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Contact-free Remote Manipulation of Hydrogel Properties using Light-triggerable Nanoparticles: A Materials Science Perspective for Biomedical Applications

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Abstract:

Considerable progress has been made in synthesizing “intelligent”, biodegradable polymeric hydrogels that undergo rapid changes in physicochemical properties once exposed to external stimuli. These advantageous properties of stimulus-triggered materials make them highly appealing to diverse biomedical applications. Of late, research on incorporation of light-triggered nanoparticles into polymeric hydrogel networks has gained momentum due to their ability to remotely tune hydrogel properties using facile, contact-free approaches, such as adjustment of wavelength and intensity of light source. These multi-functional nanoparticles, in combination

with tissue-mimicking hydrogels, are increasingly being used for on-demand drug release, preparing diagnostic kits, and fabricating smart tissue engineering scaffolds. Here, we discuss the atomic behavior of different nanoparticles in the presence of light, and critically review the mechanisms by which they convert light stimuli into heat energy. Then, we explain how these nanoparticles impact the mechnical properties and rheological behavior of nanoparticle-impregnated hydrogels. Understanding the rheological behavior of nanocomposite hydrogels using different sophisticated strategies, including computer-assisted machine learning, is critical for designing the next generation of drug delivery systems. Next, we highlight the salient strategies that have been used to apply light-induced nanocomposites for diverse biomedical applications and provide an outlook for further improvement of these nanoparticle-driven light-responsive hydrogels.

1. Introduction

Discovering smart materials capable of precisely controlling the rate of pharmaceutic drug release for medical applications without any major physical interventions has been a considerably challenging task. In recent years, material scientists have made substantial progress in this area of research with the advent of stimuli-triggered nanosized particles or nanoparticles synthesized from inorganic (e.g. metals, metal oxides, ceramics) and organic (e.g. biocompatible polymers) sources.[1] These nanoparticles are shown to respond to various physical (magnetic, thermal, electrical fields) and chemical (pH, ionic strengths, enzymes, discrete molecular recognition events) stimuli changes.[2] Based on the type of external stimuli, we can now spatially and temporally control the drug release profile from the drug-carrying nanoparticles. More importantly, this entire process can be performed in a focused and remote-controlled manner.[3] On the contrary, conventional drug delivery systems have the drawbacks of high dose requirements

due to low the bioavailability of drugs, side effects, low therapeutic indicators, multi-drug resistance development, and non-specific targeting.[4] Naturally, sustaining and predicting the slow release of therapeutics from drug vehicles has been of great interest in the past few years to minimize side effects.[3] Drug release from delivery vehicles induced by radiation absorption, heating, and heat release due to the interaction of nanoparticles with specific light sources has been of paramount interest for their safety and efficacy.[5] Light-responsive nanoparticle systems can convert light into heat energy, and thereby, have enormous potential to be used in biomedical applications, including drug delivery[6], antibacterial drug discovery[7], healing of chronic and acute wounds[8], cancer therapy[9], and bioimaging[10] (**Figure 1**). Furthermore, as a stimulus, light is relatively inexpensive, has high spatial resolution, and shows non-invasive behavior at longer wavelengths, thereby, making it an excellent dynamic medium for the contact-free manipulation of smart nanoparticles. In addition, bioactivity of drugs in the presence of long-wavelength light is unaltered and as a result, light-responsive nanomaterials make effective drug delivery systems with relatively few side effects.[11]

Research efforts to develop hydrogels for biomedical applications are among the most studied fields at the boundary between engineering and medicine. In clinical translation, hydrogels have been developed for a variety of applications such as injectable drug delivery, wound healing, and other regenerative platforms. Currently, products approved through clinical research are being applied to various fields such as cancer treatment and regenerative medicine. The Food and Drug Administration (FDA) and European Medicines Agency (EMA) have clinically approved more than 30 injectable hydrogel products. The most commercially successful of these is Infuse™ Bone Graft, a recombinant human bone morphogenetic protein that was approved by the FDA in the early 2000s for its improved osteoinductive efficacy as an autologous graft replacement therapy.[12]

