Advanced Drug Delivery Reviews 138 (2019) 3–17

Contents lists available at ScienceDirect

Advanced Drug Delivery Reviews

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

Advances on non-invasive physically triggered nucleic acid delivery from nanocarriers

Hai Doan Do, Brice Martin Couillaud, Bich-Thuy Doan, Yohann Corvis, Nathalie Mignet *

Chemical and Biological Technologies for Health (UTCBS), CNRS, INSERM, Chimie ParisTech, Paris Sorbonne Cité, PSL Research University, Paris Descartes University, 4 avenue de l'Observatoire, Paris F-75006, France

ARTICLE INFO

Article history:
Received 22 June 2018
Received in revised form 14 September 2018
Accepted 8 October 2018
Available online 12 October 2018

Keywords:
Nucleic acid delivery
Exogenous trigger
Ultrasound
Light
Magnetic
Cold-shock

ABSTRACT

Nucleic acids (NAs) have been considered as promising therapeutic agents for various types of diseases. However, their clinical applications still face many limitations due to their charge, high molecular weight, instability in biological environment and low levels of transfection. To overcome these drawbacks, therapeutic NAs should be carried in a stable nanocarrier, which can be viral or non-viral vectors, and released at specific target site. Various controllable gene release strategies are currently being evaluated with interesting results. Endogenous stimuli-responsive systems, for example pH-, redox reaction-, enzymatic-triggered approaches have been widely studied based on the physiological differences between pathological and normal tissues. Meanwhile, exogenous triggered release strategies require the use of externally non-invasive physical triggering signals such as light, heat, magnetic field and ultrasound. Compared to internal triggered strategies, external triggered gene release is time and site specifically controllable through active management of outside stimuli. The signal induces changes in the stability of the delivery system or some specific reactions which lead to endosomal escape and/or gene release. In the present review, the mechanisms and examples of exogenous triggered gene release approaches are detailed. Challenges and perspectives of such gene delivery systems are also discussed.

Contents

1. Introduction

Nucleic acids (NAs) are among the most important biomolecules. Their main function is to store and to transfer genetic information. Although being discovered very early in 1869, researches involving in

* Corresponding author.
E-mail address: nathalie.mignet@parisdescartes.fr (N. Mignet).

https://doi.org/10.1016/j.addr.2018.10.006
0169-409X/

NAs have achieved amazing progress in the past few decades. In medicine, NAs are considered as promising therapeutic agents for various types of diseases, from hereditary diseases to acquired diseases such as cancer, degenerative disorders and AIDS. Therapeutic NAs can be categorized into DNA therapeutics (antisense oligonucleotides, DNA aptamers and gene therapy) and RNA therapeutics (micro RNAs (miRNA), short interfering RNAs (siRNA), ribozymes, RNA decoys and circular RNAs) [1]. Since the first successful and accepted nuclear gene transfer in humans in May 1989, a lot of nucleic acid-based treatments have been fabricated and taken into clinical trials [2]. In 2012, Glybera®, an adeno- associated viral vector engineered to express lipoprotein lipase for the treatment of lipoprotein lipase deficiency, was approved as the first gene therapy treatment for sale in the European Union [3]. Until 2016, there are approximately 2600 gene therapies clinical trials [2] and about 20 clinical trials using miRNA and siRNA-based therapies [4]. Moreover, in 2016, the first *ex-vivo* stem cell gene therapy, Strimvelis™, was accepted in Europe for Severe Combined ImmunoDeficiency due to Adenosine DeAminase deficiency treatment [5].

Efficient cell delivery of NAs is hampered by their charge, high molecular weight and instability in biological environment. Many strategies have been proposed to obtain effective gene delivery to targeted cells [5]. An effective gene delivery system should have the following properties: (i) be able to carry and to protect the therapeutic genes; (ii) accumulate at targeted tissues, and (iii) release the entrapped payload at the targeted tissue. There are two kinds of vector for gene delivery: viral and non-viral vectors. Viral vectors are outstanding candidates for gene delivery due to their high transfection efficiency and ability to incorporate the delivered gene into the host genome [6]. Although serious side-effects of viral vectors leading to patient death and lymphoproliferative disorder were encountered [7], after numerous modifications and innovations, many viral vectors with improved efficiency, specificity and safety have been developed and transferred into clinical trials. Today, viral vectors are used in approximately two thirds of gene therapy trials performed [2]. However, there are still some drawbacks in the use of viral vectors such as: the complexity and high cost of production, and the limited size of transgene inserted in viral vectors [8]. Meanwhile, non-viral vectors are highly interesting delivery systems due to their large versatility: they can be composed of organic materials (for example: polymers, liposomes, peptides…), carbon nanotubes, or inorganic nanoparticles (such as gold NPs, magnetic NPs (MNPs)…) [6]. They can be designed to transfer different and large transgenes [8].

After administration, non-viral vectors are usually uptaken by the cells through endosomal pathway. Because of harsh environment inside endosome (low pH, digestive enzymes), NAs risk to be degraded before reaching their site of action. Endosomal escape and triggered release of the entrapped gene at the target site, therefore, are important requirements for an effective NA-based treatment. For that reason, stimuli-responsive gene delivery systems are under evaluation. Stimuli-responsive vectors should hold off the release function while they are in the blood stream and release entrapped genes inside the cells under exposure to stimuli source which can be internal or external triggers. Internal triggers are based on abnormalities of pathological area such as different pH, redox potential, temperature and over expression of some molecules like enzymes. For instance, in breast and pancreatic cancers, there is a significant increase in the expression of phospholipase A2, or in inflammatory area, there are some soluble extracellular enzymes such as lysozyme, cathepsins and matrix metalloproteinases [9]. A metalloproteinase 2 responsive block copolymer composed of poly(ethylene glycol) (PEG), matrix metalloproteinase 2 (MMP-2)-degradable peptide PLG*LAG, cationic cell penetrating peptide polyarginine r_9 and poly(ε-caprolactone) (PCL) was employed for siRNA against polo-lie kinase 1 (Plk1) delivery. The micelle carrying siRNA showed enhanced gene silencing and tumor growth inhibition. About 49% of cells treated with metalloproteinase responsive siRNA delivery system underwent apoptosis while cells treated with unresponsive system presented only about 24% of death. Furthermore, Plk1 mRNA levels was significantly lower in mice treated with responsive system compared to that with unresponsive system ($p < 0.005$) [10]. Beside, due to hypoxia, pH may drop to around 6 in the tumor area [11] or inflammation tissues [12]. Taking advantage of this difference, Du et al. designed nanomicelle system based on poly(ethylene glycol)-*co*-poly[(2, 4, 6-trimethoxybenzylidene-1, 1, 1-tris(hydroxymethyl)] ethane methacrylate-co-poly(dimethylamino glycidyl methacrylate) PEG-PTTMA-P(GMA-S-DMA) (PTMS) for pH responsive siRNA release strategy. In acidic environment, PTTMA polymers undergoes hydrophobic-to-hydrophilic transition leading to the disassembly of the nanomicelle and therefore the siRNA release. Results from *in vitro* experiments showed that in cells treated with PTMS nanomicelle-based siRNA delivery system there was a highly efficient gene silencing of about 90%, which was even better than that with Lipofectamine 2000. This result was also confirmed through *in vivo* studies: in mice group treated with PTMS/siRNA complex, tumor growth was significantly inhibited and about 45% gene knockdown efficacy was observed. This enhancing gene silencing effect was attributed to the enhanced siRNA endosomal release [13]. In addition, in cancer cells, the level of glutathione is found to be 100-fold higher than the normal ranges [14]. Glutathione, therefore, can be used as a trigger for stimulus NA release. For example, a DNA delivery nanocarrier called Pluronic-PEI-SS synthesized by conjugating reducible disulfide-linked PEI (PEI-SS) with Pluronic was fabricated. The disulfide link is broken under the action of glutathione. The Pluronic-PEI-SS system showed the highest DNA transfection efficacy into cells of about 4, 3 and 13 times higher than that of Pluronic-PEI, PEI-SS and PEI systems, respectively. Moreover, *in vivo* experiment, the Pluronic-PEI-SS nanocarrier also exhibited a significantly higher transfection efficacy than the PEI/DNA [15]. Numerous other efforts have been carried out to prompt the release of entrapped gene by internal triggers with promising results and have been recently summarized in many reviews [12,14,16].

However, triggered gene release by intrinsic physical and biological factors faces many limitations. The environment of the disease site is heterogeneous and strongly depends on patient's conditions such as illness or diet, therefore the effects are not easy to predict. In addition, after administration, it is impossible to control or modify the action of the gene delivery systems. Compared to endogenous triggers, exogenous triggered gene release is time and site specifically controllable through active management of external stimuli. Non-invasive external signal like light, heat, magnetic field or ultrasound is applied to the target site from an outside source. The signal induces changes in the stability of the delivery system or some specific reactions which lead to endosomal escape and gene release.

In this review, we will go into details of some external trigger strategies for gene delivery, including ultrasound, magnetic field, light and temperature. In each strategy, mechanism of action and examples are covered. Furthermore, challenges and perspectives of these kinds of smart-gene delivery systems are also discussed.

2. Ultrasound triggered release

Ultrasound can be defined as pressure waves through a medium, these ultrasonic signals can be reflected, deviated and absorbed according to the environment [17]. More specifically, it generates three main effects, hyperthermia, acoustic pressure and cavitation (Fig. 1) leading to molecules motion as the medium is compressed and decompressed throughout the experimentation.

Consequently, ultrasound fosters blood vessels permeability and cellular uptake of drugs, as it leads to mechanical flows and physical forces carrying nanometer drugs through the blood vessel wall. [18]. Hyperthermia is related to a temperature above 37.5 °C, it is one of the most reported effect in drug delivery as numerous NPs are thermosensitive. However, for NA triggered delivery systems, cavitation and acoustic pressure are preferred to release NA from nanocarriers as hyperthermia

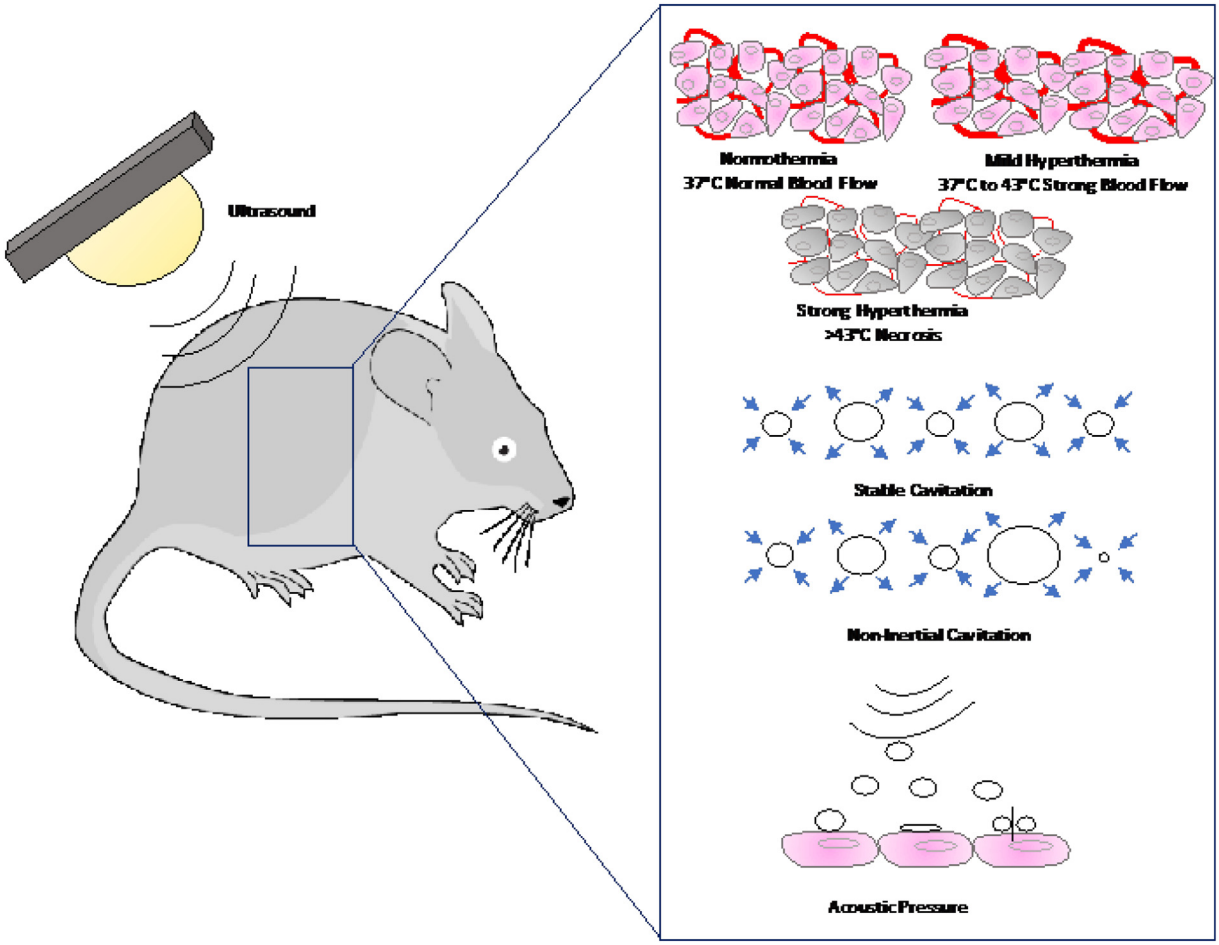

Fig. 1. Therapeutic effects of ultrasound at the region of interest to induce hyperthermia, cavitation and acoustic pressure.

could damage the loaded NA and change its physical and biological properties [19]. Three ranges of mediated temperature in human body can be defined, normothermia, mild hyperthermia and strong hyperthermia. Mild hyperthermia is often desired, as it increases blood vessel pressure promoting drug retention at the targeted tumor site without irreversibly damaging healthy tissues. At temperature above 43 °C, hyperthermia induces cells necrosis by denaturation of cellular molecules, particularly proteins [20]. However, the thermal dose used to induce hyperthermic cell mortality changes up to factor 10 among different cell types [19], hence ultrasound must be calibrated according to the specific environment to avoid cell toxicity. Cavitation refers to the oscillation of gas microbubbles in a medium exposed to ultrasound waves. If the ultrasound oscillations are stable, the cavitation is called stable and the probability of microbubbles explosion is low. As the ultrasound signal turns non-inertial, the oscillations become stronger and the microbubbles are upset to explosion, resulting in mechanical forces on the surrounding tissues, enhancing drug extravasation through membranes cells [21]. Acoustic pressure is related to ultrasonic beams creating flows that push NPs towards cells fostering rate of drug transport and drug uptake. A linear flow is expected at low acoustic pressure level and a nonlinear flow at high acoustic pressure level [22]. Hyperthermia, cavitation and acoustic pressure are controlled by two mains parameters, *i.e.* frequency and intensity.

