guided focussed ultrasound: a pre-clinical study in a genetic model of pancreatic cancer, Int. J. Hyperth. 34 (2018) 284–291, https://doi.org/10.1080/02656736.2017.1336675.
[113] B.L. Viglianti, S.A. Abraham, C.R. Michelich, P.S. Yarmolenko, J.R. MacFall, M.B. Bally, M.W. Dewhirst, In vivo monitoring of tissue pharmacokinetics of liposome/drug using MRI: illustration of targeted delivery, Magn. Reson. Med. 51 (2004) 1153–1162, https://doi.org/10.1002/mrm.20074.
[114] A.W. Wong, B.Z. Fite, Y. Liu, A. Kheirolomoom, J.W. Seo, K.D. Watson, L.M. Mahakian, S.M. Tam, H. Zhang, J. Foiret, A.D. Borowsky, K.W. Ferrara, Ultrasound ablation enhances drug accumulation and survival in mammary carcinoma models, J. Clin. Investig. 126 (2015) 99–111, https://doi.org/10.1172/JCI83312.
[115] N. Hijnen, E. Kneepkens, M. de Smet, S. Langereis, E. Heijman, H. Grüll, 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, https://doi.org/10.1073/pnas.1700790114.
[116] 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, https://doi.org/10.3109/02656736.2014.936049.
[117] 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, https://doi.org/10.1148/radiol.2018181445.
[118] T. Sun, Y. Zhang, C. Power, P.M. Alexander, J.T. Sutton, M. Aryal, N. Vykhodtseva, E.L. Miller, N.J. McDannold, Closed-loop control of targeted ultrasound drug delivery across the blood–brain/tumor barriers in a rat glioma model, Proc. Natl. Acad. Sci. 114 (2017) E10281–E10290, https://doi.org/10.1073/pnas.1713328114.
[119] M. Gyöngy, Passive Cavitation Mapping for Monitoring Ultrasound Therapy, Ph.D. University of Oxford, 2010. http://ora.ox.ac.uk/objects/uuid:af6f3c5a-bec5-4378-a617-c89d2b16d95d accessed April 30, 2018.
[120] C.D. Arvanitis, C. Crake, N. McDannold, G.T. Clement, Passive acoustic mapping with the angular spectrum method, IEEE Trans. Med. Imaging 36 (2017) 983–993, https://doi.org/10.1109/TMI.2016.2643565.
[121] J. Gateau, J.-F. Aubry, M. Pernot, M. Fink, M. Tanter, Combined passive detection and ultrafast active imaging of cavitation events induced by short pulses of high-intensity ultrasound, IEEE Trans. Ultrason. Ferroelectr. Freq. Control 58 (2011) 517–532, https://doi.org/10.1109/TUFFC.2011.1836.
[122] V.A. Salgaonkar, S. Datta, C.K. Holland, T.D. Mast, Passive cavitation imaging with ultrasound arrays, J. Acoust. Soc. Am. 126 (2009) 3071–3083, https://doi.org/10.1121/1.3238260.
[123] C. Crake, S.T. Brinker, C.M. Coviello, M.S. Livingstone, N.J. McDannold, A dual-mode hemispherical sparse array for 3D passive acoustic mapping and skull localization within a clinical MRI guided focused ultrasound device, Phys. Med. Biol. 63 (2018), 065008. https://doi.org/10.1088/1361-6560/aab0aa.
[124] Y. Liu, B. Tracey, S. Aeron, E. Miller, T. Sun, N. McDannold, J. Murphy, Artifact suppression for passive cavitation imaging using U-net CNNs with uncertainty quantification, 2019 IEEE 4th International Conference on Signal and Image Processing (ICSIP) 2019, pp. 1037–1042, https://doi.org/10.1109/SIPROCESS.2019.8868593.
[125] M.A. O'Reilly, K. Hynynen, Blood-brain barrier: real-time feedback-controlled focused ultrasound disruption by using an acoustic emissions–based controller, Radiology 263 (2012) 96–106, https://doi.org/10.1148/radiol.11111417.
[126] R.M. Jones, L. Deng, K. Leung, D. McMahon, M.A. O'Reilly, K. Hynynen, Three-dimensional transcranial microbubble imaging for guiding volumetric ultrasound-mediated blood-brain barrier opening, Theranostics 8 (2018) 2909–2926, https://doi.org/10.7150/thno.24911.
[127] N. McDannold, Y. Zhang, J.G. Supko, C. Power, T. Sun, C. Peng, N. Vykhodtseva, A.J. Golby, D.A. Reardon, Acoustic feedback enables safe and reliable carboplatin delivery across the blood-brain barrier with a clinical focused ultrasound system and improves survival in a rat glioma model, Theranostics 9 (2019) 6284–6299, https://doi.org/10.7150/thno.35892.
[128] A. Patel, S.J. Schoen, C.D. Arvanitis, Closed-loop spatial and temporal control of cavitation activity with passive acoustic mapping, IEEE Trans. Biomed. Eng. 66 (2019) 2022–2031, https://doi.org/10.1109/TBME.2018.2882337.
[129] N. Hockham, C.C. Coussios, M. Arora, A real-time controller for sustaining thermally relevant acoustic cavitation during ultrasound therapy, IEEE Trans. Ultrason. Ferroelectr. Freq. Control 57 (2010) 2685–2694, https://doi.org/10.1109/TUFFC.2010.1742.
[130] A. Sabraoui, C. Inserra, B. Gilles, J.-C. Béra, J.-L. Mestas, Feedback loop process to control acoustic cavitation, Ultrason. Sonochem. 18 (2011) 589–594, https://doi.org/10.1016/j.ultsonch.2010.07.011.
[131] C. Desjouy, A. Poizat, B. Gilles, C. Inserra, J.-C. Bera, Control of inertial acoustic cavitation in pulsed sonication using a real-time feedback loop system, J. Acoust. Soc. Am. 134 (2013) 1640–1646, https://doi.org/10.1121/1.4812973.
[132] K. Maeda, A.D. Maxwell, Controlling the Dynamics of Cloud Cavitation Bubbles through Acoustic Feedback, ArXiv:2003.05044 [Physics], http://arxiv.org/abs/2003.05044 2020 (accessed April 26, 2020).
[133] J.R. Sukovich, J.J. Macoskey, J.E. Lundt, T.I. Gerhardson, T.L. Hall, Z. Xu, Real-time transcranial histotripsy treatment localization and mapping using acoustic cavitation emission feedback, IEEE Trans. Ultrason. Ferroelectr. Freq. Control (2020) https://doi.org/10.1109/TUFFC.2020.29675861.
[134] H.A. Kamimura, J. Flament, J. Valette, A. Cafarelli, R. Aron Badin, P. Hantraye, B. Larrat, Feedback control of microbubble cavitation for ultrasound-mediated blood–brain barrier disruption in non-human primates under magnetic resonance guidance, J. Cereb. Blood Flow Metab. 39 (2019) 1191–1203, https://doi.org/10.1177/0271678X17753514.
[135] Z.M. Zhao, A. Ukidve, A. Dasgupta, S. Mitragotri, Transdermal immunomodulation: principles, advances and perspectives, Adv. Drug Deliv. Rev. 127 (2018) 3–19, https://doi.org/10.1016/j.addr.2018.03.010.
[136] S. Shabahang, S. Kim, S.-H. Yun, Light-guiding biomaterials for biomedical applications, Adv. Funct. Mater. 28 (2018), 1706635. https://doi.org/10.1002/adfm.201706635.
[137] D. Shan, E. Gerhard, C. Zhang, J.W. Tierney, D. Xie, Z. Liu, J. Yang, Polymeric biomaterials for biophotonic applications, Bioact Mater. 3 (2018) 434–445, https://doi.org/10.1016/j.bioactmat.2018.07.001.
[138] M. Yudasaka, Y. Yomogida, M. Zhang, T. Tanaka, M. Nakahara, N. Kobayashi, Y. Okamatsu-Ogura, K. Machida, K. Ishihara, K. Saeki, H. Kataura, Near-infrared photoluminescent carbon nanotubes for imaging of brown fat, Sci. Rep. 7 (2017) https://doi.org/10.1038/srep4476044760.
[139] D.P. Kuffler, Photobiomodulation in promoting wound healing: a review, Regen. Med. 11 (2015) 107–122, https://doi.org/10.2217/rme.15.82.
[140] P. Avci, A. Gupta, M. Sadasivam, D. Vecchio, Z. Pam, N. Pam, M.R. Hamblin, Low-level laser (light) therapy (LLLT) in skin: stimulating, healing, restoring, Semin. Cutan. Med. Surg. 32 (2013) 41–52.
[141] S.H. Yun, S.J.J. Kwok, Light in diagnosis, therapy and surgery, Nat. Biomed. Eng. 1 (2017), 0008. https://doi.org/10.1038/s41551-016-0008.

