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Phototriggered drug delivery using inorganic nanomaterials

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Abstract

Light has many desirable properties as the stimulus for triggerable drug delivery systems. Inorganic nanomaterials are often key components in transducing light into drug delivery events. The nature of the light and the inorganic materials can affect the efficacy and safety of the drug delivery system.

Graphical Abstract

1. Introduction

Conventional sustained release systems were designed to maintain drug levels within a therapeutic window (high enough to be effective but not so high as to be toxic) over extended periods. Triggered drug delivery systems were developed to enhance the spatial and temporal resolution of drug delivery (which could enhance efficacy and reduce toxicity), and to provide on demand drug delivery. Here we will provide an overview of photo-triggered drug delivery using inorganic nanomaterials, followed by a discussion of clinical considerations relevant to the field.

Competing interest disclosure

Drs. Kohane, Liu, and Zhan have patents but no financial interest relating to light-triggered drug delivery.

2. Light-triggered drug delivery and inorganic nanomaterials

Recently, there has been increasing interest in using external stimuli as triggers for drug delivery systems.^{1–5} Among them, light is a promising option as it is easily tuned by varying light wavelength, irradiance, and duration of exposure, and can provide spatiotemporal control by adjusting the beam diameter, anatomic target, and timing of application. The fact that light is currently used in clinical practice - for photodynamic⁶ and photothermal⁷ therapy, and to treat neonatal hyperbilirubinemia⁸ – may facilitate translation into practice for new light-triggered therapies.

The wavelength of light used is a very important characteristic of the system. The major tissue chromophores, including hemoglobin, myoglobin, and melanin, exhibit strong absorption in the UV and visible light range, leading to low penetration at those short wavelengths.^{9,10} At wavelengths > ~ 900 nm, absorbance by water prevents penetration.¹¹ NIR light (650 nm - 900 nm) has the minimum absorption and maximal penetration depth,¹² although the depth at which photo-triggered drug delivery can be achieved remains to be determined. Many approaches have been used to convert NIR light to UV in vivo, so as to allow light to penetrate deeply then be usable to cleave covalent bonds, including two-photon absorption,^{13,14} second harmonic generation,^{15,16} upconversion with lanthanide-doped materials,¹⁷ and triplet-triplet annihilation based upconversion.^{18,19} Such methods have been previously reviewed.²⁰

Currently, lasers are the most commonly used light sources in this field. They can produce high energy monochromatic light at a specific wavelength with a narrow bandwidth for a specific photo-responsive system. Laser light can be focused and, if necessary, passed down an optical fiber to reach the target site. Continuous wave diode lasers can be small enough to be hand-held and are safe as long as the exposure time and irradiance are maintained below established limits. Noncoherent light sources are generally safe, easy to use, and less expensive, but their light intensity may be too low to trigger many systems. Light emitting diodes (LED) are noncoherent light sources which can generate high energy light of the desired wavelength range and can be assembled in a range of geometries and size, but it is difficult to obtain monochromatic light with a narrow bandwidth.

A variety of light responsive materials have been used to enable light-triggered drug delivery. Most of the work in this area has been done with organic materials (Table 1), because their drug loading tends to be higher, they are easily chemically modified with light-responsive groups, and they are more commonly fully biodegradable.^{21,22} Nonetheless, inorganic materials (Table 1) do have important and useful roles. These have tended to be in two particular applications:

- a. Photothermal effect. Materials with photothermal properties absorb light, electrons make the transition from the ground state to the excited state, and the excitation energy subsequently relaxes through nonradiative decay. The photothermal effect results in heating of the local environment, which can affect thermosensitive components of drug delivery systems and lead to drug release. Photothermal agents used for triggered drug delivery include organic dyes²³ and noble metal nanoparticles.^{7,24} The absorption cross-section (the measure of a

molecule's ability to absorb a photon at a specific wavelength) of inorganic nanomaterials is typically larger than that of organic dyes.²⁵ In addition, inorganic nanostructures are generally more photostable.²⁴ Noble metal nanoparticles used for phototriggered drug delivery have a photothermal effect due to the absorption of light by surface plasmon resonance (SPR). SPR occurs when the frequency of incident photons matches the resonant oscillation frequency of electrons on the nanomaterial surface.²⁶ Electrons excited in this manner can convert light to heat in picoseconds.²⁷ The geometries of plasmonic nanoparticles affects the wavelength at which SPR absorption occurs,²⁸ and the photothermal efficiency at specific wavelengths.²⁹ Gold nanoshells, nanrods, nanocages, and nanospheres, and silver nanoparticles are among the commonly used noble metal photothermal agents.³⁰ Other inorganic photothermal nanomaterials, such as carbon nanomaterials^{31,32} and transition metal sulfide or oxide nanomaterials,^{33–35} could be used for photoresponsive drug delivery.