Commonly, ultrasound frequency for gene delivery ranges from 0.01 to 2 MHz and from 0.1 to 3 W/cm^2 regarding intensity. Low ultrasound frequencies are expected as it provides deeper tissues penetration without damaging organs. Whether ultrasounds are applied continuously, hyperthermia could appear, therefore discontinuous low-ultrasound are privileged to release NAs without injuring surrounding tissues [23]. Also, the frequency of ultrasounds must be set according to the addition of microbubbles *in vivo* to enhance drug targeting, hence ultrasound frequencies should be in agreement with the type of microbubbles and the nature of tissues [24]. The synergistic combination of ultrasound and microbubbles produces microstreams, radiation forces, and extreme stresses on cells membranes as cavitation effect is amplified by the presence of microbubbles that will be destroyed near to the epithelia cells resulting in a provisional tight junction disturbance and therefore a better permeability [25]. Plasmid DNAs carrying luciferase, β-galactosidase and enhanced green fluorescent protein (EGFP) reporter genes were mixed with BR14 microbubbles and injected into the C57BL/6 mice heart while exposed to ultrasound. The authors showed that sonoporation-mediated pDNA transfer to murine heart is greatly enhanced by the use of BR14 (1330 ± 310 Relative Light Units/mg protein/10 s) compared to Optison microbubbles where some mice died after the injection. It was probably explained by the size of BR14 microbubbles (3 μm) that is smaller than Optison microbubbles (4.5 μm) [26]. Other recent advancements in the synergic combination of ultrasound and microbubbles for drug delivery have shown that this approach can enhance gene targeted-delivery to tissues while decreasing dose and systemic toxicity. T. Li et al. compared three types of ultrasound microbubble, Albunex, Optison and Levovist mixed with plasmid DNA encoding green fluorescent protein and then injected to mice followed by irradiation with low-intensity ultrasound (1 MHz) at an intensity of 2.0 W/cm^2 for 2 min. The study evidenced tenfold higher expression of plasmid with Optison microbubbles compared to Levovist, Albunex and without microbubbles after intra-muscular injection [27]. Similarly, Y. H. Li studied the elimination of angiogenesis by the downregulation of

vascular endothelial growth factor (VEGF) expression to prevent the growth of tumors by delivering VEGF-siRNA in NP to hamper VEGF expression in PC-3 cells. It appears that VEGF-siRNA was significantly delivered to cells with ultrasound microbubble at 1 MHz and 1.2 W/cm^2 for 20 s, the results from this study revealed that ultrasound microbubble side effect, such as cell apoptosis, capillary rupture or hemolysis, could be drastically reduced to a minimum under ultrasound optimum conditions [28]. This protective effect was observed by Q. L Lu et al. when Green fluorescent protein (GFP) plasmid DNA and TNF-α siRNA was injected with Optison microbubbles in presence of polyethyleneimine (PEI)25,000 cationic polymer directly into the mouse skeletal muscle followed by ultrasound at low frequency and intensity (1 MHz, 3 W/cm^2, 60 s exposure). Ultrasound at moderate power combined with Optison, also enhanced transfection efficiency of plasmid DNA up to 300-fold over naked DNA in mice, in addition to the reduction of muscle damages [29]. Using positively charged lipid-based microbubbles and miniplasmid devoid of antibiotic resistance, Manta et al. showed a sustained expression of luciferase in the liver after a single systemic injection under ultrasound (1 MHz, 40% duty cycle, pulse repetition frequency 10 kHz) [30]. However, other researches clearly proved that combined low- ultrasound microbubbles without payload can harmed cells and even be used as a treatment approach to cure diseases. S. Yang et al. investigated this treatment effects on benign prostatic hyperplasia and observed serious tissues injury and cell apoptosis at only 21 kHz with combined ultrasound microbubbles compared to ultrasound and microbubbles separately [31]. In addition, preventive measures should be taken into consideration when correlating *in vitro* ultrasound parameters to *in vivo* conditions. Indeed, as mechanisms of interaction with cells *in vitro* are different from *in vivo* environment which presents solid tissues, therefore ultrasound calibration for both *in vitro* and *in vivo* studies are required to optimize the parameters [32].

Tables 1 and 2 obtained from C.R Mayer et al. data [33], show an overview of gene delivery systems with low frequency-intensity ultrasound applied to several biological models.

3. Magnetically triggered release

Magnetic field is considered as one of the best triggering strategies for an externally responsive drug/gene release from drug delivery systems. Contrary to light which meets limitation of non-invasive application for deep tissue, magnetic fields are able to deeply penetrate into the whole body. The penetration depth depends on wavelength and decreases by increasing the frequency. It drops from 17 cm at 85 MHz to 7 cm at 220 MHz [65]. On the other hand, magnetic field seems to be safer thanks to less interaction with biological tissues compared to other strategies such as light, ultrasound or electrical field.

Magnetic field was used the first time as a stimuli trigger from drug delivery system by Hsieh et al. In this work, a magnetic sustained-release system was prepared by embedding 1.4 mm-diameter size magnetic steel beads in the polymer along with the drug. Without magnetic field, drug was gradually released from the system. Interestingly, the system released up to 100% more drug when activated by an oscillating external bar magnet than when the magnetic field was discontinued [66]. However, use of big magnetic particles causes significant heating of surrounding tissue which can lead to clotting of the vasculature. Therefore, MNPs have been employed to overpass this limitation. In a magnetic stimuli system, MNPs, which are encapsulated in or conjugated with the carriers, act as a remote control modality. When exposed to an external magnetic field, therapeutic gene can be released from the systems through thermal or non-thermal effects depending on the type of magnetic field. Some works on the magnetically triggered release of NA are overviewed in Table 3.

Table 1
Ultrasound combined microbubbles applications for gene delivery (frequency: 40 kHz to 1 MHz).

Ultrasound conditions	Microbubbles	Payload	Model	Ref.
40 kHz, 90 s	None	siRNA(3′-dTdT) 0.33 μg, 3.3 μg PEI	Transgenic mice cells expressing CTLA4Ig	[34]
956 kHz, 60 s	Optison	Luciferase plasmid DNA, 1.5 μg	Human vascular smooth muscle cells (HIAS-117C)	[35]
1 MHz	Sonovue	ABCG2-siRNA 100 nmol/L	Breast cancer cells (MCF-7/ADR)	[36]
1 MHz, 1,2 W/cm^2, 20 s	Sonovue	hVEGF-siRNA 0.03 pmol/μL	Human prostate carcinoma cells (PC-3)	[28]
1 MHz, 2 W/cm^2, 100 Hz PR, 300 s	Sonovue	Cy3-siRNA 0.2 nmol	Wistar rats	[37]
1 MHz; 2 W/cm^2, 2 min	Optison	siRNA-glyceraldehyde-3- phosphate dehydrogenas 4 μg	Male Wistar rats paratid glands	[38]
1 MHz in frequency, 100 Hz in PR, 0.5 ~ 3.0 W/cm^2	Sonovue	Cy3-SiRNA 1 nmol	Human prostate carcinoma cells (PC-3)	[39]
1 MHz, 1.0 W/cm^2, 1 min	Liposomes NBs	siRNA 0.5 μg	Rat C6 glioma	[40]
1 MHz, 2 W/cm^2 during 10 s	Liposomes MBs	siRNA PEG-siPlexes 50 nmol/L	Huh7 and Huh7 eGFPLuc, Liver cancer cells	[41]
1 MHz, 2.5 W/cm^2, 1 min	Optison	HGF plasmid DNA 2 ng/g tissue	Sprague-Dawley rat	[42]
1 MHz, 2.5 W/cm^2, 2 min	Optison	p53 plasmid DNA 50 μg	Post-angioplastic neointimal proliferation in rat carotid model	[43]
1 MHz, 3 W/cm^2, PW, 20% DC, 60 s	Optison	GFP plasmid DNA 10 μg, TNF-α siRNA 100 μg	Mouse limb (C57 B10)	[29]
1 MHz, 2 W/cm^2, PW, 50% DC, 2 min	Optison	luciferase plasmid DNA 25 μg	Mouse limb (BALB-C)	[27]
1 MHz, 0.6 W/cm^2, 15 min	Optison	TNF-α siRNA 100 μg	Post-ischemic inflammation in Wistar rat myocardium	[44]
1 MHz, 2.5 W/cm^2, 2 min	Optison	E2F decoy 100 μg	Post angioplastic neointimal proliferation in rat carotide	[43]
1 MHz, PW, 10–50% DC, 1.0–2.0 W/cm^2, 60 s	BR14	Luciferase, β-Gal and GFP plasmid DNA, GFP siRNA 500 μg	Mouse myocardium (C57BL/6)	[45]
1 MHz, PW, 20% DC, 2 W/cm^2, 30 s	Optison and Sonovue	GFP plasmid DNA 10 μg	Mouse limb (BALB-C)	[27]
1 MHz, CW, 1.5 W/cm^2, 3 × 10 s	Optison	HGF recombinant protein 10 μg	Doxorubicin induced cardiomyopathy in mouse model (C57BL/6)	[46]
1 MHz, PW, 6% DC, 2 min	BR14	TIMP-3 plasmid DNA 33 μg/mL	Prevention of porcine saphenous vein graft model	[47]
1 MHz, 50% duty ratio, 2.0 W/cm^2 90 s	Optison	BM-MNCs 1 × 10^8	Heart failure in hamster cardiomyopathy model (BIOTO2)	[48]
1 MHz, 1 W/cm^2, 20 s	Fluorocarbon	siRNA-GFP 25 μg	Human breast adenocarcinoma (MDA-MB- 231)	[27]
1.03 MHz, 1 W/cm^2, 2 min	Cationic porphyrin MBs	siRNA- Forkhead box protein A1 30 μmol/L	Breast Cancer cells (MCF7)	[49]

Table 2
Ultrasound combined microbubbles applications for gene delivery (frequency: 1 MHz to 5 MHz).

Ultrasound conditions	Microbubbles	Payload	Model	Ref.
3 MHz, 2 W/cm^2, 1 min, 3 MHz, 2 W/cm^2, 1 min	Unknown	siRNA TNF- α 1 nmol	Renal murine (C57BL/6 – GFP)	[50]
3 MHz, 2 W/cm^2, 1 min	SV-25 MBs	siRNA TNF- α 800 pmol	Dark agouti rat (DA/HanRj) collagen-induced arthritis	[51]
1.3 MHz, PW, 20 min	Optison	VEGF165 plasmid DNA 120 μg	Angiogenesis in Sprague Dawley rat myocardium	[52]
1.3 MHz, PW, 10 min every 5 s	Cationic lipid MBs	VEGF165 Plasmide DNA 500 μg	Chronically ischemic sprague-dawley rat skeletal muscle	[42]
1.3 MHz, PW, ECG triggered, 2 min	Optison	luciferase and β-Gal plasmid DNA 60 μg	Mouse myocardium (BALB/c)	[53]
1.3 MHz, PW, 20 min	Liposome MBs	luciferase plasmid DNA 600 μg	Wild-type lean Zucker rat myocardium	[54]
1.3 MHz, PW, 20 min	Optison and lipid MBs	Luciferase plasmid DNA 350 μg	Sprague-Dawley Rat myocardium	[55]
1.3 MHz	Optison	β-Gal Adenovirus 1.0×10^{10} pfu/mL	Wild-type lean Zucker rat myocardium	[56]
1.3 MHz, PW	Cationic lipid MBs	chloramphenicol acetyltransferase 6. 5 μg/kg	Closed-chest mongrel dog heart	[57]
1.6 MHz	Phospholipid MBs	HGF plasmid DNA 2 mg	Wistar rat myocard infarctus model	[58]
1.7 MHz, PW, 3 min/1.0 MHz, CW, 3 min	Optison	luciferase plasmid DNA 100 μg	C57BL/6 mice and 33 Sprague–Dawley rats	[59]
1.75 MHz, PW, pulse every 7 s for 15 min	Cationic lipid MBs	Luciferase plasmid DNA 20–100 μg	Sprague Dawley Rat limb	[60]
1.8 MHz, PW	Optison	VEGF121 plasmid DNA 2000 μg	Angiogenesis after myocardial infarction in Wisrtar rat model	[61]
1,8 MHz, CW, 45 s	Fluorocarbon	20×10^{-9} mol/L siRNA-Acid coated per-fluoropentane	A549 adenocarcinoma human	[62]
2 MHz, intensity 2.5 W/cm^2, 10 s	None	pCMV-GL3 and 3 μg siRNA 5 μg	African green monkey fibroblast cells (COS-7). Embryonic fibroblast cells (NIH3T3). Myoblast cells (C2C12).	[63]
2.2 MHz, CW, 30 s 1 MHz, 2.5 W/cm^2, 1 min	Optison	β-Gal and eNOS plasmid DNA 20 μg	Porcine coronary arteries	[64]
2.2 MHz, CW, 30 s	Optison	luciferase and β-Gal plasmid DNA 20 μg	Rat limb	[39]
3 MHz, 2 W/cm^2, 1 min	Unknown	siRNA TNF- α « amount not given»	Renal murine (BALB/c athymic)	[23]
3 MHz, 2 W/cm^2, 1 min	SV-25 MBs	siRNA TNF- α « amount not given»	Rat collagen-induced arthritis	[24]

BM-MNCs: Bone marrow-derived mononuclear cells; CAT: Chloramphenicol acetyltransferase; CW: Continuous Wave Doppler; EGFP: enhanced green fluorescent protein; GFP: Green fluorescent protein; HGF: Hepatocyte growth factor; LV: Left ventricle; MB: Microbubble; NB: Nanobubble; NO: Nitric oxide; PR: Pulse Repetition; PW: Pulsed wave doppler; siRNA: Small interfering RNA; TIMP: Metalloproteinase inhibitor; TNF: Tumor necrosis factor; US: Ultrasound; VEGF: Vascular endothelial growth factor.