[142] R.S. Riley, E.S. Day, Gold nanoparticle-mediated photothermal therapy: applications and opportunities for multimodal cancer treatment, WIREs Nanomed. Nanobiotechnol. 9 (2017), e1449. https://doi.org/10.1002/wnan.1449.
[143] B.L. Fay, J.R. Melamed, E.S. Day, Nanoshell-mediated photothermal therapy can enhance chemotherapy in inflammatory breast cancer cells, Int. J. Nanomedicine 10 (2015) 6931–6941, https://doi.org/10.2147/IJN.S93031.
[144] C. Ash, M. Dubec, K. Donne, T. Bashford, Effect of wavelength and beam width on penetration in light-tissue interaction using computational methods, Lasers Med. Sci. 32 (2017) 1909–1918, https://doi.org/10.1007/s10103-017-2317-4.
[145] P. Zhang, M.X. Wu, A clinical review of phototherapy for psoriasis, Lasers Med. Sci. 33 (2018) 173–180, https://doi.org/10.1007/s10103-017-2360-1.
[146] M. Wang, Z. Hou, A.A. Al Kheraif, B. Xing, J. Lin, Mini review of TiO2-based multifunctional nanocomposites for near-infrared light–responsive phototherapy, Adv. Healthc. Mater. 7 (2018), 1800351. https://doi.org/10.1002/adhm.201800351.
[147] S.-R. Tsai, M.R. Hamblin, Biological effects and medical applications of infrared radiation, J. Photochem. Photobiol. B 170 (2017) 197–207, https://doi.org/10.1016/j.jphotobiol.2017.04.014.
[148] S. Wang, H. Yu, Effect of co-existing biologically relevant molecules and ions on DNA photocleavage caused by pyrene and its derivatives, Int. J. Environ. Res. Public Health 2 (2005) 132–137, https://doi.org/10.3390/ijerph2005010132.
[149] Y.M. Zheng, K. Wang, T. Li, X.L. Zhang, Z.Y. Li, Synthesis, singlet oxygen photogeneration and DNA photocleavage of porphyrins with nitrogen heterocycle tails, Molecules 16 (2011) 3488–3498, https://doi.org/10.3390/molecules16053488.
[150] Q.Q. Dou, S.S. Liow, E. Ye, R. Lakshminarayanan, X.J. Loh, Biodegradable thermogelling polymers: working towards clinical applications, Adv. Healthc. Mater. 3 (2014) 977–988, https://doi.org/10.1002/adhm.201300627.
[151] J. Shi, Y. Su, W. Liu, J. Chang, Z. Zhang, A nanoliposome-based photoactivable drug delivery system for enhanced cancer therapy and overcoming treatment resistance, Int. J. Nanomedicine 12 (2017) 8257–8275, https://doi.org/10.2147/IJN.S143776.
[152] Y. Cheng, C. He, K. Ren, Y. Rong, C. Xiao, J. Ding, X. Zhuang, X. Chen, Injectable enzymatically cross-linked hydrogels with light-controlled degradation profile, Macromol. Rapid Commun. 39 (2018), 1800272. https://doi.org/10.1002/marc.201800272.
[153] B. Zhao, Y. Wu, Y. Yuan, Z. Shi, Copper-catalysed Csp3–Csp cross-couplings between cyclobutanone oxime esters and terminal alkynes induced by visible light, Chem. Commun. (2020) https://doi.org/10.1039/D0CC00988A.
[154] E. Aznar, M.D. Marcos, R. Martínez-Máñez, F. Sancenón, J. Soto, P. Amorós, C. Guillem, pH- and photo-switched release of guest molecules from mesoporous silica supports, J. Am. Chem. Soc. 131 (2009) 6833–6843, https://doi.org/10.1021/ja810011p.
[155] J. Liu, Y. Chen, G. Li, P. Zhang, C. Jin, L. Zeng, L. Ji, H. Chao, Ruthenium(II) polypyridyl complexes as mitochondria-targeted two-photon photodynamic anticancer agents, Biomaterials 56 (2015) 140–153, https://doi.org/10.1016/j.biomaterials.2015.04.002.
[156] N. Kiseleva, P. Nazari, C. Dee, D. Busko, B.S. Richards, M. Seitz, I.A. Howard, A. Turshatov, Lanthanide sensitizers for large anti-stokes shift near-infrared-to-visible triplet–triplet annihilation photon upconversion, J. Phys. Chem. Lett. 11 (2020) 2477–2481, https://doi.org/10.1021/acs.jpclett.0c00221.
[157] A. Rakhymzhan, L. Reuter, R. Raspe, D. Bremer, R. Günther, R. Leben, J. Heidelin, V. Andresen, S. Cheremukhin, H. Schulz-Hildebrandt, M.G. Bixel, R.H. Adams, H. Radbruch, G. Hüttmann, A.E. Hauser, R.A. Niesner, Coregistered spectral optical coherence tomography and two-photon microscopy for multimodal near-instantaneous deep-tissue imaging, Cytom. A (2020) https://doi.org/10.1002/cyto.a.24012.
[158] Y. He, S. Guo, L. Wu, P. Chen, L. Wang, Y. Liu, H. Ju, Near-infrared boosted ROS responsive siRNA delivery and cancer therapy with sequentially peeled upconversion nano-onions, Biomaterials 225 (2019), 119501. https://doi.org/10.1016/j.biomaterials.2019.119501.
[159] F. Sodano, R.J. Cavanagh, A.K. Pearce, L. Lazzarato, B. Rolando, A. Fraix, T.F. Abelha, C.E. Vasey, C. Alexander, V. Taresco, S. Sortino, Enhancing doxorubicin anticancer activity with a novel polymeric platform photoreleasing nitric oxide, Biomater. Sci. 8 (2020) 1329–1344, https://doi.org/10.1039/C9BM01644A.
[160] A. Pashkovskaya, E. Kotova, Y. Zorlu, F. Dumoulin, V. Ahsen, I. Agapov, Y. Antonenko, Light-triggered liposomal release: membrane permeabilization by photodynamic action, Langmuir 26 (2010) 5726–5733, https://doi.org/10.1021/la903867a.
[161] E.G. Randles, P.R. Bergethon, A photodependent switch of liposome stability and permeability, Langmuir 29 (2013) 1490–1497, https://doi.org/10.1021/la303526k.
[162] R. Hariharan, S. Senthilkumar, A. Suganthi, M. Rajarajan, Synthesis and characterization of doxorubicin modified ZnO/PEG nanomaterials and its photodynamic action, J. Photochem. Photobiol. B Biol. 116 (2012) 56–65, https://doi.org/10.1016/j.jphotobiol.2012.08.008.
[163] Balmiki Kumar, Aparna Murali, Irshad Mattan, Supratim Giri, Near-infrared-triggered photodynamic, photothermal, and on demand chemotherapy by multifunctional upconversion nanocomposite, J. Phys. Chem. B (2019) https://doi.org/10.1021/acs.jpcb.9b01870.s001.
[164] I. Khalil, N.M. Julkapli, W.A. Yehye, W.J. Basirun, S.K. Bhargava, Graphene-gold nanoparticles hybrid-synthesis, functionalization, and application in a electrochemical and surface-enhanced Raman scattering biosensor, Materials (Basel). 9 (2016) 406, https://doi.org/10.3390/ma9060406.
[165] M. Nurunnabi, Z. Khatun, G.R. Reeck, D.Y. Lee, Y. Lee, Photoluminescent graphene nanoparticles for cancer phototherapy and imaging, ACS Appl. Mater. Interfaces (2014) https://doi.org/10.1021/am504071z.
[166] N. Kamaly, B. Yameen, J. Wu, O.C. Farokhzad, Degradable controlled-release polymers and polymeric nanoparticles: mechanisms of controlling drug release, Chem. Rev. 116 (2016) 2602–2663, https://doi.org/10.1021/acs.chemrev.5b00346.
[167] M. Karimi, P. Sahandi Zangabad, S. Baghaee-Ravari, M. Ghazadeh, H. Mirshekari, M.R. Hamblin, Smart nanostructures for cargo delivery: uncaging and activating by light, J. Am. Chem. Soc. 139 (2017) 4584–4610, https://doi.org/10.1021/jacs.6b08313.
[168] A.Y. Rwei, W. Wang, D.S. Kohane, Photoresponsive nanoparticles for drug delivery, Nano Today 10 (2015) 451–467, https://doi.org/10.1016/j.physbeh.2017.03.040.
[169] Q. Zhou, L. Zhang, T.H. Yang, H. Wu, Stimuli-responsive polymeric micelles for drug delivery and cancer therapy, Int. J. Nanomedicine 13 (2018) 2921–2942, https://doi.org/10.2147/IJN.S158696.
[170] G. Chen, B. Ma, R. Xie, Y. Wang, K. Dou, S. Gong, NIR-induced spatiotemporally controlled gene silencing by upconversion nanoparticle-based siRNA nanocarrier, J. Control. Release 282 (2018) 148–155, https://doi.org/10.1016/j.jconrel.2017.12.028.
[171] J. del Barrio, L. Oriol, R. Alcalá, C. Sánchez, Azobenzene-containing linear—dendritic diblock copolymers by click chemistry: synthesis, characterization, morphological study, and photoinduction of optical anisotropy, Macromolecules 42 (2009) 5752–5760, https://doi.org/10.1021/ma9003133.
[172] M.K.G. Jayakumar, N.M. Idris, Y. Zhang, Remote activation of biomolecules in deep tissues using near-infrared-to-UV upconversion nanotransducers, Proc. Natl. Acad. Sci. 109 (2012) 8483 LP–8488, https://doi.org/10.1073/pnas.1114551109.
[173] S. Kerruth, P. Langner, S. Raffelberg, W. Gärtner, J. Heberle, Characterization of the blue–light-activated adenylyl cyclase mPAC by flash photolysis and FTIR spectroscopy, Photochem. Photobiol. 93 (2017) 857–864, https://doi.org/10.1111/php.12746.
[174] I. Rostami, H. Rezvani Alanagh, Z. Hu, S.H. Shahmoradian, Breakthroughs in medicine and bioimaging with up-conversion nanoparticles, Int. J. Nanomedicine 14 (2019) 7759–7780, https://doi.org/10.2147/IJN.S221433.
[175] G. Chen, H. Qiu, P.N. Prasad, X. Chen, Upconversion nanoparticles: design, nanochemistry, and applications in theranostics, Chem. Rev. 114 (2014) 5161–5214, https://doi.org/10.1021/cr400425h.
[176] C. Chen, C. Li, Z. Shi, Current advances in lanthanide-doped upconversion nanostructures for detection and bioapplication, Adv. Sci. (Weinh). 3 (2016) https://doi.org/10.1002/advs.2016000291600029.
[177] S.Z.F. Phua, C. Xue, W.Q. Lim, G. Yang, H. Chen, Y. Zhang, C.F. Wijaya, Z. Luo, Y. Zhao, Light-responsive prodrug-based supramolecular nanosystems for site-specific combination therapy of cancer, Chem. Mater. 31 (2019) 3349–3358, https://doi.org/10.1021/acs.chemmater.9b00439.
[178] Y. Wang, Q. Zhao, N. Han, L. Bai, J. Li, J. Liu, E. Che, L. Hu, Q. Zhang, T. Jiang, S. Wang, Mesoporous silica nanoparticles in drug delivery and biomedical applications, Nanomedicine 11 (2015) 313–327, https://doi.org/10.1016/j.nano.2014.09.014.
[179] M. Vallet-Regí, M. Colilla, I. Izquierdo-Barba, M. Manzano, Mesoporous silica nanoparticles for drug delivery: current insights, Molecules 23 (2017) 47, https://doi.org/10.3390/molecules23010047.
[180] S. He, K. Krippes, S. Ritz, Z. Chen, A. Best, H.-J. Butt, V. Mailänder, S. Wu, Ultralow-intensity near-infrared light induces drug delivery by upconverting nanoparticles, Chem. Commun. 51 (2015) 431–434, https://doi.org/10.1039/C4CC07489K.
[181] A. Raza, U. Hayat, T. Rasheed, M. Bilal, H.M.N. Iqbal, "Smart" materials-based near-infrared light-responsive drug delivery systems for cancer treatment: A review, J. Mater. Res. Technol 8 (2019) 1497–1509, https://doi.org/10.1016/j.jmrt.2018.03.007.
[182] R. Wei, W. Xi, H. Wang, J. Liu, T. Mayr, L. Shi, L. Sun, In situ crystal growth of gold nanocrystals on upconversion nanoparticles for synergistic chemo-photothermal therapy, Nanoscale 9 (2017) 12885–12896, https://doi.org/10.1039/C7NR02280H.
[183] M.A. Evans, P.-J. Huang, Y. Iwamoto, K.N. Ibsen, E.M. Chan, Y. Hitomi, P.C. Ford, S. Mitragotri, Macrophage-mediated delivery of light activated nitric oxide prodrugs with spatial, temporal and concentration control, Chem. Sci. 9 (2018) 3729–3741, https://doi.org/10.1039/C8SC00015H.
[184] C. Conte, F. Ungaro, A. Mazzaglia, F. Quaglia, in: M.J. Alonso, M. Garcia-Fuentes (Eds.), Photodynamic Therapy for Cancer: Principles, Clinical Applications, and Nanotechnological Approaches BT – Nano-Oncologicals: New Targeting and Delivery Approaches, Springer International Publishing, Cham 2014, pp. 123–160, https://doi.org/10.1007/978-3-319-08084-0_5.
[185] G. Shafirstein, A. Battoo, K. Harris, H. Baumann, S.O. Gollnick, J. Lindenmann, C.E. Nwogu, Photodynamic therapy of non-small cell lung cancer. Narrative review and future directions, Ann. Am. Thorac. Soc. 13 (2016) 265–275, https://doi.org/10.1513/AnnalsATS.201509-650FR.
[186] S. Mallidi, S. Anbil, A.-L. Bulin, G. Obaid, M. Ichikawa, T. Hasan, Beyond the barriers of light penetration: strategies, perspectives and possibilities for photodynamic therapy, Theranostics 6 (2016) 2458–2487, https://doi.org/10.7150/thno.16183.
[187] G. Shafirstein, N.R. Rigual, H. Arshad, M.T. Cooper, D.A. Bellnier, G. Wilding, W. Tan, M. Merzianu, B.W. Henderson, Photodynamic therapy with 3-(1′-hexyloxyethyl) pyropheophorbide-a for early-stage cancer of the larynx: phase Ib study, Head Neck 38 (Suppl. 1) (2016) E377–E383, https://doi.org/10.1002/hed.24003.
[188] T.A. Debele, S. Peng, H.-C. Tsai, Drug carrier for photodynamic cancer therapy, Int. J. Mol. Sci. 16 (2015) 22094–22136, https://doi.org/10.3390/ijms160922094.
[189] R. Baskaran, J. Lee, S.-G. Yang, Clinical development of photodynamic agents and therapeutic applications, Biomater. Res. 22 (2018), 25. https://doi.org/10.1186/s40824-018-0140-z.
[190] L. Li, M. Nurunnabi, M. Nafiujjaman, Y.K. Lee, K.M. Huh, GSH-mediated photoactivity of pheophorbide a-conjugated heparin/gold nanoparticle for photodynamic therapy, J. Control. Release 171 (2013) 241–250, https://doi.org/10.1016/j.jconrel.2013.07.002.