- b.** Upconversion. Another distinct advantage of many of the inorganic materials used for light-triggered drug delivery is that they are responsive to light in the near-infrared window which – as alluded to above – allows them to be triggered at greater depth in tissue. In contrast, many organic material-based systems, which rely on cleavage of covalent bonds for triggering, require ultraviolet light (irradiated or upconverted) to act. Consequently, there has been considerable interest in developing means of irradiating targets with NIR light (for depth of penetration), then having it become UV light in situ (to break covalent bonds). Upconversion is a process of combining the energy of multiple photons of lower energy to convert long wavelength (lower energy) light into short wavelength (higher energy) light.¹⁷ Lanthanides-based upconversion nanomaterials are generally comprised of a host material (the bulk of the particle), a sensitizer (which absorbs incident light), and an activator (which takes energy from the sensitizer and emits light). The most commonly used host materials are fluorides, such as NaYF₄ and NaLuF₄. Yb³⁺ is commonly used as a sensitizer due to its large absorption cross section compared to other lanthanide ions. Dopant ions Er³⁺, Ho³⁺, and Tm³⁺ with abundant f-electron configurations are frequently selected as activators to generate upconversion emission. Please see ref 17 for more on the theory of lanthanide-based upconversion. NIR light at 980 nm, 915 nm, and 808 nm have been used as excitation sources for lanthanides-based upconversion, according to the absorption of the sensitizer. The wavelength of the emitted upconverted luminescence depends on the specific activator.

Inorganic nanomaterials can have many other functions not directly related to photo-triggered drug delivery. Inorganic nanomaterials are used for photothermal therapy³⁶ (destroying tissues directly with heat), and for photodynamic therapy³⁷ (destroying tissues by reactive oxygen species). Lanthanide-based upconversion nanomaterials have been used for bioimaging in vivo,³⁸ taking advantage of the fact that both excitation and emission wavelengths are in the NIR range and so can penetrate tissues. The broad range of capabilities of inorganic nanomaterials as enabled multifunctional devices, e.g. theranostics.

3. Clinical rationales and consequences

The clinical goals of photo-triggered drug delivery are attained in two principal ways: by spatial and/or temporal control of drug delivery events. Achieving these goals entails potential clinical consequences, as does the use of the particular inorganic nanomaterials used here.

Spatial control over drug delivery

A key purpose of spatial targeting is to increase the accumulation of systemically delivery drugs at the target site while decreasing it in off-target areas. In so doing, it is hoped that efficacy will be increased, toxicity reduced, and therefore the therapeutic index improved. Nanoparticles have been widely employed to deliver drugs to diseased tissue by a variety of approaches. One commonly employed strategy takes advantage of the fact the blood vessels in tumors is more permeable to particles below a certain size than are blood vessels elsewhere, and the draining lymphatic are defective. This situation leads to preferential nanoparticle uptake in tumors, a phenomenon referred to as enhanced permeation and retention (EPR). While EPR is cited as the basis for many nanomedicines,^{61,62} it may be highly variable from person to person and even within a given tumor.^{63,64} Additional potential targeting approaches could stem from disease-associated changes in the microenvironment, such as local pH and enzyme concentration. Light-triggered drug delivery systems have been used to further increase preferential drug delivery to diseased tissues. This can be done by increasing the local accumulation of particles, or by increasing the local release of drugs.