3.1. Gene triggered release by non-thermal effects

Entrapped gene can be triggered release from magnetic responsive vehicles through non-thermal effect when exposed to low frequency or static fields. This application was developed based on the motion of MNPs under magnetic field causing mechanical deformation of the carriers which leads to the release of the loaded NAs [74,75]. Alginate, a natural polysaccharide, has been used for a long time in various biomedical applications especially in drug delivery systems. In 2010, Zhao et al. worked on an alginate ferrogel with adipic acid dihydrazide as covalent cross-linkers. These macroporous gel presented a hierarchical structure with 10 nm Fe_3O_4 NPs coated with pluronic F127 homogeneously distributed inside. The body force on MNPs caused by magnetic field gradient led to the motion of the particles and consequently the collapse of the pores in the gel visualized by the large and prompt deformation of the gel. When the pores collapsed, they generated a force on water in the pores to flow out of the gel strong enough to trigger the release of entrapped pDNA. In fact, a significant increase in the release of entrapped pDNA was obtained when magnetic field was applied compared to un-treated samples. Nevertheless, there was only <8% of encapsulated DNA released after 4 cycles of magnetic stimulation. One reason for this low DNA release can be the ionic interaction between

Table 3
Summary of studies on magnetically triggered release of nucleic acid.

Carriers	Payload	MNPs	Magnetic field	Results	Ref
Alginate ferrogels	pDNA	Fe_3O_4 10 nm	Gradient of ~38 A/m^2	8% *in vitro* DNA release	[67]
Poly(D,L lactic acid) based multi-reservoir devices and porous polycarbonate sealing membrane	DNA	Fe_3O_4 160–220 nm	0.15; 0.5; 0.8 T	Pulsatiled DNA release profile: about 4.5% of DNA released when apply magnetic field, compared to about 100% without magnetic field	[68]
N-isopropyl acrylamide -co-acrylamide hydrogel	siRNA	Fe_3O_4-PEG-diphosphate 80 nm	760 kHz, 9.6 kA/m	80% siRNA release	[69]
Nanocapsule based on copolymer PS_{16}-b-PAA_{10}	pDNA	Oleic coated Fe_3O_4	50 kHz; 0.8, 1.2, or 2.0 kA/m	Increased DNA release of up to 80%	[70]
Thermosensitive cationic liposome composed of DPPC, MSPC, DSPE- PEG_{2000}	siRNA	Fe_3O_4 10 nm	423 kHz, 10 kA/m	Increased siRNA delivery, and gene silencing: mRNA level decreased to 40%, cell apoptosis increased up to ~ 48% (only ~1% in control group). Inhibited tumor growth of ~2. times	[71]
Dextran-coated Fe_3O_4	DNA oligonucleotide	Amine-functionalized dextran-coated Fe_3O_4 50 nm	0.55–3 kW induction heater, 400 kHz (*in vitro*), 338 Hz (*in vivo*)	Increase DNA release *in vitro* and *in vivo:* up to 160 mM (<40 mM without magnetic field)	[72]
Gold coated MNPs	DNA	Fe_3O_4@Au 70 nm	800 W, 20–25 kHz	60–70% DNA release	[73]

DNA: Deoxyribonucleic acid; DPPC: 1,2-dipalmitoyl-snglycero- 3-phosphatidylcholine, DSPE-PEG_{2000}: 1,2-distearyl-sn-glycero-3-phosphoethanolamine-N- [methoxy (polyethyleneglycol)-2000], MNPs: magnetic nanoparticles; MSPC: monostearoylphosphatidyl-choline, pDNA: plasmid deoxyribonucleic acid; PEG: polyethylene glycol; PS_{16}-b-PAA_{10}: poly(styrene-*block*-allyl alcohol); siRNA: Small interfering ribonucleic acid.

carbonyl groups of alginate and amine groups of PEI used to condense pDNA before being entrapped into the gels. Therefore, further experiments should be performed to carry out the best conditions for the capture and release of DNA in ferrogels [67].

With the ability to move under magnetic field, MNPs can also be used as switchers for the release of substrates through the pores of porous carriers. In the work of Cai et al., polymeric multi-reservoir devices based on poly(D,L-lactic acid) as the biodegradable substrate and porous polycarbonate as the sealing membrane were developed. 196.1 nm-Fe_3O_4 NPs and DNA were loaded in the reservoirs. In this device, MNPs acted as a switcher which opened or closed the pores of the membrane, leading to switching on or off the release of entrapped DNA. Results showed that the release of DNA from the device have reversible pulsatile profile when alternatively exposing to a magnetic field for on/off state: only 4.5–4.6% of DNA released when apply magnetic field, compared to about 80–100% without magnetic field or with small amount of MNPs. Further studies on the controlled DNA release properties from this kind of devices should be performed on choosing size and concentration of the NPs and the magnetic field density and strength [68].

3.2. Gene triggered release by thermal effects

The heating effect of magnetic particles in an alternating magnetic field (AMF) is mainly due to hysteresis losses or relaxational losses. For magnetic particles with diameters of about 10 nm, the critical mechanism is the relaxation losses which are divided in two kinds: (i) Neel losses due to reorientation of the magnetic moment in a particle; and (ii) Brownian losses due to reorientation of the magnetic particle itself in the fluid. These mechanisms are both characterized by relaxation times which depend on particle and magnetic field properties [76]. It is illustrated that the heating potential and mechanism for energy deposition of MNPs in an AMF depend on the conditions of the applied AMF and the properties and concentration of the particles in the tissue [77]. Within a certain range, the heating potential can be improved by increasing the magnetic field strength and frequency. However, there is a limitation for the applied AMF, which above a certain level, can cause non-specific heating due to eddy currents in tissue. Therefore, guidelines for limiting exposure to magnetic and electromagnetic fields were published by the International Commission on Non-Ionizing Radiation Protection (ICNIRP) for a safe use of electromagnetic field. These guidelines were developed on the basis of laboratory studies of cellular, tissue, and animal systems exposed to electromagnetic fields in the frequency range of 100 kHz–300 GHz. They are applied for magnetic resonance imaging (MRI) but they can be translated into estimates of maximum allowable magnetic field amplitude and frequency product. According to them, the maximum magnetic field amplitude and frequency product to avoid damage to skin should be 8.1×10^7A/(m.s) at 13.56 MHz and 1.2×10^9A/(m.s) at 200 kHz [77].

Efficiency of magnetically responsive gene delivery system also depends on the development of thermoresponsive carriers which can be polymers, liposomes, dendrimers… MNPs are encapsulated in or decorated with cationic moieties which can easily make complexes with negatively charged DNA/RNA backbone. Magnetic field is then applied to remotely trigger the release of NA from the system (Fig. 2).

Thermoresponsive polymer based systems are one of the most well studied smart carriers for stimuli-responsive gene delivery system. These materials contain thermoresponsive units which exhibit phase transition at a specific temperature called lower critical solution temperature (LCST) [78]. Below this temperature, hydrogen bonds between hydrophilic parts and water molecules make them soluble in water. When the temperature is higher than LCST, due to the strengthening of the interaction between hydrophobic parts, the polymer will contract and be insoluble in water leading to the release of the entrapped gene. Magneto-sensitive gel based on N-isopropylacrylamide (NIPAAm) and acrylamide (AAm) containing MNPs was studied as a promising candidate [69]. This gel had LCST slightly above the body temperature (about 40 °C). In this work, hydrogels were constructed of two layers of poly(NIPAAm-*co*-AAm) with *N*,*N*′-methylenebisacrylamide as a cross-linker. 80 nm diameter-polyethylene glycol coated MNPs were added to the monomer solution before gelation. The results showed that almost all the siRNA was retained in the non-irradiated magnetite hydrogel while approximately 80% of the encapsulated siRNA was released 7 min after magnetic field application. Moreover, once the irradiation was stopped, siRNA was slowly released from the system by diffusion. When the magnetic field was applied again, the hydrogel started to collapse and rapidly release the encapsulated siRNA.

Many polymeric micro/nanoparticles such as polymeric micelles, polymersomes and nanocapsules also exhibit potential thermoresponsive properties for magnetic triggered applications [79–81]. Using double

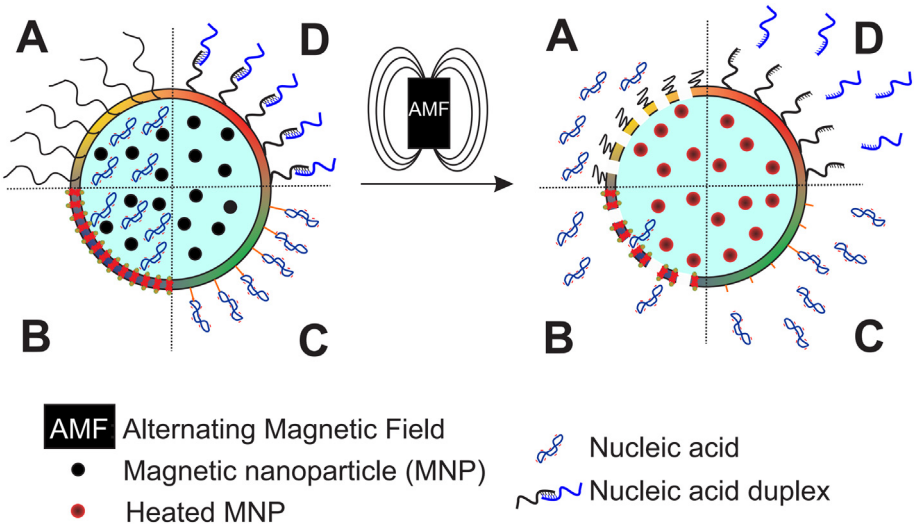

Fig. 2. Magnetically triggered gene release by thermal effect. (A) Nucleic acid and magnetic nanoparticles (MNPs) are entrapped in thermoresponsive polymer based vesicles. Below the lower critical solution temperature (LCST), the polymers are soluble, while above LCST the polymers collapse leading to the release of entrapped gene. (B) Nucleic acid and MNPs are entrapped in thermosensitive liposomes. When heated to above the transition temperature by MNPs under an external magnetic field, the phospholipid membrane undergoes a change in conformation and passes in liquid-crystal phase leading to the release of the entrapped gene. (C) Nucleic acids are decorated on the vesicles containing MNPs through thermosensitive linkers which are easily broken when heated. (D) Single nucleic acid strands were covalently attached to the vesicles containing MNPs, then the complement strand was added and formed duplex. When heated, they duplexes are dehybridized resulting in the release of the nucleic acid strands.

emulsion approach, Hu et al. prepared well dispersed and uniform nanocapsules of about 260 nm based on copolymer poly(styrene-*block*-allyl alcohol). pDNA was entrapped inside the water core of the nanocapsules with high efficiency. Meanwhile, oleic coated MNPs were trapped between the two copolymer layers. Without magnetic field, these systems showed a sustained drug release profile with only 7–25% of the encapsulated pDNA released after 2 days. A significant boost in the DNA release was obtained when high-frequency magnetic fields was applied, and the higher the magnetic field strength, the more DNA released. However, the effect on the nanocapsule structure depended on the magnetic strength. At lower magnetic strength (0.8 or 1.2 kA/m) the thermal effect did not influence the structure which meant that there was no DNA released after stopping the magnetic field. In opposite, when the field strength was set up at 2 kA/m, heat from MNPs led to permanent damages in the hydrophobic shell of the nanocapsules inducing a continuous release of DNA even in absence of magnetic field applied [70].

Another type of thermoresponsive carrier are thermosensitive liposomes, which are heat-trigger-based liposomes. In fact, all liposomes are inherently thermosensitive. All phospholipids are defined by their gel phase to fluid phase transition temperature (Tm). To be effective for drug or gene delivery, liposomes should be designed to have a Tm slightly above 37 °C. After the liposomes are targeted at the tumor site, local mild hyperthermia is applied to release the therapeutic agent. Yang et al. performed a study on thermal and magnetic dual-responsive liposomes composed of DPPC:MSPC: DSPE-PEG_{2000} encapsulating siRNA-CPPs and Fe_3O_4 MNPs. For higher translocation efficiency, cell-penetrating peptides (CPPs) were conjugated to siRNA before being encapsulated in the liposomes. The role of MNPs in this system was both liposome targeting agent and heating source. The siRNA-CPPs encapsulated liposomes had size of about 90 nm and encapsulation efficiency of approximately 87%. From *in vitro* experiments, they found that when activating the liposomes by AMF, higher cellular uptake efficiency, stronger cellular distribution, increased gene-silencing and apoptosis were obtained as compared to unactivated system. These results were also confirmed by *in vivo* studies where the most intense tumor distribution of siRNA and the best antitumor effect were found in mice treated with siRNA-CPPs magnetic liposomes exposed to AMF. These results suggest that this system can be potential for selective and efficient delivery of siRNA in cancer treatment [71].

Recently, NA conjugated on surface of inorganic NPs have been widely developed for triggered release purpose [82,83]. Liu et al. performed a novel strategy for remote-controlled release of DNA using AMF. In their work, 6-carboxyfluorescein-labeled diblock DNA were decorated on the surface of 70 nm-Fe_3O_4@Au NPs *via* the gold/adenine affinity. The latter was easily broken to release DNA because of heat released from MNPs when exposing to AMF. Under the magnetic field of 20–25 kHz, 800 W in 30 min, about 60–70% of associated DNA was released from the system. Until 800 W, the increase in the power of AMF led to a faster DNA release. However, this trend no longer existed when the power was increased from 800 to 1500 W. The magnetically responsive release behavior was still maintained in living cells [73].

NA can be remotely triggered from gene delivery system not only by breaking thermal responsive linker but also through dehybridization of the duplexes under stimuli of external agents like laser or magnetic field. With such strategy, Derfus et al. used superparamagnetic NPs as transducers to convert external electromagnetic energy at 400 Hz into heat to dehybridize complement NA strands. In this system, single DNA strands were covalently attached to the surface of NPs using 4-(*N*-Maleimidomethyl)cyclohexane-1-carboxylic acid 3-sulfo-N-hydroxysuccinimide ester sodium salt as the crosslinker, then the complement dye-labeled DNA strand was added and formed duplex through specific hydrogen bond (Watson-Crick interaction). Fluorescent DNA was released rapidly due to heat-induced dehybridization of the duplexes after being exposed to an AMF of 400 kHz, 1.25 kW for 5 min. When the field stopped, the fluorescence decreased due to the re-hybridization of the complement DNA strand. Interestingly, they found that the release property was also dependent on NA chain length and guanine-cytosine content. This renders possible the controlled release of multiple drug in the same system. *In vivo* study presented a significant growth in penetration depth of the fluorescent DNA into surrounding tissue under magnetic field application. Moreover, the distribution of MNPs was obtained by MRI. Based on all of these evidences, this kind of MNP-DNA conjugate can be a potential candidate for simultaneous diagnosis and remotely triggered release of therapeutic gene [72].