[191] L. Li, M. Nurunnabi, M. Nafiujjaman, Y.Y. Jeong, Y. Lee, K.M. Huh, A photosensitizer-conjugated magnetic iron oxide/gold hybrid nanoparticle as an activatable platform for photodynamic cancer therapy, J. Mater. Chem. B 2 (2014) 2929, https://doi.org/10.1039/c4tb00181h.

[192] C.B. Warren, L.J. Karai, A. Vidimos, E.V. Maytin, Pain associated with aminolevulinic acid-photodynamic therapy of skin disease, J. Am. Acad. Dermatol. 61 (2009) 1033–1043, https://doi.org/10.1016/j.jaad.2009.03.048.

[193] S. Mallidi, S. Anbil, S. Lee, D. Manstein, S. Elrington, G. Kositratna, D. Schoenfeld, B. Pogue, S.J. Davis, T. Hasan, Photosensitizer fluorescence and singlet oxygen luminescence as dosimetric predictors of topical 5-aminolevulinic acid photodynamic therapy induced clinical erythema, J. Biomed. Opt. 19 (2014) https://doi.org/10.1117/1.JBO.19.2.028001028001.

[194] K. Mahmoudi, K.L. Garvey, A. Bouras, G. Cramer, H. Stepp, J.G. Jesu Raj, D. Bozec, T.M. Busch, C.G. Hadjipanayis, 5-aminolevulinic acid photodynamic therapy for the treatment of high-grade gliomas, J. Neuro-Oncol. 141 (2019) 595–607, https://doi.org/10.1007/s11060-019-03103-4.

[195] M. Khafaji, M. Zamani, M. Golizadeh, O. Bavi, Inorganic nanomaterials for chemo/photothermal therapy: a promising horizon on effective cancer treatment, Biophys. Rev. 11 (2019) 335–352, https://doi.org/10.1007/s12551-019-00532-3.

[196] N.Y. Kim, S. Blake, D. De, J. Ouyang, J. Shi, N. Kong, Two-dimensional nanosheet-based photonic nanomedicine for combined gene and photothermal therapy, Front. Pharmacol. 10 (2020) https://doi.org/10.3389/fphar.2019.015731573.

[197] J. Chen, C. Ning, Z. Zhou, P. Yu, Y. Zhu, G. Tan, C. Mao, Nanomaterials as photothermal therapeutic agents, Prog. Mater. Sci. 99 (2019) 1–26, https://doi.org/10.1016/j.pmatsci.2018.07.005.

[198] Z. Li, Y. Chen, Y. Yang, Y. Yu, Y. Zhang, D. Zhu, X. Yu, X. Ouyang, Z. Xie, Y. Zhao, L. Li, Recent advances in nanomaterials-based chemo-photothermal combination therapy for improving cancer treatment, Front. Bioeng. Biotechnol. 7 (2019) https://doi.org/10.3389/fbioe.2019.00293293.

[199] H. Zhang, J. Zhang, Q. Li, A. Song, H. Tian, J. Wang, Z. Li, Y. Luan, Site-specific MOF-based immunotherapeutic nanoplatforms via synergistic tumor cells-targeted treatment and dendritic cells-targeted immunomodulation, Biomaterials 245 (2020), 119983. https://doi.org/10.1016/j.biomaterials.2020.119983.

[200] N. Yang, M. Zhu, G. Xu, N. Liu, C. Yu, A near-infrared light-responsive multifunctional nanocomposite hydrogel for efficient and synergistic antibacterial wound therapy and healing promotion, J. Mater. Chem. B (2020) https://doi.org/10.1039/D0TB00361A.

[201] Z. Khatun, M. Nurunnabi, M. Nafiujjaman, G.R. Reeck, H.A.H.A. Khan, K.J.K.J. Cho, Y.-K.Y.-K. Lee, A hyaluronic acid nanogel for photo–chemo theranostics of lung cancer with simultaneous light-responsive controlled release of doxorubicin, Nanoscale 7 (2015) 10680–10689doi:10.1039/C5NR01075F.

[202] Y. Zhu, J. Xue, W. Chen, S. Bai, T. Zheng, C. He, Z. Guo, M. Jiang, G. Du, X. Sun, Albumin-biomineralized nanoparticles to synergize phototherapy and immunotherapy against melanoma, J. Control. Release 322 (2020) 300–311, https://doi.org/10.1016/j.jconrel.2020.03.045.

[203] L. Guo, D.D. Yan, D. Yang, Y. Li, X. Wang, O. Zalewski, B. Yan, W. Lu, Combinatorial photothermal and Immuno cancer therapy using chitosan-coated hollow copper sulfide nanoparticles, ACS Nano 8 (2014) 5670–5681, https://doi.org/10.1021/nn5002112.

[204] Y. Tao, E. Ju, Z. Liu, K. Dong, J. Ren, X. Qu, Engineered, self-assembled near-infrared photothermal agents for combined tumor immunotherapy and chemo-photothermal therapy, Biomaterials 35 (2014) https://doi.org/10.1016/j.biomaterials.2014.04.0736646.

[205] A.S. Bear, L.C. Kennedy, J.K. Young, S.K. Perna, J.P. Mattos Almeida, A.Y. Lin, P.C. Eckels, R.A. Drezek, A.E. Foster, Elimination of metastatic melanoma using gold nanoshell-enabled photothermal therapy and adoptive T cell transfer, PLoS One 8 (2013) e69073, https://doi.org/10.1371/journal.pone.0069073.