One approach to enhancing nanoparticle accumulation is to decorate the surface of a nanoparticle with a ligand that targets a given tissue. The ligand is inactivated by a photolabile chemical protection (“caging”) group, so that irradiation will free the ligand, allowing binding to tissues.⁶⁵ This approach is limited by the fact that the cleavage of the bond between the ligand and the chemical protection group generally requires high-energy (UV) light, which has relatively poor tissue penetration. An analogous approach using plasmonic gold nanoshells (over a silica core) was able to achieve the same end with NIR light (Figure 1). The nanoshell was decorated with the peptide YIGSR, which binds to the integrin $\beta 1$, but the peptide was concealed by a layer of the thermosensitive polymer poly(NIPAAm). Irradiation of the nanoparticle with NIR lead led to particle heating which caused shrinkage of the polymer, revealing the ligands and allowing binding to cells.⁶⁶ Tumor phototargeting has been achieved in vivo with a gold nanostructure under irradiation with a NIR laser.⁵²

The enhancement of drug release at specific locations can combine the better drug loading of organic-based materials with the greater tissue depth at which triggering can be achieved with inorganic materials and NIR light. For example, thermosensitive liposomal nanocarriers containing doxorubicin were co-delivered with separate PEGylated gold nanorods.⁶⁷ Irradiation with NIR light triggered release of doxorubicin from the thermosensitive liposomes in a mouse tumor model. NIR-sensitive inorganic nanomaterials can also be conjugated to the organic drug depot. For example, hollow gold nanoparticles were either encapsulated within dipalmitoylphosphatidylcholine (DPPC) liposomes or tethered to the

surface by a PEG linker. Drug from the liposomes was triggered by 130-fs laser pulses at 800 nm.⁶⁸

Lanthanide-based upconversion nanomaterials have also been used to achieve NIR light-triggered drug release. For example, a yolk-shell nanostructure containing lanthanides-based upconversion nanoparticle as the core was loaded with the anticancer drug chlorambucil caged (inactivated) by covalent bonding to a hydrophobic photolabile 7-amino-coumarin derivative.⁴⁵ Under NIR irradiation, the upconversion nanoparticles transformed the NIR into UV light, which broke the chemical bond to the aminocoumarin. This uncaging then allowed release of the chlorambucil.

There has been considerable variability in the reported depth of penetration of NIR light,^{12, 69,70} depending on the wavelength, intensity, and means of detection. In the context of photo-triggered drug delivery, the sensitivity of the drug delivery system to light of a particular wavelength will have a marked effect on the tissue depth at which it can be triggered.

The clinical value of nanoparticulate drug delivery, targeted/triggered or otherwise, in enhancing localized drug accumulation continues to be debated.⁷¹ Light triggering may offer some advantages in this respect.¹⁹ As will be seen below (and has been known for centuries), direct injection to the intended site of use can yield excellent targeting.

Temporal control over drug delivery

Externally triggerable systems impart control over the time course of drug release, by virtue of the fact that an operator can determine the time at which an external energy source is applied and turned off. Modulation of the intensity and duration of irradiation can allow precise adjustment of the degree of drug release and effect. This kind of flexibility is important in applications where drug effect is expected to fluctuate considerably as patient needs and wishes change. Moreover, in situations where there is feedback on drug effect in real time (e.g. pain), toxicity could be reduced by avoiding drug release in excess of what is needed for therapeutic effect.

One example is a phototriggerable formulation enabling repeated on-demand local anesthesia. Gold nanorods (GNRs) were attached to liposomes containing local anesthetics (Figure 2).⁷² These particles were then injected directly into the rat footpad. Irradiation of the injection site caused heating of the GNRs, which caused phase transition of the liposomal lipid bilayers, releasing the payload. The timing, intensity, and duration of local anesthesia could be modulated by adjusting the irradiance.

Macroscopic implantable devices have also been used to provide on-demand photo-triggered drug delivery with inorganic nanomaterials. For example, a reservoir-type system was able to release the insulin analog aspart on demand in response to NIR light.⁷³ The triggerable component consisted of an impermeable ethylcellulose membrane penetrated by an interconnected network of thermosensitive nanogels and also containing gold nanoshells. Irradiation with NIR light caused the nanoshells to heat up, causing the nanoshells to shrink, which opened a path for drug to cross the membrane.

Consequences of phototriggered drug delivery using inorganic nanomaterials

Phototoxicity can be a major consideration with light-triggered systems, and can be either photochemical or photothermal in nature. Photochemical injury can be mediated by generation of free radicals by light-absorbing chromophores in irradiated tissues, termed photosensitization, which can induce DNA breakage,⁷⁴ protein denaturation,⁷⁵ or lipid peroxidation,⁷⁶ ultimately ending in cell death. UV light can be carcinogenic by this mechanism.⁷⁷ Photothermal toxicity occurs when the rate of delivered energy exceeds the rate of energy dissipation in irradiated tissues. Local heating induces protein denaturation and/or increased cell membrane lipid fluidity, resulting in cell death.⁷⁸ One of the dilemmas in phototriggered drug delivery is that the deeper the target, the higher the irradiance needed to reach it, and the greater the probability of tissue injury.