Beyond the application in cancer treatment and remotely triggered release, it has been pointed out that hyperthermia also has effects on the immune response due to enhancing antigen presentation, therefore increasing the activity of dendritic cells [84]. Moreover, it can also increase the recruitment of lymphocyte into tumor, make cancer cells more sensitive to lysis by NK or CD8+ cells [85]. Toraya-Brown et al. demonstrated that local hyperthermia treatment using iron oxide NPs and AMF induced CD8+ T cell – mediated resistance against distal and secondary tumors [86]. Taking advantage of various effect of MNPs, it could be promising to fabricate a multi-functional cancer treatment based on MNPs: target the system at tumor site, trigger release of entrapped gene and simultaneously induce hyperthermia under applying an AMF, and boost innate immunity.

4. Light triggered release

Photo-responsive release is a very popular on-demand gene release strategy thanks to its non-invasive property and ability to precisely control with regard to location, dose and time at which therapeutic genes are released.

Light spectrum used to trigger gene release ranges from ultraviolet (UV) (10–400 nm) to near infrared (NIR) regions (650–900 nm). Nevertheless, UV irradiation is more cytotoxic than other regions and can be absorbed by endogenous chromophores (such as hemoglobin, lipids and water) which prevent UV irradiation from penetrating into deep body tissue. On the other hand, NIR has excellent tissue penetration up to 10 cm and is more compatible with cells than UV and visible light [87].

Various nanocarriers have been studied for light-stimuli gene delivery, for example: polymeric NPs, cationic liposome, dendrimer, gold NPs… Besides, there are many approaches during the development of light-mediated gene delivery. They can be divided into three main categories: photochemical, photoisomerization, and photothermal triggers [88] (Fig. 3). Summary of works on light-triggered release of NA is proposed in Table 4.

4.1. Photochemical

Following this approach, genes are remotely triggered from gene delivery system when the covalent bonds which link genes and carriers are disrupted by light irradiation. Some common photoresponsive moieties such as: *o*-nitrobenzyl, coumarin-and pyrene-derivatives can be taken into account [108–110]. For example, 2-nitrobenzyl ester bond was used as a photolabile bridge to link a hydrophobic tail and a cationic head of an amphiphile which self-assembled into NPs. With a cationic shell, these NPs could make complexes with NA such as siRNA through electrostatic interactions. The loaded siRNA was controllably released from the system by applying an UV irradiation. Energy from UV light broke the ester bonds, therefore, leading to the degradation of the NPs of about 72% after 300 s of UV irradiation. Moreover, up to 50% of gene silencing effect was obtained after treating cells with the photosensitive NPs and UV irradiation. This value was significantly higher than that of the treated group without UV exposure (15%) [111]. In another work, UV light responsive 1-(2-nitrophenyl) ethanol (NPE) was used to prepare stimuli-responsive cationic lipids. These lipids self-assembled into cationic liposomes which could make complexes with

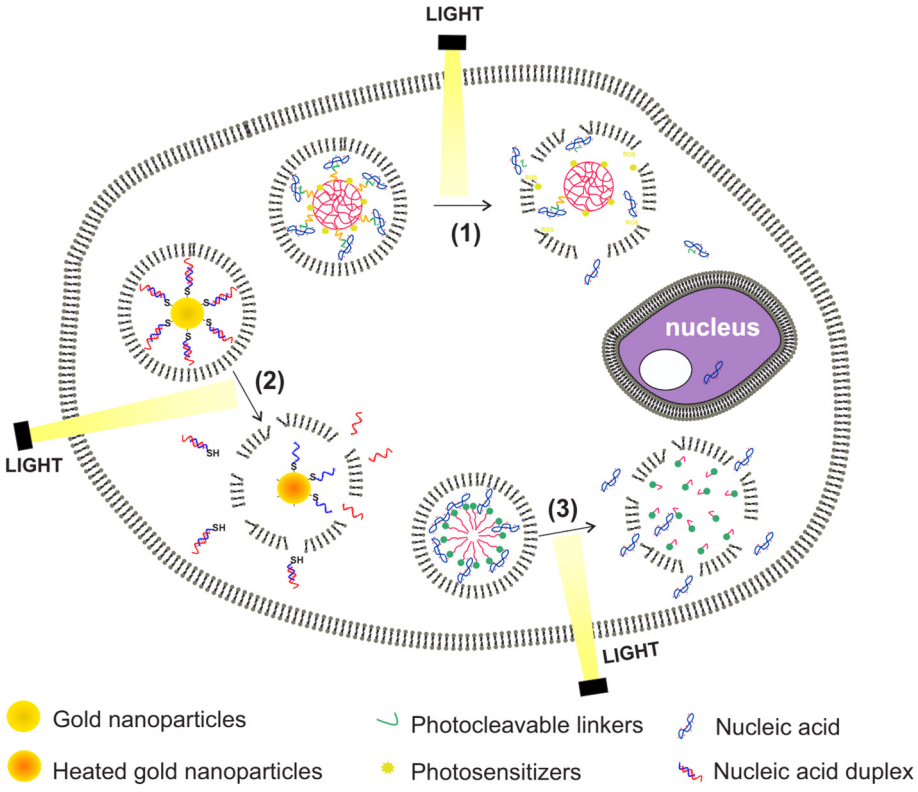

Fig. 3. Light triggered gene release through three main categories. (1) In photochemical approach, nucleic acids (NAs) interact with cationic moieties which are covalently connected to the vectors through photocleavable linkers. Upon light irradiation these links are broken leading to the release of NAs. These vesicles can also contain photosensitizers which generate reactive oxygen species upon exposing to light irradiation to disrupt endosome membrane. (2) In photothermal approach, NAs are covalently decorated onto photothermal agents (such as gold nanoparticles) through thermosensitive linkers. When light is applied, heat generated from the photothermal agents breaks the links or dehybridized the double strand NAs, resulting in the NAs release. (3) In photoisomerization approach, NAs are loaded into carriers containing materials which undergo a molecular structure change between isomers due to photoexcitation. The changes between isomers cause destabilization of the carriers to boost the release of NAs.

either DNA or siRNA. Under UV irradiation, the NPE protecting groups were cleaved to release carboxylate groups at the end of hydrophobic chain of lipids. As a result, the lipids were switched from cationic to neutral or negative charge which destabilizes the complexes resulting in NA release [90].

After reaching the target tissues, gene delivery systems are uptaken by the cells *via* endocytosis or other pathways (for example membrane fusion). In endocytic pathways, gene delivery systems are accumulated in the early endosomes (pH 6.3) and then the late endosomes (pH 5.5) before entering the lysosomes (pH 4.7) [112]. In this pathway, the therapeutic genes are at high risk of degradation instead of being transported to their site of action. Therefore, the entrapped gene must successfully escape from endosomes without degradation. Photoresponsive carriers are employed for this purpose through photochemical disruption of the endo/lysosomal membrane, termed photochemical internalization [93]. By conjugating a reactive oxygen species (ROS)-responsive linker with a photosensitizer, Yuan et al. observed a concurrent light-induced endo/lysosomal escape and DNA unpacking upon light irradiation. This design could be an effective tool for efficient gene delivery [94].

However, due to the drawbacks of UV light on live tissues, recently, NIR light has been employed in many photo-triggered release strategies thanks to its deeper penetration capacity and its lower damages to living cells. In this strategy upconversion NPs (UCNPs, which are usually composed of lanthanide- or actinide-doped transition metals) has been used. UCNPs absorb two or more low energy photons (usually NIR) and convert them into a photon at higher energy (UV to visible region) [113]. Yang et al. developed complexes between siRNA and synthesized Si-UCNPs functionalized by cationic photosensitive *o*-nitrobenzyl linkers. These linkers were cleaved by the upconverted UV light emitted from UCNPs upon 980 nm laser irradiation leading to significant siRNA release from the complexes. Gene silencing efficacy was also increased considerably in cells treated with si-UCNPs-siRNA followed by 2 h NIR light irradiation compared to the ones without light exposure [91]. Similarly, lanthanide-doped UCNPs coated with mesopourous silica were used to load siRNA and photosensitizer hypocrellin A (HA), and the obtained complexes were wrapped by polyethylene glycol (PEG) membrane through *o*-nitrobenzyl photocleavable linkers. When exposing to 980 nm irradiation, the UCNPs emit UV light which broke photocleavable linkers and blue emissions which activated HA to generate ROS. Therefore, by combining two photosensitive moieties, the on-demand siRNA release and endosomal escape could be achieved at the same time. This combination led to a significant enhancement in gene silencing and gene therapeutic efficacy [92].

NIR irradiation can also be used as a stimuli for endosomal escape. To accomplish this goal, photosensitizers have been developed. They can interact with endosomal membrane or produce ROS which destabilize endosomal membrane after exposing to NIR light. Park et al. prepared a photo-activatable ternary complex (PTC) consisting of multifunctional shielding material with photosensitizer-conjugated chondroitin sulfate and PEI based binary complexes containing epidermal growth factor receptor (EGFR)-shRNA delivery for CD44 targeted cancer therapy. Here, pheophorbide-a was used as a photosensitizer which disrupted the endosomal membrane by inducing ROS. The transfection efficiency of PTCs upon NIR irradiation was much higher than the one without light treatment. In addition, the authors found that when the laser irradiation power was above 0.5 J.cm^2, the higher the laser power, the lower the transfection efficiency. Furthermore, more shRNA diffusion and endosomal disruption were achieved after treating cells with the complexes and NIR light. As a result, there was an enhanced gene-silencing and toxic effect to cancer cells and significant tumor growth inhibition in complexes and laser treated groups [95].

Table 4
Key information of studies on light responsive gene delivery system.

Approaches	Vectors	Payload	Light sources	Key results	Ref
Photochemical	Cationic NPs based on UV-cleavable amphiphile (contain photolabile 2-nitrobenzyl bond)	siRNA	UV	Light-triggered siRNA release Enhanced gene silencing up to 50% after 300 s of UV irradiation	[89]
	Cationic liposomes based on lipids composed of either two different groups, Lysine–Glycine–Glycine (KGG) and Glycine–Glycine–Glycine (GGG) and three different hydrocarbon chain lengths (C6, C10, or C14) terminated by a UV light responsive 1-(2-nitrophenyl)ethanol (NPE) protected carboxylic acid	siRNA or DNA	UV	Stimuli responsive capture and release of nucleic acid: up to 55.1–62.9% of DNA or siRNA release after UV exposure	[90]
	Silica coated-UCNPs functionalized by cationic photosensitive o-nitrobenzyl linkers	siRNA	NIR	Enhanced siRNA release by about 2 folds Enhanced gene silencing by about 10 folds	[91]
	Mesopourous silica coated UCNPs covalently bound thin membranes of polyethylene glycol (PEG) *via* a photocleavable linker	siRNA	NIR	>80% of siRNA release after 5 cycles of 30-min intervals light exposure Down regulated mRNA and protein expression by 26.5% and 23.8% respectively	[92]
	Three-layered polyplex micelles composed of tri blocks copolymer PEG-PAsp(DET)-PLys, pDNA and dendrimer phthalocyanine	pDNA	Visible light	Endosomal escape Enhanced gene expression: ~44- and 88-fold higher gene expression (*in vitro*) Protein expression: ~4.4-fold higher fluorescence than the non-photo- irradiated tumor (*in vivo*)	[93]
	NPs based on ROS-responsive polymer p(TPECM-AA-OEI)-g-mPEG	pDNA	Visible light	Endosomal escape increased ~4 folds after 5 min of light exposureEnhanced transfection efficiency up to ~68%,	[94]
	MSM with PS-conjugated chondroitin sulfate and polyethyleneimine based binary complexes	EGFR-shRNA	NIR	Enhanced transfection efficiency by ~42,000 folds Endosomal escape Enhanced EGFR gene silencing: EGFR mRNA and protein level down to ~10% Reduced tumor growth of about 3 times	[95]
Photothermal	Temperature sensitive polymers (Y-shaped DNA hybrid, PEG corona with LCST at 39 °C and RGD shell with LCST at 43 °C) coated gold nanorods	siRNA	NIR	Enhanced gene silencing: knocked down protein to 29.4% and cell apoptotic ratio of 16.9%	[96]
	Tat peptide-lipid coated gold nanoshells	siRNA	NIR	Light-triggered gene release of 70% Endosomal escape Enhanced gene silencing to 80%	[97]
	Gold nanorods	DNA	NIR	Light induced shape transformation and DNA release of ~70% Localized gene expression	[98]
	Gold nanorods	DNA	NIR	Selective release of two distinct DNA from two different nanorods depending on laser wavelength, triggered DNA release up to 60–90%	[99]
	Gold nanorods	Oligonucleotide	NIR	Light-triggered release oligonucleotide Controlled gene silencing: protein level decreased by 55%	[100]
	Mesopourous silica coated gold nanorods	SiRNA	NIR	Light-triggered gene release and gene silencing	[101]
	Gold nanoshells or gold nanorods	DNA	NIR	Thermally triggered DNA release of 100% (nanorod) Thermally and non-thermally induced DNA release of 100% (nanoshell)	[102]
	41–57 nm Gold NPs	DNA	Visible light	Light-triggered DNA release of 20–90%	[103]
	Citrate-coated 16 nm Gold NPs	DNA	Visible light	Light-triggered DNA release up to 100% (depended on laser power)	[104]
	Lipid (DOTAP, DOPE, Cholesterol, PEG2000-DSPE) coated pDNA/TAT peptide modified gold NPs complexes	Cas9-sgPlk-1 plasmids	Visible light	Light-triggered DNA release of 79.4% 25.9% of cells underwent apoptosis compared to only 6.68% in control 65% down regulation of the Plk-1 protein compared to the control	[105]
	PEI-Chol modifed carbon nanotubes	TP53 plasmid	NIR	Light-triggered DNA release Enhanced gene expression of 7.3 or 4.5 times Increased apoptotic rate of cells of ~2.3 times and necrotic rate of ~4 times Reduced mice death ratio: 53.5% of mice still alive while 100% died in control group	[106]
Photo-isomerization	Catanionic system composed of photoresponsive azobenzene trimethylammonium bromide surfactant, sodium dodecylbenzenesulfonate or sodium dodecylsulfate	DNA	UV	Increased transfection efficiency up to ~40% (~20% without UV)	[107]

AA: aminoacrylate; DNA: Deoxyribonucleic acid; EGFR: epidermal growth factor receptor; MSM: multifunctional shielding material; NIR: near-infrared; NPs: nanoparticles; OEI: oligoethylenimine; PAsp(DET): poly(aspartamide) derivative with a 1,2-diaminoethane moiety; pDNA: plasmid deoxyribonucleic acid; PEG: polyethylene glycol; PEI-Chol: poly (ethylenimine)-cholesterol; PLys: poly(L-lysine); PS: photosensitizer; ROS: reactive oxygen species; shRNA: short hairpin ribonucleic acid; siRNA: Small interfering ribonucleic acid; TPECM: 2-(1-(4-(1,2,2-triphenylvinyl)phenyl)ethylidene)malononitrile; UCNPs: upconversion NPs; UV: ultraviolet.