Moreover, there is tremendous interest in developing effective therapeutic agent delivery strategies for pharmaceutical drug carriers in clinical practice. The incorporation of nanoparticles gives the hydrogels chemical, physical, optical, and electrical properties. It is expected that the range of therapeutic applications will be expanded with various stimulation methods (e.g., pH, temperature change, light, magnetic field) depending on the type of target tissue.[13] In addition, nanoparticles improve the hydrogel's biodegradability and cell adhesion properties, and various nanoparticles such as zinc oxide and silver nanoparticles may have antibiotic properties.[14] In tumor therapy, tumor-specific immunity-inducing nanoparticle near-infrared irradiation delivers tumor antibodies and antigenic vaccines to stimulate local and systemic immune responses to induce the removal of cancer cells.[15,16] Light-responsive nanomaterials are not only used as drug delivery in hydrogels but also have a wide range of antimicrobial properties, and tumor cell ablation *via* photothermal reaction.[17,18]

Light-responsive nanomaterials can be further incorporated inside hydrogels. Hydrogels are highly crosslinked polymer networks swollen by water molecules and known for their ability to grow cells and tissues.[19] Due to the high porosity and hydrated molecular structure of the hydrogels under physiological conditions, the resulting nanoparticle-incorporated hydrogels can be ideal for biomedical applications.[20,21] These type of nanocomposite hydrogels are increasingly being studied as controlled drug delivery vehicles because they degrade in natural biological environments and can easily encapsulate various therapeutics by simple adjustments to their chemical and mechanical properties.[22] Since the early 2000s, the development of light-responsive hydrogels has increased further (**Figure 2**A). Because gold, carbon-based nanomaterials, and silver interact with light, those nanomaterials are frequently loaded inside hydrogels (**Figure 2**B).[2] Different light sources trigger nanocomposite hydrogels at different depths of penetration.

UV light (100-400 nm) and visible light (400-750 nm) are used to treat superficial tissues, whereas, near-infrared light (NIR, 750-2500 nm), with a longer wavelength band, is used to treat tissues at greater depths (**Figure 2**C).[23] Therefore, nanocomposite hydrogels that can respond to light stimuli are ideal candidates for biomedical applications.[22] However, UV light as a stimulant should be used cautiously because of the possibility of inducing radiation-related damage or altering the bioactivity of therapeutics.

Visible or NIR light stimulation of these biomedically-relevant nanocomposite hydrogels is a relatively safer and effective method compared to other external stimulation.[24] The degree of light stimulation, such as exposure time and intensity, can also be easily adjusted, enabling customized treatment for patients. These light-responsive nanocomposite hydrogels are also used as bioimaging platforms.[22,24] In this perspective, we explain three different underlying mechanisms by which nanoparticles convert light energy to heat energy. When combined with hydrogels, these light-responsive nanoparticles change the viscous behavior of the polymeric contituents. This critical change in material property warrants the introduction of different mathematical models that can predict the viscous properties of the polymers along with the nanoparticles. Subsequently, we evaluate the current sophisticated approaches to determine their viscosity. We also aim to show the readers how dynamic this field is. New light-responsive nanoparticles are constantly being discovered and incorporated into hydrogels for biomedical applications. Through these latest applications, we highlight the relevance of these advanced nanocomposite platforms, their trend in the literature, and also propose their future modes of implementation.

2. Light-to-Heat Conversion Dynamics in Nanoparticles: Key Mechanisms of Energy flow

Heat generated from nanoparticles is essential for understanding induced photothermal effects and will facilitate the ultimate elucidation of their specific role in chemical reactions. Heat in the nanoparticles is generated because of the motion of particles.[25] When a particle moves or vibrates by the external energy, the kinetic energy of the electrons increases, causing the material to generate heat. For light to generate heat, the wavelength of light must resonate with the particles of the material that the light touches, causing the particles to vibrate.[26] This phenomenon takes place at the molecular level. For instance, the long-infrared wavelengths of sunlight resonate well with molecules, causing them to vibrate, and subsequently increase their temperature. The conversion of light energy into thermal energy occurs in the process of exciting the electrons in an atom. Atoms constantly vibrate when they absorb light of the same wavelength. The relaxation of excited atoms due to quantum transitions, which is the transition of electrons from a higher energy level to a lower energy level, is felt in the surroundings as "heat". Vibrating atoms collide with surrounding atoms and dissipate the vibrational energy to generate heat. Next, the mechanisms by which light-responsive nanoparticles convert light energy to thermal energy are provided. Mainly three types of light-heat conversion dynamics can take place in these nanoparticles. This includes (1) Surface Plasmon Resonance (2) Bandgap and (3) π-π^* transition mechanism of energy flow. We have briefly discussed each type in the next section.