The scientific creativity shown by global researchers in devising light-triggered drug-delivery systems is occasionally not matched by a comparable appreciation of the niceties of clinical relevance. Light-triggered systems have been described which would never be able to reach the intended target because the wavelength employed had inadequate penetration depth. Many formulations have been described in leading journals that operate in vitro at irradiances which would incinerate any poor mammal subjected to such therapy. Hence the considerable interest in methods of making materials that are more sensitive to light or heat.⁷⁹

The somewhat unusual nature of many of the inorganic materials used (by the standards of clinical practice) imposes a burden of assessing cytotoxicity, biodistribution, pharmacokinetics, local and systemic toxicity, etc. This is particularly problematic since the biocompatibility of the photoresponsive moieties or materials incorporated in drug delivery systems has often not been systemically studied, although there are exceptions.^{80–82} Uncertainty may persist even when there is a substantial literature on the safety of a formulation. For example, although gold nanomaterials are generally considered non-cytotoxic in vitro,⁸³ there is not yet unanimity on their biocompatibility in vivo.^{84–87} In most published works, the assessment of the biological concomitants of treatment tend to be much less extensive than the physicochemical characterization, and are occasionally not that informative. As one example, low-powered views of hematoxylin-eosin stained section and/or a lack of weight loss are very blunt (and sometimes useless) tools for assessing the toxicity of systemically-delivered particles.

Inorganic nanomaterials are less commonly biodegradable than are organic ones, which may result in longer times to elimination if excretion of the nanomaterials is not straightforward. The two principal routes for excretion are biliary or renal;⁸⁸ the latter is typically faster.⁸⁸ The rate of renal elimination is highly dependent on size (<6 nm is best⁸⁹) and charge (positively charged is best⁹⁰). Inorganic nanomaterials currently used for photo-triggered drug delivery may be too large for renal excretion, and will be captured by the reticuloendothelial system,⁸⁸ then be cleared by biliary excretion.^{88,89}

The use of unusual materials may slow penetration into clinical practice, partly because of the conservative nature of the medical thought process, and partly because new (from the medical point of view) medical entities are more likely to invoke the ire of regulatory bodies.

Numerous ingenious devices have been developed that can, for example, delivery one or more types of therapy, while also enabling one or more modalities of imaging. It is not always clear how or why clinicians would employ such devices in actual practice, particularly what questions the devices would answer that would enhance care.

Phototriggered drug delivery may be a natural fit with clinical situations where the disease is highly localized. Local delivery of a phototriggered formulation can be effective,⁷² while it is not yet clear whether systemically delivered phototargeted nanoformulation would be effective in the absence of a second mechanism such as EPR.

The role of phototriggered drug delivery in cancer treatment is perhaps not well-defined. A very localized tumor is likely to be removed surgically, but there may be benefit to using phototriggered drug delivery to treat the tumor preoperatively, or to enhance drug delivery to the tumor bed postoperatively. Moreover, there are often multiple tumors at the time of diagnosis; identification and phototriggered treatment of those tumors may not be straightforward. Thus the common demonstration in animal models of treatment of a single tumor may not fully reflect applicability in clinical cancer.

Conclusion and prospects

Phototriggered on-demand drug delivery can in principle release drugs with a broad range of temporal profiles, and enable dosing regimens that are not achievable by conventional means. The range of clinical conditions in which photo-triggered nanomaterials can be employed remains to be determined, as is the context, method, and timing in which they will be used.

Apart from improving treatment efficacy and safety, phototriggering puts control of some therapies back in the hands of patients. This may be particularly valuable in treating rapidly changing and/or painful conditions. There is also an increasing awareness that the timing of drug dosing with respect to the patient's circadian rhythms could affect efficacy.⁹¹ Here again, the control over timing due to triggerability offers benefits.

Challenges remain in overcoming the drawbacks of photo-triggered drug delivery systems. One major hurdle is in delivering enough energy to have a given therapeutic effect at a given tissue depth without causing tissue injury and without requiring extremely expensive equipment (such as a femtosecond laser). This involves developing drug delivery systems that are more sensitive to light (but not so sensitive as to be triggered by ambient light). Another approach to address in the issue of depth of light penetration is to develop materials that can upconvert NIR all the way to the UV range without requiring impractically high irradiances. Addressing issues of biocompatibility, stability, and biodegradability will be important for translation. So will be demonstration of reproducibility: showing that the drug release from any given irradiance results in a predictable release of drug. Developing simple, cheap, and portable light sources will allow widespread use of such systems, e.g. at home.