4.2. Photothermal

In contrast to photochemical triggered release, in photothermal triggers, genes are released from gene delivery systems not directly by light irradiation but by the heat generated from photothermal agents upon light irradiation. A photothermally triggered gene delivery system is composed of two main parts: a chromophore (photothermal agent) which can convert light energy into thermal energy and thermoresponsive materials that exhibit changes upon temperature variations.

As mentioned in Part 3, thermoresponsive materials can be polymer, liposome, inorganic NPs… Besides, the most popular photothermal agents used in photothermally triggered gene delivery are gold NPs thanks to its manageable optical and photothermal properties depending on their size and shape. There are some common shapes of gold NPs: spheres, shells, hollow spheres and rods. Hollow nanospheres and nanoshells can convert light at different wavelengths ranging from visible to NIR by adjusting their size [114]. Meanwhile, nanorods seem to be more selective and effective than nanoshells [115], and nanorods can be reshaped into nanospheres upon exposure to laser [116,117].

An effective drug/gene delivery system for cancer treatment must be stable in the circulation, accumulate at site of action, and be selectively uptaken by tumor cells. Stealth NPs based on PEGylation are very popular for their long circulation time. However, the PEG layer on the surface of the NPs hinders the uptake of the NPs by cancer cells. For this reason, sheddable PEG coronas, which can change the surface state due to endogenous or exogenous stimuli have been employed. Zhang et al. performed smart gene delivery systems which are stealth, specifically uptaken by cancer cells and photo-responsive by combining many components in a particle. These smart nanocarriers were constructed with photoresponsive DNA Y-motifs as scaffolds to carry both Doxorubicin and siRNA, gold nanorods as a photothermal agent and temperature sensitive polymers whose surfaces could be switched between PEG and RGD (a tumor cell-targeting peptide) states *via* photothermal conversion. After accumulating at tumor tissue through enhanced permeability and retention effect, the systems were heated to 39 °C by the gold nanorods under mild NIR irradiation, resulted in the collapse of PEG coronas and therefore the exposure of RGD. After internalization, the NIR laser power was increased leading to an increase of temperature and consequently the switch from RGD- to Y-motif-surface state, when the loaded Doxorubicin and siRNA were released. This design is a promising tool for gene therapy [96].

NA is usually coated on the surface of gold NPs through Au—S link. For photothermally triggered strategy, this link is cleaved by either heat release from the NPs or hot electron interaction with the ligand [97,118]. Different from gold nanoshells, gold nanorods have a very interesting property that is shape transformation upon NIR irradiation. Taking advantage of this property, Chen et al. prepared conjugates between EGFP - a plasmid DNA, and gold nanorods through Au—S bond. Energy of the laser transforms a single nanorod into nearly spherical NPs. When treating cells with EGFP-gold nanorod conjugates, GFP expression was observed only in cells exposed to NIR irradiation [118]. Moreover, by using two different gold nanorods with different longitudinal surface plasmon resonance (SPR_{long}), Wijaya et al. obtained selective release of two distinct DNA strands from two different nanorods depending on laser wavelength [99].

Beside Au—S bond cleavage, another possible mechanism is thermal dehybridization of double-stranded NA. When exposing to NIR irradiation, the temperature of the gold NPs increases. When the temperature reaches the melting temperature of the double-stranded oligonucleotides, the antisense oligonucleotides are released [100,101]. In photoinduced dehybridization process, nonthermal mechanism can give some contribution. Due to laser irradiation, hot electrons from the NPs surface are transferred to the DNA, leading to the increase in the electrostatic repulsion between two DNA strands and therefore the dehybridization of the DNA [102]. In fact, there are many studies indicating that both Au—S bond cleavage and dehybridization contributed to the release of NA from the conjugation [103,104,118].

CRISPR/Cas9 system is a very powerful gene editing technology [119]. However, due to its large size, *in vivo* delivery of CRISPR/Cas9 system has been challenging. As a solution, plasmid encoding Cas9/sgRNA has been developed. Thermal responsive system can be a promising tool for effectively delivery of Cas9/sgRNA plasmid. Wang et al. designed complexes between Cas9-sgPlk-1 plasmids and Tat-AuNPs, then coated the complexes by lipids and PEG2000-DSPE. When exposed to 514 nm laser irradiation, the NPs acted as localized heat sources for pDNA release from the complexes. Photo-triggered DNA release led to significant enhancement in both gene knock-out and tumor inhibition compared to the non-irradiated group [105].

Recently, carbon nanotubes exhibited many unique properties which give much potential for development of novel gene delivery. Single-walled carbon nanotubes (SWNTs) can be wrapped with a cationic layer which makes conjugate with anionic DNA/siRNA. Kong et al. found that PEI-Cholesterol modifed SWNTs/pDNA was uptaken by cancer cells through caveolae-dependent pathway. Under NIR laser irradiation, the carbon nanotubes exhibited a photothermal conversion which promoted DNA release. This effect led to more apoptosis and necrosis of treated cells and higher tumor growth inhibition in comparison with the control groups [106].

4.3. Photoisomerization

Photoisomerization is the introduction of a molecular structure change between isomers due to photoexcitation. In gene delivery, reversible isomerization can lead to stabilization/destabilization of gene delivery system and therefore can be applied in photo-remotely triggered gene release. Azobenzene derivatives, for instance, are composed of two phenyl groups connected by N═N linkage which undergoes transition from *trans* to *cis* conformation upon UV light irradiation (300–400 nm). The transition process is reversed upon exposure to light irradiation at longer wavelength (above 400 nm) [120]. Based on this mechanism, photoresponsive catanionic vesicles composed of azobenzene trimethylammonium bromide cationic surfactant, anionic surfactant and EGFP DNA were prepared by Liu et al. In *trans* conformation, the cationic azobenzene-containing surfactants are relatively hydrophobic and self-assemble into vesicles which can establish stable complexes with DNA. Upon exposure to 350 nm UV light, the surfactants were converted into the relatively hydrophilic *cis* conformation, which destabilized the vesicles leading to DNA release. For cell transfection, UV irradiation exposure following endocytosis led to significant enhancement in the transfection efficiencies. Moreover, the authors also indicated that the structure and concentration of cationic and anionic surfactants were important parameters for the vesicles to make complexes with DNA and to be internalized by endocytosis [107].

5. Hypothermia triggered release

As mentioned in Part 3 and Part 4, thermosensitive materials can be used for remote-triggered release of NA. Besides release by hyperthermia, gene release by hypothermia can be developed based on a treatment called “cold-shock” (Fig. 4). In this strategy, thermosensitive polymers with LCST of lower than body temperature are employed. At temperature above LCST, they are collapsed so they form dense NPs which can encapsulate or complex with NA. When the temperature is reduced to lower than LCST, they are soluble in water and therefore increase the distance between core and shell, or increase the volume of particles leading to endosomal escape. PNIPAAm has been widely used thanks to its thermosensitive properties. To prolong circulation time, it was PEGylated. Yang et al. used PEG-PNIPAAm and 3β [N-(N′, *N*′-dimethylaminoethane)-carbamoyl] cholesterol to encapsulate siRNA at high encapsulation efficacy. At 37 °C, the complex size was about 200 nm with a spherical shape. When the temperature was below

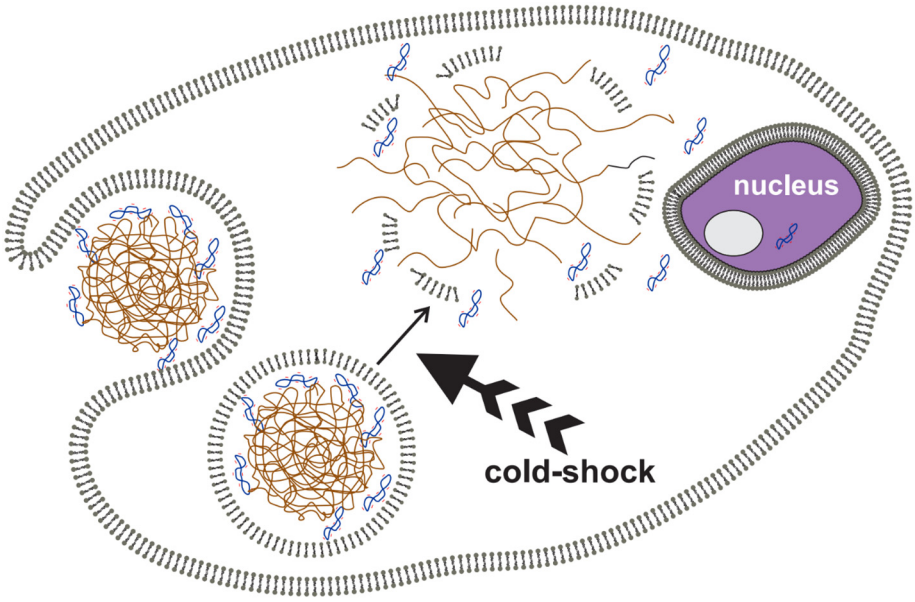

Fig. 4. Triggered gene release by "cold-shock". Thermosensitive polymer based nanoparticles are formed at temperature above the lower critical solution temperature (LCST) of the polymer, while at temperature below LCST, they expand, disrupt the endosome membrane and release the entrapped nucleic acids.

LCST, the polymer became water soluble and started to dissociate from the surface. *In vitro* release of siRNA was significant enhanced after treated by a 15 min cold shock at 4 °C. About 2.2 folds higher siRNA release after 7 days in cold-shock treated group was obtained compared to the control group. Moreover, a cold shock also significantly enhanced luciferase silencing efficiency [121].

The thermoresponsive conformation changes under cold-shock have also been developed for endosomal escape. By using pluronic/poly(ethylenimine) Lee et al. prepared thermally reversible volume expansion nanocapsules which are at collapse state and positively charged at 37 °C. SiRNA was conjugated on the surface of nanocapsules through electrostatic interaction. Immediately after endocytosis, a cold-shock treatment was applied. When the temperature was below LCST, the nanocapsules went through rapid volume expansion leading to endosomal membrane eruption. Gene silencing was greatly enhanced after a brief cold-shock treatment at 15 °C [122].

In fact, the cold-shock treatment seems to be efficient *in vitro* or *ex vivo* cell therapy, however, it is not easy to apply to practical *in vivo* and clinical uses. One possible application of hypothermia-triggered gene release is in cell based delivery. In this protocol, cells derived from human (stem cells, for example) could be treated with a brief cold shock after gene transfection. Then the modified cells are multiplied *in vitro* and readministrated to the patients.

6. Conclusion, challenges and perspectives

Mild Hyperthermia or therapeutic hyperthermia (40–42 °C) is already used in clinic to treat cancer, in particular peritoneal metastases using heated perfused chemotherapy, or hepatic metastases using radiofrequency. Combination therapy of hyperthermia with radiation therapy is currently being investigated in a phase I/II for soft tissue carcinoma of the limbs with a compatible magnetic field.

Magnetic resonance-guided focused ultrasound (MRg-FU) is also being investigated for the thermal treatment of cancer. In this technique, a transducer is specially designed to focus a beam of low intensity ultrasound energy at a specific target site in the body. Therapeutic hyperthermia is provided into a small volume by the focused ultrasound, while MR is used to provide real-time thermal mapping and delineate the tumor. The feasibility was proposed for soft tissue carcinomas, but unfortunately was withdrawn (Clinical trial NCT03007771). Interestingly, a first pilot study in rectal cancer was recently proposed (Clinical trial NCT02528175) to evaluate the feasibility in this cancer. Association of MR-HIFU with Doxil (liposomal doxorubicin) is also evaluated in phase I clinical trial for its safety for the treatment of pediatric and young adult patients with recurrent and refractory solid tumors (ClinicalTrial NCT02557854).

Iron oxide NPs and microbubbles have been used in clinic as imaging agents for cancer diagnosis. Magnetic thermoablation has also been proposed in a phase O to men with prostate cancer. The safety and location of escalating doses of iron oxide injection without heat was evaluated (NCT02033447), unfortunately no results were posted. If the NPs would not reach surrounding tissues, the next step would be to design the proper instrument to activate the NPs. One can easily sense that the main issue is to conceive instruments which will provide hyperthermia without any toxicity for the tissues.

Hyperthermia by itself is being investigated in broader applications as it can be read above, however, only one application to release drugs from a carrier has reached clinical trials. ThermoDox® is a thermosensitive liposome containing doxorubicin. The company Celsion reached with ThermoDox® phase I/II in combination with microwave in treatment of breast cancer [123], phase II as adjuvant therapy with thermal ablation (RFA) in colorectal cancer in the United States, and terminated a phase III in hepatocellular carcinoma with RFA in China. Among the main adverse effects, neutropenia and leukopenia were reported for 16.3 and 5.5% of the 354 people treated with liposome + RFA group as regard to 0% for sham + RFA. Feasibility of combining ultrasound-mediated hyperthermia with ThermoDox® was also shown [124].