[206] R.A. Burga, S. Patel, C.M. Bollard, C.R.Y. Cruz, R. Fernandes, Conjugating Prussian blue nanoparticles onto antigen-specific T cells as a combined nanoimmunotherapy, Nanomedicine (London, England). 11 (2016) 1759–1767, https://doi.org/10.2217/nnm-2016-0160.

[207] F. Chen, W. Cai, Nanomedicine for targeted photothermal cancer therapy: where are we now? Nanomedicine (London, England). 10 (2015) 1–3, https://doi.org/10.2217/nnm.14.186.

[208] A.R. Rastinehad, H. Anastos, E. Wajswol, J.S. Winoker, J.P. Sfakianos, S.K. Doppalapudi, M.R. Carrick, C.J. Knauer, B. Taouli, S.C. Lewis, A.K. Tewari, J.A. Schwartz, S.E. Canfield, A.K. George, J.L. West, N.J. Halas, Gold nanoshell-localized photothermal ablation of prostate tumors in a clinical pilot device study, Proc. Natl. Acad. Sci. 116 (2019) https://doi.org/10.1073/pnas.190692911618590 LP – 18596.

[209] C. Liang, J. Song, Y. Zhang, Y. Guo, M. Deng, W. Gao, J. Zhang, Facile approach to prepare rGO@Fe3O4 microspheres for the magnetically targeted and NIR-responsive chemo-photothermal combination therapy, Nanoscale Res. Lett. 15 (2020), 86. https://doi.org/10.1186/s11671-020-03320-1.

[210] L. Li, J. Li, Y. Shi, P. Du, Z. Zhang, T. Liu, R. Zhang, Z. Liu, On-demand biodegradable boron nitride nanoparticles for treating triple negative breast cancer with boron neutron capture therapy, ACS Nano 13 (2019) 13843–13852, https://doi.org/10.1021/acsnano.9b04303.

[211] V. Urbanová, M. Pumera, Biomedical and bioimaging applications of 2D pnictogens and transition metal dichalcogenides, Nanoscale 11 (2019) 15770–15782, https://doi.org/10.1039/C9NR04658E.

[212] M. Xie, N. Yang, J. Cheng, M. Yang, T. Deng, Y. Li, C. Feng, Layered MoS2 nanosheets modified by biomimetic phospholipids: enhanced stability and its synergistic treatment of cancer with chemo-photothermal therapy, Colloids Surf. B: Biointerfaces 187 (2020), 110631. https://doi.org/10.1016/j.colsurfb.2019.110631.

[213] S. Wu, X. Liu, J. Ren, X. Qu, Glutathione depletion in a benign manner by MoS2-based nanoflowers for enhanced hypoxia-irrelevant free-radical-based cancer therapy, Small 15 (2019), 1904870. https://doi.org/10.1002/smll.201904870.

[214] G. Darabdhara, M.R. Das, S.P. Singh, A.K. Rengan, S. Szunerits, R. Boukherroub, Ag and Au nanoparticles/reduced graphene oxide composite materials: synthesis and application in diagnostics and therapeutics, Adv. Colloid Interf. Sci. 271 (2019), 101991. https://doi.org/10.1016/j.cis.2019.101991.

[215] W. Ma, Y. Hu, H. Yang, Y. Zhang, J. Ding, L. Chen, Au-aided reduced graphene oxide-based nanohybrids for photo-chemotherapy, Mater. Sci. Eng. C 95 (2019) 256–263, https://doi.org/10.1016/j.msec.2018.10.072.

[216] T. Kavinkumar, K. Varunkumar, V. Ravikumar, S. Manivannan, Anticancer activity of graphene oxide-reduced graphene oxide-silver nanoparticle composites, J. Colloid Interface Sci. 505 (2017) 1125–1133, https://doi.org/10.1016/j.jcis.2017.07.002.

[217] Y. Liao, W. Wang, X. Huang, Y. Sun, S. Tian, P. Cai, Reduced graphene oxide triggered epithelial-mesenchymal transition in A549 cells, Sci. Rep. 8 (2018), 15188. https://doi.org/10.1038/s41598-018-33414-x.

[218] X. Wu, Y. Xing, D. Pierce, J.X. Zhao, One-pot synthesis of reduced graphene oxide/metal (oxide) composites, ACS Appl. Mater. Interfaces 9 (2017) 37962–37971, https://doi.org/10.1021/acsami.7b12539.

[219] P. Rochowski, P. Niedziałkowski, S.J. Pogorzelski, The benefits of photoacoustics for the monitoring of drug stability and penetration through tissue-mimicking membranes, Int. J. Pharm. 580 (2020), 119233. https://doi.org/10.1016/j.ijpharm.2020.119233.

[220] M. Wu, T. Mei, C. Lin, Y. Wang, J. Chen, W. Le, M. Sun, J. Xu, H. Dai, Y. Zhang, C. Xue, Z. Liu, B. Chen, Melanoma cell membrane biomimetic versatile CuS nanoprobes for homologous targeting photoacoustic imaging and photothermal chemotherapy, ACS Appl. Mater. Interfaces 12 (2020) 16031–16039, https://doi.org/10.1021/acsami.9b23177.

[221] A.S. Jeevarathinam, J.E. Lemaster, F. Chen, E. Zhao, J.V. Jokerst, Photoacoustic imaging quantifies drug release from nanocarriers via redox chemistry of dye-labeled cargo, Angew. Chem. Int. Ed. 59 (2020) 4678–4683, https://doi.org/10.1002/anie.201914120.

[222] N.B. Roozen, C. Glorieux, L. Liu, M. Rychtáriková, T. Van der Donck, A. Jacobs, Converting sunlight into audible sound by means of the photoacoustic effect: the heliophone, J. Acoust. Soc. Am. 140 (2016) 1697–1706, https://doi.org/10.1121/1.4962493.

[223] G. Ferrauto, F. Carniato, E. Di Gregorio, M. Botta, L. Tei, Photoacoustic ratiometric assessment of mitoxantrone release from theranostic ICG-conjugated mesoporous silica nanoparticles, Nanoscale 11 (2019) 18031–18036, https://doi.org/10.1039/C9NR06524E.

[224] H.-C. Zhou, N. Chen, H. Zhao, T. Yin, J. Zhang, W. Zheng, L. Song, C. Liu, R. Zheng, Optical-resolution photoacoustic microscopy for monitoring vascular normalization during anti-angiogenic therapy, Photoacoustics 15 (2019), 100143. https://doi.org/10.1016/j.pacs.2019.100143.

[225] W. Wang, T. Jing, X. Xia, L. Tang, Z. Huang, F. Liu, Z. Wang, H. Ran, M. Li, J. Xia, Melanin-loaded biocompatible photosensitive nanoparticles for controlled drug release in combined photothermal-chemotherapy guided by photoacoustic/ultrasound dual-modality imaging, Biomater. Sci. 7 (2019) 4060–4074, https://doi.org/10.1039/C9BM01052A.

[226] Y. Zhang, J. Yu, A. Kahkoska, Z. Gu, Photoacoustic drug delivery, Sensors 17 (2017) 1400, https://doi.org/10.3390/s17061400.

[227] A. Comerón, C. Muñoz-Porcar, F. Rocadenbosch, A. Rodríguez-Gómez, M. Sicard, Current research in lidar technology used for the remote sensing of atmospheric aerosols, Sensors (Basel, Switzerland) 17 (2017), 1450. https://doi.org/10.3390/s17061450.

[228] C. Moore, J.V. Jokerst, Strategies for image-guided therapy, surgery, and drug delivery using photoacoustic imaging, Theranostics 9 (2019) 1550–1571, https://doi.org/10.7150/thno.32362.

[229] J. Zhong, S. Yang, L. Wen, D. Xing, Imaging-guided photoacoustic drug release and synergistic chemo-photoacoustic therapy with paclitaxel-containing nanoparticles, J. Control. Release 226 (2016) 77–87, https://doi.org/10.1016/j.jconrel.2016.02.010.

[230] G.D. Moon, S.-W. Choi, X. Cai, W. Li, E.C. Cho, U. Jeong, L.V. Wang, Y. Xia, A new theranostic system based on gold nanocages and phase-change materials with unique features for photoacoustic imaging and controlled release, J. Am. Chem. Soc. 133 (2011) 4762–4765, https://doi.org/10.1021/ja200894u.

[231] C. Zhang, D. Li, P. Pei, W. Wang, B. Chen, Z. Chu, Z. Zha, X. Yang, J. Wang, H. Qian, Rod-based urchin-like hollow microspheres of Bi2S3: facile synthesis, photo-controlled drug release for photoacoustic imaging and chemo-photothermal therapy of tumor ablation, Biomaterials 237 (2020), 119835. https://doi.org/10.1016/j.biomaterials.2020.119835.

[232] A. Barhoumi, Q. Liu, D.S. Kohane, Ultraviolet light-mediated drug delivery: principles, applications, and challenges, J. Control. Release 219 (2015) 31–42, https://doi.org/10.1016/j.jconrel.2015.07.018.

[233] G. Lee, Y.I. Park, Lanthanide-doped upconversion nanocarriers for drug and gene delivery, Nanomaterials (Basel). 8 (2018) 511, https://doi.org/10.3390/nano8070511.

[234] J.G. Croissant, J.I. Zink, L. Raehm, J.-O. Durand, Two-photon-excited silica and organosilica nanoparticles for spatiotemporal cancer treatment, Adv. Healthc. Mater. 7 (2018), 1701248. https://doi.org/10.1002/adhm.201701248.

[235] A. Yavlovich, B. Smith, K. Gupta, R. Blumenthal, A. Puri, Light-sensitive lipid-based nanoparticles for drug delivery: design principles and future considerations for biological applications, Mol. Membr. Biol. 27 (2010) 364–381, https://doi.org/10.3109/09687688.2010.507788.

[236] Q. Li, W. Li, H. Di, L. Luo, C. Zhu, J. Yang, X. Yin, H. Yin, J. Gao, Y. Du, J. You, A photosensitive liposome with NIR light triggered doxorubicin release as a combined photodynamic-chemo therapy system, J. Control. Release 277 (2018) 114–125, https://doi.org/10.1016/j.jconrel.2018.02.001.