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Figure 1. Schematic illustration of a NIR-triggered, gold nanoshell-based targeting system. pNIPAAm: poly(N-isopropylacrylamine), pAAM: polyacrylamide. YIGSR is a peptide ligand that can binds a widely distributed receptor (integrin β_1).

Figure 2.

Schematic illustration of a NIR-triggered liposome-based drug release system. Upon irradiation with NIR light, the plasmonic photothermal effect of gold nanorods heats the liposome membranes, leading to the release of encapsulated cargo. TTX is the ultrapotent local anesthetic tetrodotoxin. This system can be used for photo-responsive on demand nerve blockade.

Table 1

Selected inorganic nanomaterials for phototriggered drug delivery.

Mechanism	Inorganic nanomaterial	Effector molecule	Drug	Drug Carrier	In vitro/in vivo	Ref.
Up-conversion	NaYF ₄ :Yb, Tm	Nitrobenzene	Doxorubicin	NaYF ₄ :Yb, Tm	In vivo	39
	NaYF ₄ :Yb, Tm@ NaGdF ₄ : Yb	Pt(IV) pro-drug	Pt(III) drug	NaYF ₄ :Yb, Tm@ NaGdF ₄ : Yb	In vivo	40
	NaYF ₄ :Yb, Tm	Nitrobenzene	siRNA	NaYF ₄ :Yb, Tm	In vitro	41
	NaYF ₄ :Yb, Tm@NaYF ₄	Azobenzene	Doxorubicin	Mesoporous silica	In vitro	42
	NaYF ₄ :Yb, Tm@NaYF ₄	Nitrobenzene	Doxorubicin	Mesoporous silica	In vitro	43
	NaYF ₄ :Yb, Tm@NaYF ₄	Nitrobenzene	5-fluorouracil	NaYF ₄ :Yb, Tm@NaYF ₄	In vitro	44
	NaYF ₄ :Yb, Tm@NaLuF ₄	Amino-coumarin	Chlorambucil	Silica yolk-shell structure	In vivo	45
	NaYF ₄ :Yb, Tm@SiO ₂	Pt(IV) pro-drug	Pt(III) drug	NaYF ₄ :Yb, Tm@ SiO ₂	In vitro	46
	NaYF ₄ :Gd/Yb/Tm@ NaGdF ₄	Azobenzene	Doxorubicin	Amphiphilic copolymers	In vitro	47
	NaYF ₄ :Yb, Tm	Spiropyran	Doxorubicin	Mesoporous silica	In vivo	48
Photo-Thermal	NaYF ₄ :Yb, Tm@NaYF ₄	Nitrobenzene	Doxorubicin	polypeptide copolymer	In vitro	49
	NaYF ₄ :Yb, Tm	Nitrobenzene	Doxorubicin	Polyamidoamine dendrimer	In vitro	50
	NaYF ₄ :Yb, Tm@NaYF ₄	Ru complex	Doxorubicin	Mesoporous silica	In vitro	51
	Gold nanorods	pNIPAAmco-pAAm	Doxorubicin/siRNA	DNA	In vivo	52
	Gold nanorods	Poly (e-caprolactone)	Doxorubicin	Poly (e-caprolactone)	In vitro	53
	Gold nanorods	DNA	Doxorubicin	Mesoporous silica	In vitro	54
	Gold nanorods	Lipid	Tetradotoxin	Liposome	In vivo	55
	Gold nanorods	Lipid	Doxorubicin	liposome	In vivo	56
	Gold nanoshells	pNIPAAmco-pAAm	YIGSR peptide	Gold nanoshells	In vitro	57
	Hollow gold nanoshells	pNIPAAmco-pAAm	Insulin	silicone	In vivo	58
	Gold nanocages	pNIPAAmco-pAAm	Doxorubicin	Nanocages	In vitro	59
	Reduced graphene oxide	Endosome	Doxorubicin	Endosome	In vitro	32
	Ag nanocube	pNIPAAm	Doxorubicin	Mesoporous silica	In vitro	60

Effector molecules: the molecule which are sensitive to the light or temperature; pNIPAAm: poly(N-isopropylacrylamine); pAAm: polyacrylamide.