Apart from the delivery of small molecules, the combined approach of hyperthermia with NA delivery systems has not reached the step of clinical trial, although, from all these literature reports that have been described in this review, one can easily see the potential of this approach. NAs more than other any molecules suffer from degradation, need protection and cell transfer, but also require an additional help to be released effectively from its carrier which should deliver its payload from an optimal transfection efficiency. Drug delivery systems reported have shown efficient *in vitro* profile, but rather low *in vivo* efficiency in preclinical studies, in particular due to the low amount of NA delivered to the target site. Combining triggered delivery to these delivery systems gives a clear improvement as reported in the present review. As mentioned above, with the development of many fields of science recently, numerous drawbacks of external triggered NA delivery

systems have been overcome. For example, the poor penetration depth of UV irradiation and the harmfulness of high laser power density were avoided by using photosensitizers that respond to higher wavelength irradiation or upconversion nanoparticles which can absorb two or more low energy photons (usually NIR) and convert them into a photon at higher energy (UV to visible region). Moreover, stability and passive targeting ability of microbubble can be enhanced by reducing its size from micro-size to nano-size (nanobubble) [125]. Meanwhile, cold-shock triggered NAs release could be further studied in *ex vivo* cell therapy, for example, thanks to its very interesting properties.

Targeting capacity of NA delivery systems is always a big obstacle. Many strategies using targeting agents such as aptamer, peptide, antibodies, or small molecules have been developed. Furthermore, multi-triggering strategy which combines external and internal stimuli responsive moieties can be applied for better specificity on tumor. The internal triggers are based on the difference between tumor tissue and normal tissue, therefore the cellular uptake and action of the system will be more specific on tumor cells. Cell internalization can also be enhanced by not only using cell-penetrating peptide but also uncaging the protecting groups (like PEG) or changing surface charge of the system at lower pH. Such kinds of delivery system were reported in the literature for drug delivery [126–129], and could also be promising for NA delivery.

Combination of multiple functional groups in one system should be an ideal strategy, work of Zhang et al. [96] is a good example. This system was composed of PEG – a stealth coating for prolonging circulation time, RGD – a tumor cell targeting peptide for tumor selectivity, and light responsive material. The unique of this system is that the action of each component is controlled at each stage. At first, PEG layer was expand to protect the system from opsonization during circulation time. When it reached tumor tissue, PEG layer was collapsed to present the targeting agent RGD. Finally, after internalization, both PEG and RGD were contracted to expose the active agent which then was triggered released under action of laser. Further studies on this kind of strategy should be explored and transferred to clinical trials.

The limited translation of stimulus triggering NA delivery system from preclinical to clinical trial can be explained by their complexity in large-scale manufacture, reproducibility and quality control. The difficulty in upgrading the stimulus condition from *in vitro* experiment to clinical practice is also a big challenge. At least three parts should be improved in order to find the way to high NA expression. First, drug delivery systems should be designed to be good responders to the trigger. Second, equipment should be adapted to trigger drug delivery for preclinical and clinical studies. Last, crucial information are still missing on the level of energy required to deliver the NA. Cellular or/and nuclear membranes should be destabilized transiently without toxicity. The variation between patients must be examined to develop personalized triggered release NA delivery system. Moreover, when set up a clinical trial, patient compliance should be considered. Advances on these most important points will help gaining a step towards transfer of NA delivery systems.

Conflict of interest

The authors declare no conflict of interest in the publication of this work.

Acknowledgement

This project has received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No 665850.

References

[1] K. Sridharan, N.J. Gogtay, Therapeutic nucleic acids: current clinical status, Br. J. Clin. Pharmacol. (2016) 659–672, https://doi.org/10.1111/bcp.12987.
[2] S.L. Ginn, A.K. Amaya, I.E. Alexander, M. Edelstein, M.R. Abedi, Gene therapy clinical trials worldwide to 2017 - an update, J. Gene Med. (2018), e3015. https://doi.org/10.1002/jgm.3015.
[3] S. Ylä-Herttuala, Endgame: Glybera finally recommended for approval as the first gene therapy drug in the European union, Mol. Ther. 20 (2012) 1831–1832, https://doi.org/10.1038/mt.2012.194.
[4] C. Chakraborty, A.R. Sharma, G. Sharma, C.G.P. Doss, S.S. Lee, Therapeutic miRNA and siRNA: moving from Bench to Clinic as Next Generation Medicine, Mol. Ther. - Nucleic Acids. 8 (2017) 132–143, https://doi.org/10.1016/j.omtn.2017.06.005.
[5] A.M. Keeler, M.K. Elmallah, T.R. Flotte, Gene therapy 2017: Progress and future directions, Clin. Transl. Sci. 10 (2017) 242–248, https://doi.org/10.1111/cts.12466.
[6] M. Riley, W. Vermerris, Recent advances in Nanomaterials for Gene Delivery—a Review, Nano 7 (2017) 94, https://doi.org/10.3390/nano7050094.
[7] C.E. Thomas, A. Ehrhardt, M.A. Kay, Progress and problems with the use of viral vectors for gene therapy, Nat. Rev. Genet. 4 (2003) 346–358, https://doi.org/10.1038/nrg1066.
[8] D. Ibraheem, A. Elaissari, H. Fessi, Gene therapy and DNA delivery systems, Int. J. Pharm. 459 (2014) 70–83, https://doi.org/10.1016/j.ijpharm.2013.11.041.
[9] S. Bibi, E. Lattmann, A.R. Mohammed, Y. Perrie, Trigger release liposome systems: local and remote controlled delivery? J. Microencapsul. 29 (2012) 262–276, https://doi.org/10.3109/02652048.2011.646330.
[10] H.X. Wang, X.Z. Yang, C.Y. Sun, C.Q. Mao, Y.H. Zhu, J. Wang, Matrix metalloproteinase 2-responsive micelle for siRNA delivery, Biomaterials 35 (2014) 7622–7634, https://doi.org/10.1016/j.biomaterials.2014.05.050.
[11] J.L. Wike-Hooley, J. Havemann, H.S. Reinhold, The relevance of tumor pH to the treatment of malignant disease, Radiother. Oncol. 2 (1984) 343–366, https://doi.org/10.1007/978-3-658-09837-7.
[12] M. Sun, K. Wang, D. Oupický, Advances in stimulus-responsive polymeric materials for systemic delivery of nucleic acids, Adv. Healthc. Mater. 7 (2018) 1–17, https://doi.org/10.1002/adhm.201701070.
[13] L. Du, J. Zhou, L. Meng, X. Wang, C. Wang, Y. Huang, S. Zheng, L. Deng, H. Cao, Z. Liang, A. Dong, Q. Cheng, The pH-triggered triblock nanocarrier enabled highly efficient siRNA delivery for cancer therapy, Theranostics. 7 (2017) 3432–3445, https://doi.org/10.7150/thno.20297.
[14] V.P. Torchilin, Multifunctional, stimuli-sensitive nanoparticulate systems for drug delivery, Nat. Rev. Drug Discov. 13 (2014) 813–827, https://doi.org/10.1038/nrd4333.
[15] L. Zhang, Y. Zhang, Z. Chen, Y. He, Intracellular redox-responsive nanocarrier for plasmid delivery: in vitro characterization and in vivo studies in mice, Int. J. Nanomedicine 11 (2016) 5245–5256, https://doi.org/10.2147/IJN.S94995.
[16] M.S. Shim, Y.J. Kwon, Stimuli-responsive polymers and nanomaterials for gene delivery and imaging applications, Adv. Drug Deliv. Rev. 64 (2012) 1046–1059, https://doi.org/10.1016/j.addr.2012.01.018.
[17] W.G. Pitt, G.A. Husseini, B.J. Staples, Ultrasonic drug delivery–a general review, Expert Opin. Drug Deliv. 1 (2004) 37–56, https://doi.org/10.1517/17425247.1.1.37.
[18] S. Mullick Chowdhury, T. Lee, J.K. Willmann, Ultrasound-guided drug delivery in cancer, Ultrason. (Seoul, Korea). 36 (2017) 171–184, https://doi.org/10.14366/usg.17021.
[19] B. Hildebrant, P. Wust, O. Ahlers, A. Dieing, G. Sreenivasa, T. Kerner, R. Feliz, H. Riess, The cellular and molecular basis of hyperthermia, Crit. Rev. Oncol. Hematol. 43 (2002) 33–56.
[20] A.S. Song, A.M. Najjar, K.R. Diller, Thermally induced apoptosis, necrosis, and heat shock protein expression in 3D culture, J. Biomech. Eng. 136 (2014), 071006. https://doi.org/10.1115/1.4027272.
[21] C.D. Arvanitis, M. Bazan-Peregrino, B. Rifai, L.W. Seymour, C.C. Coussios, Cavitation-enhanced extravasation for drug delivery, Ultrasound Med. Biol. 37 (2011) 1838–1852, https://doi.org/10.1016/j.ultrasmedbio.2011.08.004.
[22] A. Partanen, M. Tillander, P.S. Yarmolenko, B.J. Wood, M.R. Dreher, M.O. Köhler, Reduction of peak acoustic pressure and shaping of heated region by use of multifoci sonications in MR-guided high-intensity focused ultrasound mediated mild hyperthermia, Med. Phys. 40 (2013) 1–13, https://doi.org/10.1118/1.4769116.
[23] S. Tardoski, J. Ngo, E. Gineyts, J.P. Roux, P. Clézardin, D. Melodelima, Low-intensity continuous ultrasound triggers effective bisphosphonate anticancer activity in breast cancer, Sci. Rep. 5 (2015) 1–15, https://doi.org/10.1038/srep16354.
[24] J.O. Eloy, R. Petrilli, R.F.V. Lopez, R.J. Lee, Stimuli-responsive nanoparticles for siRNA delivery, Curr. Pharm. Des. 21 (2015) 4131–4144, https://doi.org/10.2174/1381612821666150901095349.
[25] P.A. Dijkmans, L.J.M. Juffermans, R.J.P. Musters, A. van Wamel, F.J. ten Cate, W. van Gilst, C.A. Visser, N. de Jong, O. Kamp, Microbubbles and ultrasound: from diagnosis to therapy, Eur. J. Echocardiogr. 5 (2004) 245–256, https://doi.org/10.1016/j.euje.2004.02.001.
[26] S. Tsunoda, O. Mazda, Y. Oda, Y. Iida, S. Akabame, T. Kishida, M. Shin-Ya, H. Asada, S. Gojo, J. Imanishi, H. Matsubara, T. Yoshikawa, Sonoporation using microbubble BR14 promotes pDNA/siRNA transduction to murine heart, Biochem. Biophys. Res. Commun. 336 (2005) 118–127, https://doi.org/10.1016/j.bbrc.2005.08.052.
[27] T. Li, K. Tachibana, M. Kuroki, M. Kuroki, Gene transfer with echo-enhanced contrast agents: comparison between Albunex, Optison, and Levovist in mice–initial results, Radiology 229 (2003) 423–428, https://doi.org/10.1148/radiol.2292020500.
[28] Y.H. Li, Q.S. Shi, J. Du, L.F. Jin, F. Du, P.F. Liu, Y.R. Duan, Targeted delivery of biodegradable nanoparticles with ultrasound-targeted microbubble destruction-mediated hVEGF-siRNA transfection in human PC-3 cells in vitro, Int. J. Mol. Med. 31 (2013) 163–171.
[29] Q.L. Lu, H.D. Liang, T. Partridge, M.J.K. Blomley, Microbubble ultrasound improves the efficiency of gene transduction in skeletal muscle in vivo with reduced tissue damage, Gene Ther. 10 (2003) 396–405, https://doi.org/10.1038/sj.gt.3301913.

[30] S. Manta, G. Renault, A. Delalande, O. Couture, I. Lagoutte, J. Seguin, F. Lager, P. Houzé, P. Midoux, M. Bessodes, D. Scherman, M.F. Bureau, C. Marie, C. Pichon, N. Mignet, Cationic microbubbles and antibiotic-free miniplasmid for sustained ultrasound–mediated transgene expression in liver, J. Control. Release 262 (2017) 170–181, https://doi.org/10.1016/j.jconrel.2017.07.015.

[31] S. Yang, K. Tang, W. Bai, Y.-W. Zhao, E. Shen, J. Tao, B. Hu, Combined low-frequency ultrasound and microbubble contrast agent for the treatment of benign prostatic hyperplasia, J. Endourol. 27 (2013) 1020–1026, https://doi.org/10.1089/end.2012.0637.

[32] Z. Izadifar, P. Babyn, D. Chapman, Mechanical and biological effects of ultrasound: a review of present knowledge, Ultrasound Med. Biol. 43 (2017) 1085–1104, https://doi.org/10.1016/j.ultrasmedbio.2017.01.023.

[33] C.R. Mayer, N.A. Geis, H.A. Katus, R. Bekeredjian, Ultrasound Targeted Microbubble Destruction for Drug and Gene Delivery, 2008.

[34] S.-H. Cheon, K.-H. Lee, J.-Y. Kwon, S.-H. Choi, M.-N. Song, D.-I. Kim, Enhanced delivery of siRNA complexes by sonoporation in transgenic rice cell suspension cultures, J. Microbiol. Biotechnol. 19 (2009) 781–786, https://doi.org/10.4014/jmb.0901.057.

[35] A. Lawrie, A.F. Brisken, S.E. Francis, D.C. Cumberland, D.C. Crossman, C.M. Newman, Microbubble-enhanced ultrasound for vascular gene delivery, Gene Ther. 7 (2000) 2023–2027, https://doi.org/10.1038/sj.gt.3301339.

[36] M. Bai, M. Shen, Y. Teng, Y. Sun, F. Li, X. Zhang, Y. Xu, Y. Duan, L. Du, Enhanced therapeutic effect of Adriamycin on multidrug resistant breast cancer by the ABCG2-siRNA loaded polymeric nanoparticles assisted with Ultrasound, Oncotarget 6 (2015)https://doi.org/10.18632/oncotarget.6085.

[37] X. Zheng, P. Ji, J. Hu, Sonoporation using microbubbles promotes lipofectamine - mediated siRNA transduction to rat retina, Bosn. J. Basic Med. Sci. 11 (2011) 147–152.

[38] T. Sakai, M. Kawaguchi, Y. Kosuge, SiRNA-mediated gene silencing in the salivary gland using in vivo microbubble-enhanced sonoporation, Oral Dis. 15 (2009) 505–511, https://doi.org/10.1111/j.1601-0825.2009.01579.x.

[39] Q. Shi, P. Liu, Y. Sun, H. Zhang, J. Du, F. Li, L. Du, Y. Duan, SiRNA delivery mediated by copolymer nanoparticles, phospholipid stabilized Sulphur hexafluoride microbubbles and ultrasound, J. Biomed. Nanotechnol. 10 (2014) 436–444, https://doi.org/10.1166/jbn.2014.1728.

[40] 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.