[237] F. Li, T. Li, W. Cao, L. Wang, H. Xu, Near-infrared light stimuli-responsive synergistic therapy nanoplatforms based on the coordination of tellurium-containing block polymer and cisplatin for cancer treatment, Biomaterials. 133 (2017) 208–218, https://doi.org/10.1016/j.biomaterials.2017.04.032.

[238] J. Yang, S. Zhai, H. Qin, H. Yan, D. Xing, X. Hu, NIR-controlled morphology transformation and pulsatile drug delivery based on multifunctional phototheranostic nanoparticles for photoacoustic imaging-guided photothermal-chemotherapy, Biomaterials 176 (2018) 1–12, https://doi.org/10.1016/j.biomaterials.2018.05.033.

[239] M. Roustit, S. Blaise, J.L. Cracowski, Trials and tribulations of skin iontophoresis in therapeutics, Br. J. Clin. Pharmacol. 77 (2014) 63–71, https://doi.org/10.1111/bcp.12128.

[240] M.J. Pikal, Transport mechanisms in iontophoresis. I. a theoretical model for the effect of electroosmotic flow on flux enhancement in transdermal iontophoresis, Pharm. Res. 7 (1990) 118–126, https://doi.org/10.1023/a:1015816532532.

[241] K. Ita, Perspectives on transdermal electroporation, Pharmaceutics 8 (2016) https://doi.org/10.3390/pharmaceutics8010009.

[242] K. Ita, Transdermal iontophoretic drug delivery: advances and challenges, J. Drug Target. 24 (2016) 386–391, https://doi.org/10.3109/1061186x.2015.1090442.

[243] Y.N. Kalia, A. Naik, J. Garrison, R.H. Guy, Iontophoretic drug delivery, Adv. Drug Deliv. Rev. 56 (2004) 619–658, https://doi.org/10.1016/j.addr.2003.10.026.

[244] J. Gehl, Electroporation: theory and methods, perspectives for drug delivery, gene therapy and research, Acta Physiol. Scand. 177 (2003) 437–447, https://doi.org/10.1046/j.1365-201X.2003.01093.x.

[245] A. Banerjee, R.W. Chen, S. Arafin, S. Mitragotri, Intestinal iontophoresis from mucoadhesive patches: a strategy for oral delivery, J. Control. Release 297 (2019) 71–78, https://doi.org/10.1016/j.jconrel.2019.01.037.

[246] A.R. Denet, R. Vanbever, V. Preat, Skin electroporation for transdermal and topical delivery, Adv. Drug Deliv. Rev. 56 (2004) 659–674, https://doi.org/10.1016/j.addr.2003.10.027.

[247] E. Eljarrat-Binstock, A.J. Domb, Iontophoresis: a non-invasive ocular drug delivery, J. Control. Release 110 (2006) 479–489, https://doi.org/10.1016/j.jconrel.2005.09.049.

[248] F. Li, Y. Qin, J. Lee, H. Liao, N. Wang, T.P. Davis, R. Qiao, D. Ling, Stimuli-responsive nano-assemblies for remotely controlled drug delivery, J. Control. Release 322 (2020) 566–592, https://doi.org/10.1016/j.jconrel.2020.03.051.

[249] V. Dhote, P. Bhatnagar, P.K. Mishra, S.C. Mahajan, D.K. Mishra, Iontophoresis: a potential emergence of a transdermal drug delivery system, Sci. Pharm. 80 (2012) 1–28, https://doi.org/10.3797/scipharm.1108-20.

[250] L.C. Li, R.A. Scudds, Iontophoresis: an overview of the mechanisms and clinical application, Arthritis Rheum. 8 (1995) 51–61, https://doi.org/10.1002/art.1790080111.

[251] H. Kalluri, A.K. Banga, Transdermal delivery of proteins, AAPS PharmSciTech 12 (2011) 431–441, https://doi.org/10.1208/s12249-011-9601-6.

[252] M.J. Pikal, The role of electroosmotic flow in transdermal iontophoresis, Adv. Drug Deliv. Rev. 9 (1992) 201–237, https://doi.org/10.1016/0169-409x(92)90024-K.

[253] M.R. Prausnitz, S. Mitragotri, R. Langer, Current status and future potential of transdermal drug delivery, Nat. Rev. Drug Discov. 3 (2004) 115–124, https://doi.org/10.1038/nrd1304.

[254] V. Mannem, C. Nanjarapalle, G. Stagni, Iontophoresis of amoxicillin and cefuroxime: rapid therapeutic concentrations in skin, Drug Dev. Ind. Pharm. 40 (2014) 325–329, https://doi.org/10.3109/03639045.2012.760579.

[255] M.B. Delgadocharro, A.M. Rodriguezbayon, R.H. Guy, Iontophoresis of nafarelin – effects of current-density and concentration on electrotransport in-vitro, J. Control. Release 35 (1995) 35–40, https://doi.org/10.1016/0168-3659(95)00015-Z.

[256] A. Femenia-Font, C. Balaguer-Fernandez, V. Merino, A. Lopez-Castellano, Iontophoretic transdermal delivery of sumatriptan: effect of current density and ionic strength, J. Pharm. Sci. 94 (2005) 2183–2186, https://doi.org/10.1002/jps.20447.

[257] A. Juluri, P. Peddikotla, M.A. Repka, S.N. Murthy, Transdermal iontophoretic delivery of propofol: a general anaesthetic in the form of its phosphate salt, J. Pharm. Sci. 102 (2013) 500–507, https://doi.org/10.1002/jps.23373.

[258] M. Hellmann, M. Roustit, F. Gaillard-Bigot, J.L. Cracowski, Cutaneous iontophoresis of treprostinil, a prostacyclin analog, increases microvascular blood flux in diabetic malleolus area, Eur. J. Pharmacol. 758 (2015) 123–128, https://doi.org/10.1016/j.ejphar.2015.03.066.

[259] O. Pillai, N. Kumar, C.S. Dey, S. Borkute, S. Nagalingam, R. Panchagnula, Transdermal iontophoresis of insulin. Part 1: a study on the issues associated with the use of platinum electrodes on rat skin, J. Pharm. Pharmacol. 55 (2003) 1505–1513, https://doi.org/10.1211/0022357022197.

[260] O. Pillai, S.D. Borkute, N. Sivaprasad, R. Panchagnula, Transdermal iontophoresis of insulin – II. Physicochemical considerations, Int. J. Pharm. 254 (2003) 271–280, https://doi.org/10.1016/S0378-5173(03)00034-6.

[261] O. Pillai, N. Kumar, C.S. Dey, N. Borkute, R. Panchagnula Sivaprasad, Transdermal iontophoresis of insulin: III. Influence of electronic parameters, Methods Find. Exp. Clin. Pharmacol. 26 (2004) 399–408.

[262] O. Pillai, V. Nair, R. Panchagnula, Transdermal iontophoresis of insulin: IV. Influence of chemical enhancers, Int. J. Pharm. 269 (2004) 109–120, https://doi.org/10.1016/j.ijpharm.2003.09.032.

[263] O. Pillai, R. Panchagnula, Transdermal iontophoresis of insulin – V. Effect of terpenes, J. Control. Release 88 (2003) 287–296, https://doi.org/10.1016/S0168-3659(03)00065-8.

[264] B.A. Medi, J. Singh, Electronically facilitated transdermal delivery of human parathyroid hormone (1-34), Int. J. Pharm. 263 (2003) 25–33, https://doi.org/10.1016/S0378-5173(03)00337-5.

[265] K. Tomoda, A. Watanabe, K. Suzuki, T. Inagi, H. Terada, K. Makino, Enhanced transdermal permeability of estradiol using combination of PLGA nanoparticles system and iontophoresis, Colloids Surf. B Biointerfaces 97 (2012) 84–89, https://doi.org/10.1016/j.colsurfb.2012.04.002.

[266] S.F. Taveira, D.C.A.S. De Santana, L.M.P.C. Araujo, F. Marquele-Oliveira, A. Nomizo, R.F.V. Lopez, Effect of iontophoresis on topical delivery of doxorubicin-loaded solid lipid nanoparticles, J. Biomed. Nanotechnol. 10 (2014) 1382–1390, https://doi.org/10.1166/jbn.2014.1834.

[267] M.B. Dohnert, M. Venancio, J.C. Possato, R.C. Zeferino, L.H. Dohnert, A.I. Zugno, C.T. De Souza, M.M.S. Paula, T.F. Luciano, Gold nanoparticles and diclofenac diethylammonium administered by iontophoresis reduce inflammatory cytokines expression in *Achilles tendinitis*, Int. J. Nanomedicine 7 (2012) 1651–1657, https://doi.org/10.2147/Ijn.S25164.

[268] I. Takeuchi, T. Takeshita, T. Suzuki, K. Makino, Iontophoretic transdermal delivery using chitosan-coated PLGA nanoparticles for positively charged drugs, Colloids Surf. B Biointerfaces 160 (2017) 520–526, https://doi.org/10.1016/j.colsurfb.2017.10.011.

[269] K. Tomoda, H. Terashima, K. Suzuki, T. Inagi, H. Terada, K. Makino, Enhanced transdermal delivery of indomethacin using combination of PLGA nanoparticles and iontophoresis in vivo, Colloids Surf. B Biointerfaces 92 (2012) 50–54, https://doi.org/10.1016/j.colsurfb.2011.11.016.

[270] S. Labala, A. Jose, S.R. Chawla, M.S. Khan, S. Bhatnagar, O.P. Kulkarni, V.V.K. Venuganti, Effective melanoma cancer suppression by iontophoretic co-delivery of STAT3 siRNA and imatinib using gold nanoparticles, Int. J. Pharm. 525 (2017) 407–417, https://doi.org/10.1016/j.ijpharm.2017.03.087.