2.1 Surface Plasmon Resonance

Plasmon is the collective vibration of free electrons in metal or metal-like substances, especially gold (Au) or silver (Ag).[25] The phenomenon of vibration of the plasmon is also called surface plasmon resonance (SPR) because they resonate locally on the surface of the metal. There are many free electrons in metals that are conductors, and since these free electrons are not bound to

the metal atom, they can be sensitive to certain external stimuli such as light.[26,27] Metals interact with photons of light to cause resonant oscillations of the free electrons at the interface between negative and positive charges. (**Figure 3**A).[26] Here, the nanoparticles excited by incident light generate collective vibrating plasmon electrons in the conduction band, which, in turn, causes vibrations of electric charges similar to waves.[27] When the frequency of oscillation of these collective vibrating electrons matches the frequency of the incident light wave, the phenomenon of surface plasmon resonance takes place.[28] This phenomenon is then followed by Landau damping, where the energy of the oscillating electron-hole pair reduces either by the reemission of light energy or by interacting with surrounding electrons through electron-electron scattering. The excited energy of this electron-hole pair is greater than the ambient temperature and this is regarded as a 'hot carrier'. Finally, by rapid energy relaxation, these hot carriers convert the incident light energy to heat energy.[29] Overall, this phenomenon leads to the excitation of metal nanoparticles by absorbed photons from light irradiation, where particle vibrations and charge separation occur, resulting in hot electrons. These hot electrons are very rapidly non-radiatively emitted within the noble metal lattice in picoseconds. This is followed by the dissipation of the generated heat to the surrounding metallic nanostructure by thermal conduction.[26] The induced photothermal response of SPR, which occurs when plasmonic nanostructures convert light energy to thermal energy, has attracted attention in various fields due to its wide potential applications. SPR-induced light-to-thermal energy conversion is frequently implemented for photothermal ablation of cancer cells *in vivo*. However, the origin of heat generation in these nanomaterials is not uniform, and methods that can directly control local temperatures within the nanometer-scale region are still limited.[30] In addition, it is difficult to predict the temperature of nanoparticles or the required time scale for efficient killing of cancer cells. Therefore, it would be more insightful

if efficient treatment methods with adjustable heating in spatial and highly localized treatment sites were discussed.

2.2 Bandgap

Bandgap refers to the energy difference between a valence band, in which electrons are filled in an energy band, and a conduction band, in which no electrons are present. It is also the range of energy in which electrons in a solid can transit from the valence band to the conduction band due to the absorption of external energy.[31] Many atoms are very tightly bonded to a solid. The heavier the atom, the greater the number of electrons, and these electrons are distributed according to their energy level. Electrons close to the nucleus cannot be separated easily due to strong interactions with the nucleus and do not participate in bonding with other atoms.[32] Because electrons further from the nucleus have weaker interactions, these electrons are involved in the bonding of atoms, and are called valence electrons. Adjacent atoms affect the orbits of valence electrons. These orbits overlap with other electron orbits, forming a continuous band called an energy band. All energy levels of a solid take the form of a band, which is divided into a region where electrons can exist and a region where electrons cannot exist. The size of the bandgap is an critical factor in determining the electrical conductivity of a solid. The bandgap has no electrons since there are no energy bands, and its size varies from solid to solid. By varying the range of the bandgap, a solid can have a variety of electrical properties. In general, this difference is divided into the properties of conductors, semiconductors, and insulators in solids. Electrons need a minimum energy to change the oribits from the valence band to the conduction band, and the minimum energy depends on the material. Electrons can absorb energy from the photons of the incident light to move to the conduction band (**Figure 3**B). Photons with energy higher than the bandgap excite the electrons and move them from the valence band to the conduction band. The excited electrons release

thermal energy as they return to the edge of the valence band to stabilize the energy level.[33] Therefore, this phenomenon is dependent on the energy of the incident light and the size of the bandgap, which varies between nanoparticles.