[41] R.E. Vandenbroucke, I. Lentacker, J. Demeester, S.C. De Smedt, N.N. Sanders, Ultrasound assisted siRNA delivery using PEG-siPlex loaded microbubbles, J. Control. Release 126 (2008) 265–273, https://doi.org/10.1016/j.jconrel.2007.12.001.

[42] Y. Taniyama, K. Tachibana, K. Hiraoka, T. Namba, K. Yamasaki, N. Hashiya, M. Aoki, T. Ogihara, K. Yasufumi, R. Morishita, Local delivery of plasmid DNA into rat carotid artery using ultrasound, Circulation 105 (2002) 1233–1239, https://doi.org/10.1161/hc1002.105228.

[43] N. Hashiya, M. Aoki, K. Tachibana, Y. Taniyama, K. Yamasaki, K. Hiraoka, H. Makino, K. Yasufumi, T. Ogihara, R. Morishita, Local delivery of E2F decoy oligodeoxynucleotides using ultrasound with microbubble agent (Optison) inhibits intimal hyperplasia after balloon injury in rat carotid artery model, Biochem. Biophys. Res. Commun. 317 (2004) 508–514, https://doi.org/10.1016/j.bbrc.2004.03.070.

[44] J.M. Erikson, G.L. Freeman, B. Chandrasekar, Ultrasound-targeted antisense oligonucleotide attenuates ischemia/reperfusion-induced myocardial tumor necrosis factor-alpha, J. Mol. Cell. Cardiol. 35 (2003) 119–130, https://doi.org/10.1016/S0022-2828(02)00289-4.

[45] S. Tsunoda, O. Mazda, Y. Oda, Y. Iida, S. Akabame, T. Kishida, M. Shin-Ya, H. Asada, S. Gojo, J. Imanishi, H. Matsubara, T. Yoshikawa, Sonoporation Using Microbubble BR14 Promotes pDNA/siRNA Transduction to Murine heart, 336, 2005 118–127, https://doi.org/10.1016/j.bbrc.2005.08.052.

[46] M. Iwasaki, Y. Adachi, T. Nishiue, K. Minamino, Y. Suzuki, Y. Zhang, K. Nakano, Y. Koike, J. Wang, H. Mukaide, S. Taketani, F. Yuasa, H. Tsubouchi, E. Gohda, T. Iwasaka, S. Ikehara, Hepatocyte growth factor delivered by ultrasound-mediated destruction of microbubbles induces proliferation of cardiomyocytes and amelioration of left ventricular contractile function in doxorubicin-induced cardiomyopathy, Stem Cells 23 (2005) 1589–1597, https://doi.org/10.1634/stemcells.2005-0049.

[47] E.F. Akowuah, C. Gray, A. Lawrie, P.J. Sheridan, C.H. Su, T. Bettinger, A.F. Brisken, J. Gunn, D.C. Crossman, S.E. Francis, A.H. Baker, C.M. Newman, Ultrasound-mediated delivery of TIMP-3 plasmid DNA into saphenous vein leads to increased lumen size in a porcine interposition graft model, Gene Ther. 12 (2005) 1154–1157, https://doi.org/10.1038/sj.gt.3302498.

[48] K. Zen, M. Okigaki, Y. Hosokawa, Y. Adachi, Y. Nozawa, M. Takamiya, T. Tatsumi, N. Urao, K. Tateishi, T. Takahashi, H. Matsubara, Myocardium-targeted delivery of endothelial progenitor cells by ultrasound-mediated microbubble destruction improves cardiac function via an angiogenic response, J. Mol. Cell. Cardiol. 40 (2006) 799–809, https://doi.org/10.1016/j.yjmcc.2006.03.012.

[49] R. Zhao, X. Liang, B. Zhao, M. Chen, R. Liu, S. Sun, X. Yue, S. Wang, Ultrasound Assisted Gene and Photodynamic Synergistic Therapy with Multifunctional FOXA1-siRNA Loaded Porphyrin Microbubbles for Enhancing Therapeutic Efficacy for Breast Cancer, vol. 173, 2018 58–70.

[50] R. Ishida, D. Kami, T. Kusaba, Y. Kirita, T. Kishida, O. Mazda, T. Adachi, S. Gojo, Kidney-specific sonoporation-mediated gene transfer, Mol. Ther. 24 (2016) 125–134, https://doi.org/10.1038/mt.2015.171.

[51] H. Inoue, Y. Arai, T. Kishida, M. Shin-Ya, R. Terauchi, S. Nakagawa, M. Saito, S. Tsuchida, A. Inoue, T. Shirai, H. Fujiwara, O. Mazda, T. Kubo, Sonoporation-mediated transduction of siRNA ameliorated experimental arthritis using 3 MHz pulsed ultrasound, Ultrasonics 54 (2014) 874–881, https://doi.org/10.1016/j.ultras.2013.10.021.

[52] G. Korpanty, S. Chen, R.V. Shohet, J. Ding, B. Yang, P.A. Frenkel, P.A. Grayburn, Targeting of VEGF-mediated angiogenesis to rat myocardium using ultrasonic destruction of microbubbles, Gene Ther. 12 (2005) 1305–1312, https://doi.org/10.1038/sj.gt.3302532.

[53] D.-P. Guo, X.-Y. Li, P. Sun, Z.-G. Wang, X.-Y. Chen, Q. Chen, L.-M. Fan, B. Zhang, L.-Z. Shao, X.-R. Li, Ultrasound/microbubble enhances foreign gene expression in ECV304 cells and murine myocardium, Acta Biochim. Biophys. Sin. Shanghai 36 (2004) 824–831.

[54] S. Chen, R.V. Shohet, R. Bekeredjian, P. Frenkel, P.A. Grayburn, Optimization of ultrasound parameters for cardiac gene delivery of adenoviral or plasmid deoxyribonucleic acid by ultrasound-targeted microbubble destruction, J. Am. Coll. Cardiol. 42 (2003) 301–308, https://doi.org/10.1016/S0735-1097(03)00627-2.

[55] R. Bekeredjian, S. Chen, P.A. Frenkel, P.A. Grayburn, R.V. Shohet, Ultrasound-targeted microbubble destruction can repeatedly direct highly specific plasmid expression to the heart, Circulation 108 (2003) 1022–1026, https://doi.org/10.1161/01.CIR.0000084535.35435.AE.

[56] R.V. Shohet, S. Chen, Y.T. Zhou, Z. Wang, R.S. Meidell, R.H. Unger, P.A. Grayburn, Echocardiographic destruction of albumin microbubbles directs gene delivery to the myocardium, Circulation 101 (2000) 2554–2556, https://doi.org/10.1161/01.CIR.101.22.2554.

[57] M. Vannan, T. McCreery, P. Li, Z. Han, E. Unger, B. Kuersten, E. Nabel, S. Rajagopalan, Ultrasound-mediated transfection of canine myocardium by intravenous administration of cationic microbubble-linked plasmid DNA, J. Am. Soc. Echocardiogr. 15 (2002) 214–218, https://doi.org/10.1067/mje.2002.119913.

[58] X. Li, Z. Wang, H. Ran, X. Li, Experimental Research on Therapeutic Angiogenesis Induced by Hepatocyte Growth Factor Directed by Ultrasound-Targeted Microbubble Destruction in Rats, 2008 453–460.

[59] J.P. Christiansen, B.A. French, A.L. Klibanov, S. Kaul, J.R. Lindner, Targeted tissue transfection with ultrasound destruction of plasmid-bearing cationic microbubbles, Ultrasound Med. Biol. 29 (2003) 1759–1767, https://doi.org/10.1016/S0301-5629(03)00976-1.

[60] S.V. Pislaru, C. Pislaru, R.R. Kinnick, R. Singh, R. Gulati, J.F. Greenleaf, R.D. Simari, Optimization of ultrasound-mediated gene transfer: Comparison of contrast agents and ultrasound modalities, Eur. Heart J. 24 (2003) 1690–1698, https://doi.org/10.1016/S0195-668X(03)00469-X.

[61] W. Zhigang, L. Zhiyu, R. Haitao, R. Hong, Z. Qunxia, H. Ailong, L. Qi, Z. Chunjing, T. Hailin, G. Lin, P. Mingli, P. Shiyu, Ultrasound-mediated microbubble destruction enhances VEGF gene delivery to the infarcted myocardium in rats, Clin. Imaging 28 (2004) 395–398, https://doi.org/10.1016/j.clinimag.2004.04.003.

[62] 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. Healthc. Mater. 6 (2017) 1–9, https://doi.org/10.1002/adhm.201601246.

[63] Y. Negishi, Y. Endo, T. Fukuyama, R. Suzuki, T. Takizawa, D. Omata, K. Maruyama, Y. Aramaki, Delivery of siRNA into the cytoplasm by liposomal bubbles and ultrasound, J. Control. Release 132 (2008) 124–130, https://doi.org/10.1016/j.jconrel.2008.08.019.

[64] C. Teupe, S. Richter, B. Fisslthaler, V. Randriamboavonjy, C. Ihling, I. Fleming, R. Busse, A.M. Zeiher, S. Dimmeler, Vascular gene transfer of phosphomimetic endothelial nitric oxide synthase (S1177D) using ultrasound-enhanced destruction of plasmid-loaded microbubbles improves vasoreactivity, Circulation 105 (2002) 1104–1109, https://doi.org/10.1161/hc0902.104720.

[65] P. Rüschmann, Radiofrequency penetration and absorption in the human body: Limitations to high field whole body nuclear magnetic resonance imaging, Med. Phys. 14 (1987) 922–931, https://doi.org/10.1118/1.595995.

[66] D.S.T. Hsieh, R. Langer, J. Folkman, Magnetic modulation of release of macromolecules from polymers (sustained release/drug delivery system/diabetes/hormones/controlled release), Med. Sci. 78 (1981) 1863–1867.

[67] X. Zhao, J. Kim, C.A. Cezar, N. Huebsch, K. Lee, K. Bouhadir, D.J. Mooney, Active scaffolds for on-demand drug and cell delivery, Proc. Natl. Acad. Sci. 108 (2011) 67–72, https://doi.org/10.1073/pnas.1007862108.

[68] K. Cai, Z. Luo, Y. Hu, X. Chen, Y. Liao, L. Yang, L. Deng, Magnetically triggered reversible controlled drug delivery from microfabricated polymeric multireservoir devices, Adv. Mater. 21 (2009) 4045–4049, https://doi.org/10.1002/adma.200900593.

[69] M. Babincova, J. Novotny, J. Rosenecker, P. Babinec, Remote radio-control of siRNA release from magnetite-hydrogel composite, Optoelectron. Adv. Mater. Commun. 1 (2007) 644–647.

[70] S.-H. Hu, S.-Y. Chen, X. Gao, Multifunctional nanocapsules for simultaneous encapsulation of hydrophilic and hydrophobic compounds and on-demand release, ACS Nano 6 (2012) 2558–2565, https://doi.org/10.1021/nn205023w.

[71] Y. Yang, X. Xie, X. Xu, X. Xia, H. Wang, L. Li, W. Dong, P. Ma, Y. Yang, Y. Liu, X. Mei, Thermal and magnetic dual-responsive liposomes with a cell-penetrating peptide-siRNA conjugate for enhanced and targeted cancer therapy, Colloids Surfaces B Biointerfaces. 146 (2016) 607–615, https://doi.org/10.1016/j.colsurfb.2016.07.002.

[72] A.M. Derfus, G. Von Maltzahn, T.J. Harris, T. Duza, K.S. Vecchio, E. Ruoslahti, S.N. Bhatia, Remotely triggered release from magnetic nanoparticles, Adv. Mater. 19 (2007) 3932–3936, https://doi.org/10.1002/adma.200700091.

[73] M. Liu, Z. Wang, S. Zong, H. Chen, D. Zhu, Y. Zhong, Y. Cui, Remote-controlled DNA release from Fe3O4@Author has rejected a copyediting change here. "A" is retained. Author has rejected a copyediting change here. "a" is deleted.u nanoparticles using an alternating electromagnetic field, J. Biomed. Nanotechnol. 11 (2015) 979–987, https://doi.org/10.1166/jbn.2015.2013.

[74] J. Qin, I. Asempah, S. Laurent, A. Fornara, R.N. Muller, M. Muhammed, Injectable superparamagnetic ferrogels for controlled release of hydrophobic drugs, Adv. Mater. 21 (2009) 1354–1357, https://doi.org/10.1002/adma.200800764.

[75] 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 multi-component nanochain with radiofrequency-tunable drug release, ACS Nano 6 (2012) 4157–4168, https://doi.org/10.1021/nn300652p.

[76] C.L. Dennis, R. Ivkov, Physics of heat generation using magnetic nanoparticles for hyperthermia, Int. J. Hyperth. 29 (2013) 715–729, https://doi.org/10.3109/02656736.2013.836758.

[77] B. Kozissnik, A.C. Bohorquez, J. Dobson, C. Rinaldi, Magnetic fluid hyperthermia: advances, challenges, and opportunity, Int. J. Hyperth. 29 (2013) 706–714, https://doi.org/10.3109/02656736.2013.837200.

[78] C. Gong, T. Qi, X. Wei, Y. Qu, Q. Wu, F. Luo, Z. Qian, Thermosensitive polymeric hydrogels as drug delivery systems, Curr. Med. Chem. 20 (2013) 79–94.

[79] A. Monsalve, A.C. Bohorquez, C. Rinaldi, J. Dobson, Remotely triggered activation of TGF- with magnetic nanoparticles, IEEE Magn. Lett. 6 (2015) 1–4, https://doi.org/10.1109/LMAG.2015.2477271.

[80] J.-P. Chen, C.-H. Liu, H.-L. Hsu, T. Wu, Y.-J. Lu, Y.-H. Ma, Magnetically controlled release of recombinant tissue plasminogen activator from chitosan nanocomposites for targeted thrombolysis, J. Mater. Chem. B 4 (2016) 2578–2590, https://doi.org/10.1039/C5TB02579F.

[81] P.V. Finotelli, D. Da Silva, M. Sola-Penna, A.M. Rossi, M. Farina, L.R. Andrade, A.Y. Takeuchi, M.H. Rocha-Leão, Microcapsules of alginate/chitosan containing magnetic nanoparticles for controlled release of insulin, Colloids Surfaces B Biointerfaces. 81 (2010) 206–211, https://doi.org/10.1016/j.colsurfb.2010.07.008.