[271] D.S. Bernardi, C. Bitencourt, D.S.C. da Silveira, E.L.C.M. da Cruz, M.A. Pereira-da-Silva, L.H. Faccioli, R.F.V. Lopez, Effective transcutaneous immunization using a combination of iontophoresis and nanoparticles, Nanomed. Nanotechnol. Biol. Med. 12 (2016) 2439–2448, https://doi.org/10.1016/j.nano.2016.07.001.

[272] J.H. Jung, B. Chiang, H.E. Grossniklaus, M.R. Prausnitz, Ocular drug delivery targeted by iontophoresis in the suprachoroidal space using a microneedle, J. Control. Release 277 (2018) 14–22, https://doi.org/10.1016/j.jconrel.2018.03.001.

[273] J.F. Shi, Y.F. Ma, J. Zhu, Y.X. Chen, Y.T. Sun, Y.C. Yao, Z.G. Yang, J. Xie, A review on electroporation-based intracellular delivery, Molecules 23 (2018)3044, https://doi.org/10.3390/molecules23113044.

[274] J.C. Weaver, Electroporation: a general phenomenon for manipulating cells and tissues, J. Cell. Biochem. 51 (1993) 426–435, https://doi.org/10.1002/jcb.2400510407.

[275] E. Neumann, M. Schaeferridder, Y. Wang, P.H. Hofschneider, Gene-transfer into mouse lyoma cells by electroporation in high electric-fields, EMBO J. 1 (1982) 841–845, https://doi.org/10.1002/j.1460-2075.1982.tb01257.x.

[276] G. Saulis, The loading of human erythrocytes with small molecules by electroporation, Cell. Mol. Biol. Lett. 10 (2005) 23–35.

[277] E.R.A. Van Gulck, P. Ponsaerts, L. Heyndrickx, K. Vereecken, F. Moerman, A. De Roo, R. Colebunders, G. Van den Bosch, D.R. Van Bockstaele, V.F.I. Van Tendeloo, S. Allard, B. Verrier, C. Maranon, G. Hoeffel, A. Hosmalin, Z.N. Berneman, G. Vanham, Efficient stimulation of HIV-1-specific T cells using dendritic cells electroporated with mRNA encoding autologous HIV-1 Gag and Env proteins, Blood 107 (2006) 1818–1827, https://doi.org/10.1182/blood-2005-01-0339.

[278] A. Michiels, S. Tuyaerts, A. Bonehill, J. Corthals, K. Breckpot, C. Heirman, S. Van Meirvenne, M. Dullaers, S. Allard, F. Brasseur, P. van der Bruggen, K. Thielemans, Electroporation of immature and mature dendritic cells: implications for dendritic cell-based vaccines, Gene Ther. 12 (2005) 772–782, https://doi.org/10.1038/sj.gt.3302471.

[279] E.G. Guignet, T. Meyer, Suspended-drop electroporation for high-throughput delivery of biomolecules into cells, Nat. Methods 5 (2008) 393–395, https://doi.org/10.1038/Nmeth.1201.

[280] T.L. Roth, C. Puig-Saus, R. Yu, E. Shifrut, J. Carnevale, P.J. Li, J. Hiatt, J. Saco, P. Krystofinski, H. Li, V. Tobin, D.N. Nguyen, M.R. Lee, A.L. Putnam, A.L. Ferris, J.W. Chen, J.N. Schickel, L. Pellerin, D. Carmody, G. Alkorta-Aranburu, D. del Gaudio, H. Matsumoto, M. Morell, Y. Mao, M. Cho, R.M. Quadros, C.B. Gurumurthy, B. Smith, M. Haugwitz, S.H. Hughes, J.S. Weissman, K. Schumann, J.H. Esensten, A.P. May, A. Ashworth, G.M. Kupfer, S.A.W. Greeley, R. Bacchetta, E. Meffre, M.G. Roncarolo, N. Romberg, K.C. Herold, A. Ribas, M.D. Leonetti, A. Marson, Reprogramming human T cell function and specificity with non-viral genome targeting, Nature 559 (2018) 405–+, https://doi.org/10.1038/s41586-018-0326-5.

[281] J.P. Giraldo-Vela, W. Kang, R.L. McNaughton, X.M. Zhang, B.M. Wile, A. Tsourkas, G. Bao, H.D. Espinosa, Single-cell detection of mRNA expression using nanofountain-probe electroporated molecular beacons, Small 11 (2015) 2386–2391, https://doi.org/10.1002/smll.201401137.

[282] R. Vanbever, E. LeBoulenge, V. Preat, Transdermal delivery of fentanyl by electroporation 1. Influence of electrical factors, Pharm. Res. 13 (1996) 559–565, https://doi.org/10.1023/A:1016093920875.

[283] R. Vanbever, V. Preat, Factors affecting transdermal delivery of metoprolol by electroporation, Bioelectrochem. Bioenerg. 38 (1995) 223–228, https://doi.org/10.1016/0302-4598(95)01830-8.

[284] S. Kagatani, T. Shinoda, Y. Konno, M. Fukui, T. Ohmura, Y. Osada, Electroresponsive pulsatile depot delivery of insulin from poly(dimethylaminopropylacrylamide) gel in rats, J. Pharm. Sci. 86 (1997) 1273–1277, https://doi.org/10.1021/js9700762.

[285] A. Misra, S. Ganga, P. Upadhyay, Needle-free, non-adjuvanted skin immunization by electroporation-enhanced transdermal delivery of diphtheria toxoid and a candidate peptide vaccine against hepatitis B virus, Vaccine 18 (1999) 517–523, https://doi.org/10.1016/S0264-410x(99)00212-1.

[286] L. Zhang, L.N. Li, Z.L. An, R.M. Hoffman, G.A. Hofmann, In vivo transdermal delivery of large molecules by pressure-mediated electroincorporation and electroporation: a novel method for drug and gene delivery, Bioelectrochem. Bioenerg. 42 (1997) 283–292, https://doi.org/10.1016/S0302-4598(96)05128-8.

[287] T.E. Zewert, U.F. Pliquett, R. Vanbever, R. Langer, J.C. Weaver, Creation of transdermal pathways for macromolecule transport by skin electroporation and a low toxicity, pathway-enlarging molecule, Bioelectrochem. Bioenerg. 49 (1999) 11–20, https://doi.org/10.1016/S0302-4598(99)00056-2.

[288] A. Sen, Y.L. Zhao, S.W. Hui, Saturated anionic phospholipids enhance transdermal transport by electroporation, Biophys. J. 83 (2002) 2064–2073, https://doi.org/10.1016/S0006-3495(02)73967-2.

[289] J.C. Weaver, R. Vanbever, T.E. Vaughan, M.R. Prausnitz, Heparin alters transdermal transport associated with electroporation, Biochem. Biophys. Res. Commun. 234 (1997) 637–640, https://doi.org/10.1006/bbrc.1997.6701.

[290] S. Tokumoto, N. Higo, K. Sugibayashi, Effect of electroporation and pH on the iontophoretic transdermal delivery of human insulin, Int. J. Pharm. 326 (2006) 13–19, https://doi.org/10.1016/j.ijpharm.2006.07.002.

[291] K. Yan, H. Todo, K. Sugibayashi, Transdermal drug delivery by in-skin electroporation using a microneedle array, Int. J. Pharm. 397 (2010) 77–83, https://doi.org/10.1016/j.ijpharm.2010.06.052.

[292] Y. Zhao, A.C. Tavares, M.A. Gauthier, Nano-engineered electro-responsive drug delivery systems, J. Mater. Chem. B 4 (2016) 3019–3030, https://doi.org/10.1039/c6tb00049e.

[293] R.V. Kulkarni, S. Biswanath, Electrically responsive smart hydrogels in drug delivery: a review, J. Appl. Biomater. Biomech. 5 (2007) 125–139, https://doi.org/10.1177/228080000700500301.

[294] P.M. George, D.A. LaVan, J.A. Burdick, C.Y. Chen, E. Liang, R. Langer, Electrically controlled drug delivery from biotin-doped conductive polypyrrole, Adv. Mater. 18 (2006) 577−+, https://doi.org/10.1002/adma.200501242.

[295] M.C. Koetting, J.T. Peters, S.D. Steichen, N.A. Peppas, Stimulus-responsive hydrogels: theory, modern advances, and applications, Mater. Sci. Eng. R. Rep. 93 (2015) 1–49, https://doi.org/10.1016/j.mser.2015.04.001.

[296] C.L. Recksiedler, B.A. Deore, M.S. Freund, A novel layer-by-layer approach for the fabrication of conducting polymer/RNA multilayer films for controlled release, Langmuir 22 (2006) 2811–2815, https://doi.org/10.1021/la053031m.

[297] D. Esrafilzadeh, J.M. Razal, S.E. Moulton, E.M. Stewart, G.G. Wallace, Multifunctional conducting fibres with electrically controlled release of ciprofloxacin, J. Control. Release 169 (2013) 313–320, https://doi.org/10.1016/j.jconrel.2013.01.022.

[298] L.P. Lv, Y. Zhao, N. Vilbrandt, M. Gallei, A. Vimalanandan, M. Rohwerder, K. Landfester, D. Crespy, Redox responsive release of hydrophobic self-healing agents from polyaniline capsules, J. Am. Chem. Soc. 135 (2013) 14198–14205, https://doi.org/10.1021/ja405279t.

[299] M. Sharma, G.I.N. Waterhouse, S.W.C. Loader, S. Garg, D. Svirskis, High surface area polypyrrole scaffolds for tunable drug delivery, Int. J. Pharm. 443 (2013) 163–168, https://doi.org/10.1016/j.ijpharm.2013.01.006.

[300] X.L. Luo, C. Matranga, S.S. Tan, N. Alba, X.Y.T. Cui, Carbon nanotube nanoreservior for controlled release of anti-inflammatory dexamethasone, Biomaterials 32 (2011) 6316–6323, https://doi.org/10.1016/j.biomaterials.2011.05.020.