2.3 π-π* transition

Pi (π) bonds are covalent chemical bonds formed by overlapping the electron orbits of each of the neighboring atoms in a molecule. Carbon-based materials are well known to have many orbital hybridizations, such as sp, sp2, and sp3. The π-bonds formed by these orbital hybridizations are weak chemical bonds such that the energy levels of the π electrons are close to each other and thus, have the ability to absorb broadband light.[34] Carbon-based nanomaterials including carbon black and graphite have π-electron conjugates, and the π bond is loosely shared by the electrons such that the energy levels of the π electrons are close to each other. This enables carbon-based nanomaterials to have excitation electrons with excellent properties of absorbing broadband light.[35,36] For example, carbon black and graphite can effectively convert light energy into thermal energy.[37] To make this energy conversion possible, the phenomenon of π–π* transition needs to take place.[38,39] Here, the electron transition of π-bonds occurs when electrons in a molecule are excited to a higher energy level (**Figure 3**C). This is called π–π * transition, and it is usually found in the bonding of carbon-based molecules.[40] The π–π* transition occurs when electrons are transferred at a high energy level due to the absorption of light. Subsequently, these electrons restore to their original state, and the absorbed wavelength is emitted in the form of long-wavelength light and/or thermal energy.[41] These nanoparticles have been broadly studied as drug delivery vehicles capable of loading drugs through π–π* interactions.[42] For example, carbon nanotubes (CNTs) are hollow one-dimensional carbon-based nanomaterials composed of thin sheets of aromatic rings. Various aromatic structures and π–π* interactions enable the loading of

high-dose drugs with a large surface area. The π–π* interactions of CNTs are photoreactive to NIR stimulation and thereby, facilitate the application of photothermal controllable drug delivery systems.[43] As discussed earlier, these light-responsive nanoparticles are often paired with hydrogels for biomedical applications. Recent publications using nanomaterials to construct light-responsive nanocomposite hydrogels have been highlighted in **Table 1**. Next, we discuss different mathematical models to predict the viscous behavior of nanocomposite hydrogels.

3. Light-triggered Nanocomposite Hydrogels: Synergistic Benefits of Nanoparticle and Polymeric Hydrogel

Polymeric hydrogels have been used to encapsulate drugs and deliver therapeutics due to their ability to absorb a wide range of water with hydrophilic functional groups on the polymer backbone.[44–46] Depending on the polymer used and the density of the network structure, the polymeric hydrogels can hold up to 40 times more water contents and biological fluids, and therapeutic agents.[47] Due to these unique physical properties, polymeric hydrogels can form structures of various sizes and shapes. The hydrogel has a structure and composition comparable to the native extracellular matrix (ECM) of mammalian tissues, which can allow the attachment of cells and biomolecules and its excellent biodegradability so that it is excreted from the body without any immune or inflammatory responses.[48] However, while these traditional polymeric hydrogels have the advantage of being easy to fabricate for various therapeutic applications, they are poor at controlling the release of drugs. This key disadvantage makes it necessary to implement multiple doses, which can lead to patient-specific side effects from excessive drug exposure.[49] To overcome this limitation, polymeric hydrogels incorporated with external stimuli-responsive nanomaterials have been designed.[1] These "smart" materials have attracted attention for on-demand targeted drug delivery by using external stimuli, such as pH, light, magnetic field, among