[82] G. Salzano, D.F. Costa, V.P. Torchilin, S. Arabia, siRNA delivery by stimuli-sensitive nanocarriers, Curr. Pharm. Des. 21 (2015) 4566–4573, https://doi.org/10.2174/1381612821315101319041O.

[83] M. Uz, S. Alsoy Altinkaya, S.K. Mallapragada, Stimuli responsive polymer-based strategies for polynucleotide delivery, J. Mater. Res. 32 (2017) 2930–2953, https://doi.org/10.1557/jmr.2017.116.

[84] G. Baronzio, A. Gramaglia, G. Fiorentini, Hyperthermia and immunity. A brief overview, In Vivo (Brooklyn). 20 (2006) 689–696.

[85] T. Chen, J. Guo, M. Yang, X. Zhu, X. Cao, Chemokine-containing exosomes are released from heat-stressed tumor cells via lipid raft-dependent pathway and act as efficient tumor vaccine, J. Immunol. 186 (2011) 2219–2228, https://doi.org/10.4049/jimmunol.1002991.

[86] S. Toraya-Brown, M.R. Sheen, P. Zhang, L. Chen, J.R. Baird, E. Demidenko, M.J. Turk, P.J. Hoopes, J.R. Conejo-Garcia, S. Fiering, Local hyperthermia treatment of tumors induces CD8+T cell-mediated resistance against distal and secondary tumors, Nanomed. Nanotechnol. 10 (2014) 1273–1285, https://doi.org/10.1016/j.nano.2014.01.011.

[87] M. Karimi, A. Ghasemi, P. Sahandi Zangabad, R. Rahighi, S.M. Moosavi Basri, H. Mirshekari, M. Amiri, Z. Shafaei 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, Royal Society of Chemistry, 2016.

[88] C.S. Linsley, B. Wu, Recent advances in light-responsive on- demand drug-delivery systems, Ther. Deliv. 8 (2017) 89–107, https://doi.org/10.4155/tde-2016-0060.

[89] H.-J. Li, H.-X. Wang, C.-Y. Sun, J.-Z. Du, J. Wang, Shell-detachable nanoparticles based on a light-responsive amphiphile for enhanced siRNA delivery, RSC Adv. 4 (2014) 1961–1964, https://doi.org/10.1039/C3RA44866E.

[90] J.S. Hersey, C.M. Lamanna, H. Lusic, M.W. Grinstaff, Stimuli responsive charge-switchable lipids: Capture and release of nucleic acids, Chem. Phys. Lipids 196 (2016) 52–60, https://doi.org/10.1016/j.chemphyslip.2016.02.005.

[91] Y. Yang, F. Liu, X. Liu, B. Xing, NIR light controlled photorelease of siRNA and its targeted intracellular delivery based on upconversion nanoparticles, Nanoscale 5 (2013) 231–238, https://doi.org/10.1039/C2NR32835F.

[92] Y. Zhang, K. Ren, X. Zhang, Z. Chao, Y. Yang, D. Ye, Z. Dai, Y. Liu, H. Ju, Photo-tearable tape close-wrapped upconversion nanocapsules for near-infrared modulated efficient siRNA delivery and therapy, Biomaterials 163 (2018) 55–66, https://doi.org/10.1016/j.biomaterials.2018.02.019.

[93] T. Nomoto, S. Fukushima, M. Kumagai, K. Machitani, Y. Arnida, M. Matsumoto, K. Oba, K. Miyata, N. Osada, K. Kataoka Nishiyama, Three-layered polyplex micelle as a multifunctional nanocarrier platform for light-induced systemic gene transfer, Nat. Commun. 5 (2014) 1–10, https://doi.org/10.1038/ncomms4545.

[94] Y. Yuan, C.J. Zhang, B. Liu, A photoactivatable AIE polymer for light-controlled gene delivery: concurrent endo/lysosomal escape and DNA unpacking, Angew. Chemie - Int. Ed. 54 (2015) 11419–11423, https://doi.org/10.1002/anie.201503640.

[95] S. Jung Park, W. Park, K. Na, Photo-activatable ternary complex based on a multifunctional shielding material for targeted shRNA delivery in cancer treatment, Biomaterials 34 (2013) 8991–8999, https://doi.org/10.1016/j.biomaterials.2013.08.012.

[96] P. Zhang, C. Wang, J. Zhao, A. Xiao, Q. Shen, L. Li, J. Li, J. Zhang, Q. Min, J. Chen, H.Y. Chen, J.J. Zhu, Near infrared-guided smart nanocarriers for MicroRNA-controlled release of doxorubicin/siRNA with intracellular ATP as fuel, ACS Nano 10 (2016) 3637–3647, https://doi.org/10.1021/acsnano.5b08145.

[97] G.B. Braun, A. Pallaoro, G. Wu, D. Missirlis, J.A. Zasadzinski, M. Tirrell, N.O. Reich, Laser-activated gene silencing via gold nanoshell⁄siRNA conjugates, ACS Nano 3 (2009) 2007–2015.

[98] C. Chen, Y. Lin, C. Wang, H. Tzeng, Y. Chen, C. Chen, L. Chen, Y. Wu, C. Chen, Y. Lin, C. Wang, H. Tzeng, C. Wu, Y. Chen, C. Chen, L. Chen, DNA — gold nanorod conjugates for remote control of localized gene expression by near infrared irradiation DNA, J. Am. Chem. Soc. 128 (2006) 3709–3715, https://doi.org/10.1021/ja0570180.

[99] A. Wijaya, S.B. Schaffer, I.G. Pallares, K. Hamad-Schifferli, Selective release of multiple DNA oligonucleotides from gold nanorods, ACS Nano 3 (2009) 80–86, https://doi.org/10.1021/nn800702n.

[100] S.E. Lee, G.L. Liu, F. Kim, L.P. Lee, Remote optical switch for localized and selective control of gene interference, Nano Lett. 9 (2009) 562–570, https://doi.org/10.1021/n1802689k.

[101] Y.T. Chang, P.Y. Liao, H.S. Sheu, Y.J. Tseng, F.Y. Cheng, C.S. Yeh, Near-infrared light-responsive intracellular drug and sirna release using au nanoensembles with oligonucleotide-capped silica shell, Adv. Mater. 24 (2012) 3309–3314, https://doi.org/10.1002/adma.201200785.

[102] R. Huschka, J. Zuloaga, M.W. Knight, L.V. Brown, P. Nordlander, N.J. Halas, Light-induced release of DNA from gold nanoparticles: Nanoshells and nanorods, J. Am. Chem. Soc. 133 (2011) 12247–12255, https://doi.org/10.1021/ja204578e.

[103] F. Thibaudau, Ultrafast photothermal release of DNA from gold nanoparticles, J. Phys. Chem. Lett. 3 (2012) 902–907, https://doi.org/10.1021/jz3001213.

[104] L. Poon, W. Zandberg, D. Hsiao, Z. Erno, D. Sen, B.D. Gates, N.R. Branda, Photothermal release of single-stranded DNA from the surface of gold nanoparticles through controlled denaturating and Au-S bond breaking, ACS Nano 4 (2010) 6395–6403, https://doi.org/10.1021/nn1016346.

[105] P. Wang, L. Zhang, W. Zheng, L. Cong, Z. Guo, Y. Xie, L. Wang, R. Tang, Q. Feng, Y. Hamada, K. Gonda, Z. Hu, X. Wu, X. Jiang, Thermo-triggered release of CRISPR-Cas9 system by lipid-encapsulated gold nanoparticles for tumor therapy, Angew. Chemie - Int. Ed. 57 (2018) 1491–1496, https://doi.org/10.1002/anie.201708689.

[106] F. Kong, F. Liu, W. Li, X. Guo, Z. Wang, H. Zhang, Q. Li, L. Luo, Y. Du, Y. Jin, J. You, Smart carbon nanotubes with laser-controlled behavior in gene delivery and therapy through a non-digestive trafficking pathway, Small 12 (2016) 6753–6766, https://doi.org/10.1002/smll.201601092.

[107] Y.C. Liu, A.L.M.L. Ny, J. Schmidt, Y. Talmon, B.F. Chmelka, C.T. Lee, Photo-assisted gene delivery using light-responsive catanionic vesicles, Langmuir 25 (2009) 5713–5724, https://doi.org/10.1021/la803588d.

[108] H. Zhao, E.S. Sterner, E.B. Coughlin, P. Theato, O-Nitrobenzyl alcohol derivatives: Opportunities in polymer and materials science, Macromolecules 45 (2012) 1723–1736, https://doi.org/10.1021/ma201924h.

[109] A.P. Pelliccioli, J. Wirz, Photoremovable protecting groups: reaction mechanisms and applications, Photochem. Photobiol. Sci. 1 (2002) 441–458, https://doi.org/10.1039/b200777k.

[110] H. Wang, W. Zhang, C. Gao, Shape transformation of light-responsive pyrene-containing micelles and their influence on cytoviability, Biomacromolecules 16 (2015) 2276–2281, https://doi.org/10.1021/acs.biomac.5b00497.

[111] H.-J. Li, H.-X. Wang, C.-Y. Sun, J.-Z. Du, J. Wang, Shell-Detachable Nanoparticles Based on a Light-Responsive Amphiphile for Enhanced siRNA Delivery, Vol. 4, RSC Adv, 2013 1961–1964, https://doi.org/10.1039/C3RA44866E.

[112] S. Rajendrakumar, S. Uthaman, C. Cho, I.-K. Park, Trigger-responsive gene transporters for anticancer therapy, Nano 7 (2017) 120, https://doi.org/10.3390/nano7060120.

[113] F. Auzel, Upconversion and anti-stokes processes with f and d ions in solids, Chem. Rev. 104 (2004) 139–173, https://doi.org/10.1021/cr020357g.

[114] A.M. Schwartzberg, T.Y. Olson, C.E. Talley, J.Z. Zhang, Synthesis, characterization, and tunable optical properties of hollow gold nanospheres, J. Phys. Chem. B 110 (2006) 19935–19944, https://doi.org/10.1021/jp062136a.

[115] X. Huang, M.A. El-Sayed, Gold nanoparticles: Optical properties and implementations in cancer diagnosis and photothermal therapy, J. Adv. Res. 1 (2010) 13–28, https://doi.org/10.1016/j.jare.2010.02.002.

[116] H. Takahashi, T. Niidome, A. Nariai, Y. Niidome, S. Yamada, Gold nanorod-sensitized cell death: Microscopic observation of single living cells irradiated by pulsed near-infrared laser light in the presence of gold nanorods, Chem. Lett. 35 (2006) 500–501, https://doi.org/10.1246/cl.2006.500.

[117] H. Takahashi, T. Niidome, A. Nariai, Y. Niidome, S. Yamada, Photothermal reshaping of gold nanorods prevents further cell death, Nanotechnology 17 (2006) 4431–4435, https://doi.org/10.1088/0957-4484/17/17/024.

[118] C. Chen, Y. Lin, C. Wang, H. Tzeng, Y. Chen, C. Chen, L. Chen, Y. Wu, C. Chen, Y. Lin, C. Wang, H. Tzeng, C. Wu, Y. Chen, C. Chen, L. Chen, Article DNA — gold nanorod conjugates for remote control of localized gene expression by near infrared irradiation, 2006 1209–1212, https://doi.org/10.1021/ja0570180.

[119] D.M. Thurtle-Schmidt, T.W. Lo, Molecular biology at the cutting edge: a review on CRISPR/CAS9 gene editing for undergraduates, Biochem. Mol. Biol. Educ. 46 (2018) 195–205, https://doi.org/10.1002/bmb.21108.

[120] B.B.P. Timko, T. Dvir, D.S. Kohane, Remotely triggerable drug delivery systems, Adv. Mater. 22 (2010) 4925–4943, https://doi.org/10.1002/adma.201002072.

[121] Z. Yang, Q. Cheng, Q. Jiang, L. Deng, Z. Liang, A. Dong, Thermo-sensitive nanoparticles for triggered release of siRNA, J. Biomater. Sci. Polym. Ed. 26 (2015) 264–276, https://doi.org/10.1080/09205063.2014.997559.

[122] S.H. Lee, S.H. Choi, S.H. Kim, T.G. Park, Thermally sensitive cationic polymer nanocapsules for specific cytosolic delivery and efficient gene silencing of siRNA: Swelling induced physical disruption of endosome by cold shock, J. Control. Release 125 (2008) 25–32, https://doi.org/10.1016/j.jconrel.2007.09.011.

[123] J.P. May, S. Li, Hyperthermia-Induced Drug Targeting, 2013 511–527.

[124] P.C. Lyon, L.F. Griffiths, J. Lee, D. Chung, R. Carlisle, F. Wu, M.R. Middleton, F.V. Gleeson, C.C. Coussios, Clinical trial protocol for TARDOX: a phase I study to investigate the feasibility of targeted release of lyso-thermosensitive liposomal doxorubicin (ThermoDox®) using focused ultrasound in patients with liver tumours, J. Ther. Ultrasound. 5 (2017) 1–8, https://doi.org/10.1186/s40349-017-0104-0.

[125] W. Bin Cai, H.L. Yang, J. Zhang, J.K. Yin, Y.L. Yang, L.J. Yuan, L. Zhang, The Optimized Fabrication of Nanobubbles as Ultrasound Contrast Agents for Tumor Imaging, Nat. Publ. Group 1–11. doi:https://doi.org/10.1038/srep13725.

[126] W. Fang, J. Yang, J. Gong, N. Zheng, Photo- and pH-Triggered Release of Anticancer Drugs from Mesoporous Silica-Coated Pd @ Ag Nanoparticles, 2012 842–848, https://doi.org/10.1002/adfm.201101960.

[127] A. Baeza, E. Guisasola, E. Ruiz-Herna, Magnetically Triggered Multidrug Release by Hybrid Mesoporous Silica Nanoparticles, 2012https://doi.org/10.1021/cm203000u.
[128] D. Han, X. Tong, Y. Zhao, Block Copolymer Micelles with a Dual-Stimuli-Responsive Core for Fast or Slow Degradation, 2012, https://doi.org/10.1021/la204930n.
[129] R. Nahire, S. Paul, M.D. Scott, R.K. Singh, W.W. Muhonen, J. Shabb, K.N. Gange, D.K. Srivastava, K. Sarkar, S. Mallik, Ultrasound Enhanced Matrix Metalloproteinase - 9 Triggered Release of Contents from Echogenic Liposomes, 2012, https://doi.org/10.1021/mp300165s.