[301] K.C. Wood, N.S. Zacharia, D.J. Schmidt, S.N. Wrightman, B.J. Andaya, P.T. Hammond, Electroactive controlled release thin films, Proc. Natl. Acad. Sci. U. S. A. 105 (2008) 2280–2285, https://doi.org/10.1073/pnas.0706994105.

[302] C.L. Weaver, J.M. LaRosa, X.L. Luo, X.T. Cui, Electrically controlled drug delivery from graphene oxide nanocomposite films, ACS Nano 8 (2014) 1834–1843, https://doi.org/10.1021/nn406223e.

[303] M. Karimi, A. Ghasemi, P.S. Zangabad, R. Rahighi, S.M.M. Basri, H. Mirshekari, M. Amiri, Z.S. Pishabad, A. Aslani, M. Bozorgomid, D. Ghosh, A. Beyzavi, A. Vaseghi, A.R. Aref, L. Haghani, S. Bahrami, M.R. Hamblin, Smart micro/nanoparticles in stimulus-responsive drug/gene delivery systems, Chem. Soc. Rev. 45 (2016) 1457–1501, https://doi.org/10.1039/c5cs00798d.

[304] D. Mertz, S. Harlepp, J. Goetz, D. Bégin, G. Schlatter, S. Bégin-Colin, A. Hébraud, Nanocomposite Polymer Scaffolds Responding under External Stimuli for Drug Delivery and Tissue Engineering Applications, Adv. Therap. 3 (2020) 1900143, https://doi.org/10.1002/adtp.201900143.

[305] N. Hosseini-Nassab, D. Samanta, Y. Abdolazimi, J.P. Annes, R.N. Zare, Electrically controlled release of insulin using polypyrrole nanoparticles, Nanoscale 9 (2017) 143–149, https://doi.org/10.1039/c6nr08288b.

[306] D. Samanta, N. Hosseini-Nassab, R.N. Zare, Electroresponsive nanoparticles for drug delivery on demand, Nanoscale 8 (2016) 9310–9317, https://doi.org/10.1039/c6nr01884j.

[307] J. Ge, E. Neofytou, T.J. Cahill, R.E. Beygui, R.N. Zare, Drug release from electric-field-responsive nanoparticles, ACS Nano 6 (2012) 227–233, https://doi.org/10.1021/nn203430m.

[308] Y. Takeoka, T. Aoki, K. Sanui, N. Ogata, M. Yokoyama, T. Okano, Y. Sakurai, M. Watanabe, Electrochemical control of drug-release from redox-active micelles, J. Control. Release 33 (1995) 79–87, https://doi.org/10.1016/0168-3659(94)00078-9.

[309] L. Peng, A.C. Feng, H.J. Zhang, H. Wang, C.M. Jian, B.W. Liu, W.P. Gao, J.Y. Yuan, Voltage-responsive micelles based on the assembly of two biocompatible homopolymers, Polym. Chem. 5 (2014) 1751–1759, https://doi.org/10.1039/c3py01204b.

[310] G.L. Li, T.J. Van Steeg, H. Putter, J. Van Der Spek, S. Pavel, M. Danhof, J.A. Bouwstra, Cutaneous side-effects of transdermal iontophoresis with and without surfactant pretreatment: a single-blinded, randomized controlled trial, Br. J. Dermatol. 153 (2005) 404–412, https://doi.org/10.1111/j.1365-2133.2005.06741.x.

[311] Lesions and shocks during iontophoresis, Health Dev. 26 (1997) 123–125.

[312] G.D. Warden, Electrical safety in iontophoresis, Rehab Manag. 20 (2007) 22–23.

[313] A. Farzin, S.A. Etesami, J. Quint, A. Memic, A. Tamayol, Magnetic nanoparticles in cancer therapy and diagnosis, Adv. Healthc. Mater. (2020), 1901058. https://doi.org/10.1002/adhm.201901058.

[314] R.E. Rosensweig, Heating magnetic fluid with alternating magnetic field, J. Magn. Magn. Mater. 252 (2002) 370–374, https://doi.org/10.1016/S0304-8853(02)00706-0.

[315] F.-C. Lin, J.I. Zink, Probing the local nanoscale heating mechanism of a magnetic core in mesoporous silica drug-delivery nanoparticles using fluorescence depolarization, J. Am. Chem. Soc. 142 (2020) 5212–5220, https://doi.org/10.1021/jacs.9b13082.

[316] J. Dobson, Magnetic nanoparticles for drug delivery, Drug Dev. Res. 67 (2006) 55–60, https://doi.org/10.1002/ddr.20067.

[317] M. Gonzales, K.M. Krishnan, Synthesis of magnetoliposomes with monodisperse iron oxide nanocrystal cores for hyperthermia, J. Magn. Magn. Mater. 293 (2005) 265–270, https://doi.org/10.1016/j.jmmm.2005.02.020.

[318] P. Pradhan, J. Giri, F. Rieken, C. Koch, O. Mykhaylyk, M. Döblinger, R. Banerjee, D. Bahadur, C. Plank, Targeted temperature sensitive magnetic liposomes for thermo-chemotherapy, J. Control. Release 142 (2010) 108–121, https://doi.org/10.1016/j.jconrel.2009.10.002.

[319] K. Katagiri, Y. Imai, K. Koumoto, T. Kaiden, K. Kono, S. Aoshima, Magnetoresponsive on-demand release of hybrid liposomes formed from Fe3O4 nanoparticles and thermosensitive block copolymers, Small 7 (2011) 1683–1689, https://doi.org/10.1002/smll.201002180.

[320] T. Hoare, B.P. Timko, J. Santamaria, G.F. Goya, S. Irusta, S. Lau, C.F. Stefanescu, D. Lin, R. Langer, D.S. Kohane, Magnetically triggered nanocomposite membranes: a versatile platform for triggered drug release, Nano Lett. 11 (2011) 1395–1400, https://doi.org/10.1021/nl200494t.

[321] E.G. Fuller, H. Sun, R.D. Dhavalikar, M. Unni, G.M. Scheutz, B.S. Sumerlin, C. Rinaldi, Externally triggered heat and drug release from magnetically controlled nanocarriers, ACS Appl. Polym. Mater. 1 (2019) 211–220, https://doi.org/10.1021/acsapm.8b00100.

[322] W. Chen, C.-A. Cheng, J.I. Zink, Spatial, temporal, and dose control of drug delivery using noninvasive magnetic stimulation, ACS Nano 13 (2019) 1292–1308, https://doi.org/10.1021/acsnano.8b06655.

[323] J.F. Liu, N. Neel, P. Dang, M. Lamb, J. McKenna, L. Rodgers, B. Litt, Z. Cheng, A. Tsourkas, D. Issadore, Radiofrequency-triggered drug release from nanoliposomes with millimeter-scale resolution using a superimposed static gating field, Small. 14 (2018), 1802563. https://doi.org/10.1002/smll.201802563.

[324] A. Muela, D. Muñoz, R. Martín-Rodríguez, I. Orue, E. Garaio, A. Abad Díaz de Cerio, J. Alonso, J.Á. García, M.L. Fdez-Gubieda, Optimal parameters for hyperthermia treatment using biomineralized magnetite nanoparticles: theoretical and experimental approach, J. Phys. Chem. C 120 (2016) 24437–24448, https://doi.org/10.1021/acs.jpcc.6b07321.

[325] S. Laurent, S. Dutz, U.O. Häfeli, M. Mahmoudi, Magnetic fluid hyperthermia: focus on superparamagnetic iron oxide nanoparticles, Adv. Colloid Interf. Sci. 166 (2011) 8–23, https://doi.org/10.1016/j.cis.2011.04.003.

[326] P.M. Price, W.E. Mahmoud, A.A. Al-Ghamdi, L.M. Bronstein, Magnetic drug delivery: where the field is going, Front. Chem. 6 (2018) https://doi.org/10.3389/fchem.2018.00619.

[327] K. Yang, Y. Liu, Y. Liu, Q. Zhang, C. Kong, C. Yi, Z. Zhou, Z. Wang, G. Zhang, Y. Zhang, N.M. Khashab, X. Chen, Z. Nie, Cooperative assembly of magneto-nanovesicles with tunable wall thickness and permeability for MRI-guided drug delivery, J. Am. Chem. Soc. 140 (2018) 4666–4677, https://doi.org/10.1021/jacs.8b00884.

[328] L. Che Rose, J.C. Bear, P.D. McNaughter, P. Southern, R.B. Piggott, I.P. Parkin, S. Qi, A.G. Mayes, A SPION-eicosane protective coating for water soluble capsules: evidence for on-demand drug release triggered by magnetic hyperthermia, Sci. Rep. 6 (2016) 1–5, https://doi.org/10.1038/srep20271.

[329] J.C. Bear, P.S. Patrick, A. Casson, P. Southern, F.-Y. Lin, M.J. Powell, Q.A. Pankhurst, T. Kalber, M. Lythgoe, I.P. Parkin, A.G. Mayes, Magnetic hyperthermia controlled drug release in the GI tract: solving the problem of detection, Sci. Rep. 6 (2016), 34271. https://doi.org/10.1038/srep34271.

[330] J. Kost, J. Wolfrum, R. Langer, Magnetically enhanced insulin release in diabetic rats, J. Biomed. Mater. Res. 21 (1987) 1367–1373, https://doi.org/10.1002/jbm.820211202.

[331] P.M. Peiris, L. Bauer, R. Toy, E. Tran, J. Pansky, E. Doolittle, E. Schmidt, E. Hayden, A. Mayer, R.A. Keri, M.A. Griswold, E. Karathanasis, Enhanced delivery of chemotherapy to tumors using a multicomponent nanochain with radio-frequency-tunable drug release, ACS Nano 6 (2012) 4157–4168, https://doi.org/10.1021/nn300652p.