others.[1,47,50] Among the various external stimuli, light is lucrative for non-invasive spatiotemporal control of drug release from implanted hydrogels.[24] The degree of light stimulation can be finely adjusted according to the exposure time or intensity. A wide range of wavelengths can be used depending on the wavelength at which nanoparticles interact with light. Light is a less detrimental way to control biomaterials from a physiological perspective. Light-stimulated nanoparticles can change the physical state of polymeric hydrogels, switching the crosslinked polymer between contracted and expanded form, thereby allowing the controled release of encapsulated drugs.[24] These light-responsive nanoparticle-incorporated polymeric hydrogels can be designed by three different approaches **(Figure 4**A**)**.[51] First, nanoparticles can be simply added to pre-formed hydrogels to form the nanocomposite polymer network. Second, nanoparticles can be added to pre-polymer solutions before crosslinking to form the hydrogel. Third, the nanoparticles can be combined with the monomers, followed by subsequent polymerization and crosslinking to form the nanocomposite hydrogels. In addition to using nanoparticles to create various types of light-responsive hydrogels, different hydrogel forms have also been exploited. This includes stable, self-healing, and injectable forms of hydrogels with varied mechanical properties **(Figure 4**B**)**.[52–55] Stable light-triggered nanocomposite hydrogels are formed primarily by the covalent crosslinking of polymers, which helps the hydrogels retain their shapes for extended periods of time.[54] The degree of network degradation or transformation is affected by the concentration of the polymer and the type of crosslinking.[52] Upon ligh-texposure, these hydrogels undergo a change in network structure, releasing any entrapped cargo. Self-healing light-triggered nanocomposite hydrogels, on the other hand, are formed primarily by reversible covalent crosslinking.[56] Such hydrogels can heal their form by creating new bonds after getting physically damaged.[56,57] These hydrogels exhibit favorable properties for cell penetration due to their rapid degradability *in vivo*.[58,59] The

physical and chemical properties of dynamic covalent crosslinking can vary depending on the polymer's crosslinking concentration, group, and structure. In this form of healable nanocomposite material, light activation leads to the disruption of the chemical bonds that hold the hydrogels together.[54] The subsequent physical transformation of the hydrogel results in the release of entrapped therapeutics. Lastly, injectable light-triggered nanocomposite hydrogels are formed mainly by physical crosslinking.[60] The weaker physical bonds, in this case, allow for the hydrogel to behave as a fluid upon the application of shear stress. However, upon the release of shear stress, such hydrogels return to a more solid-like structure. Hydrogels fabricated by dynamic, electrostatic crosslinking have also been shown to have shear thinning properties.[52] These shear-thinning nanocomposites are ideal candidates for biomedical applications, including 3D bioprinting, low-risk, non-invasive drug delivery, and so on.[59] Through these applications, it has been demonstrated that light-responsive nanoparticles can not only improve the mechanical properties (e.g. toughness, stiffness, compressive and elastic modulus) of these different forms of hydrogels but also can affect their rheological properties.[61] In the following section, we will discuss the rheological properties of light-triggered nanocomposite hydrogels.

4. Biodegradation of Mutifuctional Hydrogels

The light-triggered hydrogel implated or injected into the body must be removed without side effects over time through physico-chemical decomposition. Understanding various biodegradation mechanisms makes it possible to identify hydrogel degradation products, factors affecting degradation, and subsequently, design stable hydrogels. The degradation of hydrogels can be classified into mechanisms such as solubilization, enzymatic dissolution, and nutrient exchange following cellular activities.[62] An efficient hydrogel is required to have a homogeneous dispersion of the therapeutic agent and show constant biodegradability.[63] First, the

biodegradability of the hydrogel can control the release time and concentration of the therapeutic agent into the required tissue, which is dependent on the degree of crosslinking. Second, *in vivo* biodegradability can be achieved by controlling physical structures such as appropriate porosity and pore size to allow space for new tissues to form through cellular activity and the exchange of oxygen and nutrients. Third, the hydrogel crosslinker must be biodegradable by hydrolysis and enzymatic degradation, and as the tissue regeneration proceeds, the hydrogel is replaced by the extracellular matrix. As such, material selection determines the biocompatibility, porosity, degradability, and release rate of the therapeutic agent. Further, the material of the hydrogel is one of the important considerations for controlling the biodegradable properties. These material parameters can also be influenced by the local physiological environment in which the hydrogel will be placed.[62]

5. Physico-chemical and Mechanical Property Considerations for Designing Nanocomposite Hydrogels

The incorporation of light-responsive nanoparticles alters the polymeric network of hydrogels, which has an impact on the rheological behavior of the nanocomposite material. When exposed to light, such nanoparticles convert light to heat energy, increasing the temperature of the hydrogel in the process. For thermo-responsive polymers, this increase in temperature leads to a phase transition of the material.[64] Prior to light-exposure, the hydrogel remains at the gel-phase, where the elastic modulus (G′) is higher than the viscous modulus (G′′). After triggering the nanocomposite hydrogel with light, the subsequent increase in temperature transitions the hydrogel into sol-phase, where the viscous modulus is higher than the elastic modulus. This gel-to-sol transition loosens the network structure of the hydrogel, thereby increasing the porosity and fluidity of the material. For poly(*N*-isopropylacrylamide), a thermo-responsive polymer, the

increase in temperature changes the chain structure from coils to globules.[65] Any changes to the network structure is particularly effective in on-demand drug delivery, where rapid release of entrapped therapeutic molecules is achieved by remotely triggering the thermosensitive nanocomposite hydrogels using light.

To quantify this light-triggered phase transition, rheological experiments are performed. With the important assumption of small deformation under applied stress, the gel behavior can be represented using the theory of linear viscoelasticity.[66,67] Linear viscoelastic models are best suited for ideal systems. However, with the inclusion of multiple materials, non-linearity sets in, which leads to errors in interpretation. As a result, empirical non-linear models have been developed to describe stress relaxation of polymeric materials as a function of time.[68] One such simple model is described by the Debye exponential function. In the case of large deviations for non-Newtonian materials, the viscoelastic model can be represented by the Kohlrausch-Williams-Watts exponential function (**Equation** 1)

$$K(t) = \exp[\left(-\frac{t}{\tau_0}\right)^{\beta}] \quad (1)$$

Where, K(t) is the stress applied at time t, τ_0 is the relaxation time, and β is the stretching exponent, whose value falls between 0 and 1. With the help of empirical models, the viscoelastic behavior of light-triggered nanocomposite hydrogels can be determined. However, machine learning, a superior artificial intelligence-based technique scan be used to better predict the viscosity of these nanocomposite materials.

Emerging Machine Learning approaches to estimate the viscosity of light-triggered nanocomposite hydrogels: The viscosities of hydrogels change with the inclusion of nanoparticles, which makes it critical to evaluate the rheological parameters of every

nanocomposite hydrogel formulation. However, in practice, examining every formulation is cumbersome and expensive. There may be certain formulations that are rheologically not feasible at all, and examining such materials waste valuable resources. Naturally, computational predictions then become extremely critical in optimizing hydrogel formulations. Machine learning is an advanced computational predictive strategy that can model complex systems by recognizing patterns from available data.[69] Predicting the viscosity of light-responsive nanocomposite hydrogels by using machine learning reduces the time and expenses involved with conducting individual experiments. Machine learning is at its nascent stages in polymer science, where it is being implemented in discovering new synthetic polymers.[70] Beyond discovering new synthetic polymers, latest strategies have used this computer-assisted technique to determine the viscosity of polymeric materials.[71] A better understanding of the rheological properties of polymeric materials may be exploited to design injectable hydrogels that can be 3D printed. Recently, an inductive logic programming-based method was used to evaluate the relationship between rheological properties and printability of FDA-approved natural polymers (**Figure 5**A).[72] This powerful programming tool, along with other machine learning strategies, falls under the subset of artificial intelligence, where large volumes of data are processed by advanced computational models to identify patterns.[73] There are two primary strategies of machine learning, including (a) supervised learning, (b) unsupervised learning (**Figure 5**B). Recently, a robust supervised machine learning model was implemented to predict the viscosity of nanoparticle-polymer composites.[74] However, this is an emerging field and new studies must be designed to predict the rheological behavior of light-triggered nanocomposite hydrogels. Next, we discuss the current state of light-triggered nanocomposite hydrogels in relations to their application in diverse biomedical fields.