[332] P.M. Peiris, A. Abramowski, J. Mcginnity, E. Doolittle, R. Toy, R. Gopalakrishnan, S. Shah, L. Bauer, K.B. Ghaghada, C. Hoimes, S.M. Brady-Kalnay, J.P. Basilion, M.A. Griswold, E. Karathanasis, Treatment of invasive brain tumors using a chain-like nanoparticle, Cancer Res. 75 (2015) 1356–1365, https://doi.org/10.1158/0008-5472.CAN-14-1540.

[333] Y. Qiu, S. Tong, L. Zhang, Y. Sakurai, D.R. Myers, L. Hong, W.A. Lam, G. Bao, Magnetic forces enable controlled drug delivery by disrupting endothelial cell-cell junctions, Nat. Commun. 8 (2017), 15594. https://doi.org/10.1038/ncomms15594.

[334] R.K. Das, A. Pramanik, M. Majhi, S. Mohapatra, Magnetic mesoporous silica gated with doped carbon dot for site-specific drug delivery, fluorescence, and MR imaging, Langmuir 34 (2018) 5253–5262, https://doi.org/10.1021/acs.langmuir.7b04268.

[335] P. Das, P. Fatehbasharzad, M. Colombo, L. Fiandra, D. Prosperi, Multifunctional magnetic gold nanomaterials for cancer, Trends Biotechnol. 37 (2019) 995–1010, https://doi.org/10.1016/j.tibtech.2019.02.005.

[336] H. Unterweger, D. Subatzus, R. Tietze, C. Janko, M. Poettler, A. Stiegelschmitt, M. Schuster, C. Maake, A.R. Boccaccini, C. Alexiou, Hypericin-bearing magnetic iron oxide nanoparticles for selective drug delivery in photodynamic therapy, Int. J.

Nanomedicine 10 (2015) 6985–6996, https://doi.org/10.2147/IJN.S92336. https://www.dovepress.com/hypericin-bearing-magnetic-iron-oxide-nanoparticles-for-selective-drug-peer-reviewed-fulltext-article-IJN.
[337] X. Cai, F. Yang, N. Gu, Applications of magnetic microbubbles for theranostics, Theranostics 2 (2012) 103–112, https://doi.org/10.7150/thno.3464.
[338] Y. Heun, S. Hildebrand, A. Heidsieck, B. Gleich, M. Anton, J. Pircher, A. Ribeiro, O. Mykhaylyk, D. Eberbeck, D. Wenzel, A. Pfeifer, M. Woernle, F. Krötz, U. Pohl, H. Mannell, Targeting of magnetic nanoparticle-coated microbubbles to the vascular wall empowers site-specific lentiviral gene delivery in vivo, Theranostics 7 (2017) 295–307, https://doi.org/10.7150/thno.16192.
[339] L. Duan, F. Yang, W. He, L. Song, F. Qiu, N. Xu, L. Xu, Y. Zhang, Z. Hua, N. Gu, A multi-gradient targeting drug delivery system based on RGD-l-TRAIL-Labeled magnetic microbubbles for cancer theranostics, Adv. Funct. Mater. 26 (2016) 8313–8324, https://doi.org/10.1002/adfm.201603637.
[340] C.-H. Fan, Y.-H. Cheng, C.-Y. Ting, Y.-J. Ho, P.-H. Hsu, H.-L. Liu, C.-K. Yeh, Ultrasound/magnetic targeting with SPIO-DOX-microbubble complex for image-guided drug delivery in brain tumors, Theranostics 6 (2016) 1542–1556, https://doi.org/10.7150/thno.15297.
[341] Y. Sheng, E. Beguin, H. Nesbitt, S. Kamila, J. Owen, L.C. Barnsley, B. Callan, C. O'Kane, N. Nomikou, R. Hamoudi, M.A. Taylor, M. Love, P. Kelly, D. O'Rourke, E. Stride, A.P. McHale, J.F. Callan, Magnetically responsive microbubbles as delivery vehicles for targeted sonodynamic and antimetabolite therapy of pancreatic cancer, J. Control. Release 262 (2017) 192–200, https://doi.org/10.1016/j.jconrel.2017.07.040.
[342] B. Chertok, R. Langer, Circulating magnetic microbubbles for localized real-time control of drug delivery by ultrasonography-guided magnetic targeting and ultrasound, Theranostics. 8 (2018) 341–357, https://doi.org/10.7150/thno.20781.
[343] J. Dulińska-Litewka, A. Łazarczyk, P. Hałubiec, O. Szafrański, K. Karnas, A. Karewicz, Superparamagnetic Iron oxide nanoparticles—current and prospective medical applications, Materials 12 (2019) 617, https://doi.org/10.3390/ma12040617.
[344] N. Singh, G.J.S. Jenkins, R. Asadi, S.H. Doak, Potential toxicity of superparamagnetic iron oxide nanoparticles (SPION), Nano Rev. 1 (2010) 5358, https://doi.org/10.3402/nano.v1i0.5358.
[345] R. Jin, B. Lin, D. Li, H. Ai, Superparamagnetic iron oxide nanoparticles for MR imaging and therapy: design considerations and clinical applications, Curr. Opin. Pharmacol. 18 (2014) 18–27, https://doi.org/10.1016/j.coph.2014.08.002.
[346] A.S. Thakor, J.V. Jokerst, P. Ghanouni, J.L. Campbell, E. Mittra, S.S. Gambhir, Clinically approved nanoparticle imaging agents, J. Nucl. Med. 57 (2016) 1833–1837, https://doi.org/10.2967/jnumed.116.181362.
[347] T. Aoki, M. Saito, H. Koseki, K. Tsuji, A. Tsuji, K. Murata, H. Kasuya, A. Morita, S. Narumiya, K. Nozaki, Macrophage imaging of cerebral aneurysms with ferumoxytol: an exploratory study in an animal model and in patients, J. Stroke Cerebrovasc. Dis. 26 (2017) 2055–2064, https://doi.org/10.1016/j.jstrokecerebrovasdis.2016.10.026.
[348] F.D. Birkhäuser, U.E. Studer, J.M. Froehlich, M. Triantafyllou, L.J. Bains, G. Petralia, P. Vermathen, A. Fleischmann, H.C. Thoeny, Combined ultrasmall superparamagnetic particles of iron oxide-enhanced and diffusion-weighted magnetic resonance imaging facilitates detection of metastases in normal-sized pelvic lymph nodes of patients with bladder and prostate cancer, Eur. Urol. 64 (2013) 953–960, https://doi.org/10.1016/j.eururo.2013.07.032.
[349] A. Karakatsanis, H. Olofsson, P. Stålberg, L. Bergkvist, S. Abdsaleh, F. Wärnberg, Simplifying logistics and avoiding the unnecessary in patients with breast cancer undergoing sentinel node biopsy. A prospective feasibility trial of the preoperative injection of super paramagnetic Iron oxide nanoparticles, Scand. J. Surg. 107 (2018) 130–137, https://doi.org/10.1177/1457496917738867.
[350] J.-L. Houpeau, M.-P. Chauvet, F. Guillemin, C. Bendavid-Athias, H. Charitansky, A. Kramar, S. Giard, Sentinel lymph node identification using superparamagnetic iron oxide particles versus radioisotope: the French Sentimag feasibility trial, J. Surg. Oncol. 113 (2016) 501–507, https://doi.org/10.1002/jso.24164.
[351] M. Thill, A. Kurylcio, R. Welter, V. van Haasteren, B. Grosse, G. Berclaz, W. Polkowski, N. Hauser, The central-European SentiMag study: sentinel lymph node biopsy with superparamagnetic iron oxide (SPIO) vs. radioisotope, Breast 23 (2014) 175–179, https://doi.org/10.1016/j.breast.2014.01.004.
[352] M. Ghilli, E. Carretta, F. Di Filippo, C. Battaglia, L. Fustaino, I. Galanou, S. Di Filippo, P. Rucci, M.P. Fantini, M. Roncella, The superparamagnetic iron oxide tracer: a valid alternative in sentinel node biopsy for breast cancer treatment, Eur. J. Cancer Care (Engl) 26 (2017) https://doi.org/10.1111/ecc.12385.
[353] K. Taruno, T. Kurita, A. Kuwahata, K. Yanagihara, K. Enokido, Y. Katayose, S. Nakamura, H. Takei, M. Sekino, M. Kusakabe, Multicenter clinical trial on sentinel lymph node biopsy using superparamagnetic iron oxide nanoparticles and a novel handheld magnetic probe, J. Surg. Oncol. 120 (2019) 1391–1396, https://doi.org/10.1002/jso.25747.
[354] K. Ulbrich, K. Holá, V. Šubr, A. Bakandritsos, J. Tuček, R. Zbořil, Targeted drug delivery with polymers and magnetic nanoparticles: covalent and noncovalent approaches, release control, and clinical studies, Chem. Rev. 116 (2016) 5338–5431, https://doi.org/10.1021/acs.chemrev.5b00589.
[355] A.S. Lübbe, C. Bergemann, H. Riess, F. Schriever, P. Reichardt, K. Possinger, M. Matthias, B. Dörken, F. Herrmann, R. Gürtler, P. Hohenberger, N. Haas, R. Sohr, B. Sander, A.-J. Lemke, D. Ohlendorf, W. Huhnt, D. Huhn, Clinical experiences with magnetic drug targeting: a phase I study with 4′-epidoxorubicin in 14 patients with advanced solid tumors, Cancer Res. 56 (1996) 4686–4693.
[356] J. Koda, A. Venook, E. Walser, S. Goodwin, A multicenter, phase I/II trial of hepatic intra-arterial delivery of doxorubicin hydrochloride adsorbed to magnetic targeted carriers in patients with hepatocellular carcinoma, Eur. J. Cancer 38 (2002) S18, https://doi.org/10.1016/S0959-8049(02)80690-6.
[357] H. Hancock, M.R. Dreher, N. Crawford, C.B. Pollock, J. Shih, B.J. Wood, K. Hunter, V. Frenkel, Evaluation of pulsed high intensity focused ultrasound exposures on metastasis in a murine model, Clin. Exp. Metastasis 26 (2009) 729–738, https://doi.org/10.1007/s10585-009-9272-9.