6. Light-triggered Nanocomposite Hydrogels for Diverse Biomedical Applications

6.1 Progress in Antimicrobial Research

The current overuse of antibiotics has increased the occurrence of drug-resistant bacteria, further worsening infections.[75,76] This rise in drug-resistant bacterial strains has created a need to treat these infections while avoiding the use of conventional antibiotic treatments. Recently, light-triggered nanomaterials were shown to be effective bactericidal agents by inducing hyperthermal effects.[77] Alongside, the nanocomposite hydrogels are also being used as drug delivery system for infectious diseases like AIDS, malaria, tuberculosis, influenza, and Ebola. In particular, unlike other treatment methods, it has excellent potential for reducing drug resistance in treating infectious diseases. In clinical applications, there are many advantages due to hydrogels that can modify and improve the specificity and efficacy of drugs to detect viruses and bacteria in the body of patients.[78]

Polydopamine nanoparticle is one such light-responsive nanomaterial capable of generating heat that can kill bacteria.[79] Here, polydopamine nanoparticles were further loaded with the therapeutic molecule, curcumin to reduce inflammation and treat infected non-healing wounds (**Figure 6**A). This mesoporous NP system was loaded inside a poly(ethylene glycol) diacrylate hydrogel network, and showed remarkable photothermal properties. NIR irradiation increased the local temperatures of the wound to 50 ºC, which killed bacteria by necrosis (**Figure 6**B).[80] This antimicrobial nanocomposite hydrogel was shown to be effective both *in vitro* and *in vivo* (**Figure 6**C, D). In another *in vivo* study, the same poly(ethylene glycol) diacrylate hydrogel was loaded with polyoxometalate, a photothermal nanoparticle, and 2,2′-azobis[2-(2-imidazolin-2-yl) propane] dihydrochloride (AIPH), a thermo-responsive initiator to kill drug-resistant bacteria.[88] Under NIR laser (1060 nm), polyoxometalate generated heat that triggered alkyl radical formation

from AIPH, which together, destroyed bacterial integrity. Other common nanoparticles with light-controlled antibacterial properties include graphene, gold, silver, and copper.[81–83] Overall, metallic and naturally derived materials with photothermal properties can be used in conjunction with hydrogels to temporally and spatially target microbes with high precision, while avoiding the ever-growing problem of antibiotic resistance.

6.2 Progress with Minimally Invasive Tumor Ablation Therapy

Recent advancements in immunotherapy have led to an explosion of research in the area of pharmaceutics, material science, and polymer-based drug delivery. Among different materials, hydrogels have gained enormous attention in cancer immunotherapy and tumor ablation.[84,85] Chemotherapy, radiotherapy, and surgeries are some of the most common anti-cancer therapies, yet possess serious side effects with potential incomplete elimination of tumors that may lead to reocurrence. Therefore, there is an urgent need to develop biomaterials with effective tumor-killing characteristics like light-responsive hydrogels. Photothermal therapy has received increasing attention as a newer form of cancer therapy.[86–89] This approach uses light-triggered nanoparticles incorporated within the polymeric hydrogel to generate heat at the tumor site, thereby, killing tumor cells. In cancer immunotherapy, hydrogels have been developed as systems for delivering immunomodulatory molecules such as antigens, cytokines, peptides, and nucleic acids. When injected into the tumor site, the hydrogel undergoes swelling and degradation due to the low pH of the tumor, releasing the loaded therapeutic agent, thereby stimulating dendritic cells or pre-stimulated tumor-specific T cells to attract immune cells to the tumor site.[85,90]

In vitro and *in vivo* studies of malignant melanoma have taken advantage of the excellent photothermal properties resulting from the incorporation of manganese into silicates. For example, Wu et al. have synthesized sodium alginate hydrogels incorporated with manganese-doped

calcium silicate nanowires for *in situ* photothermal ablation of melanoma.[91] Here, sodium alginate, a naturally derived polysaccharide from algae, has been used due to its biocompatibility, biodegradability, and its applications in tissue engineering.[92] It was reported that in the absence of manganese, the temperature of nanowaires did not increase under 808 nm irradiation. However, addition of manganese with increasing doping amounts caused a rapid increase of the temperature in the nanowires to above 90 ^{o}C in 30 seconds after NIR irradiation. This photothermal effect significantly inhibited skin melanoma tumors in rats, and showed gradual healing in 14 days.[91] In dense and hyperbaric tumor tissues, the insertion of light-responsive nanoparticles can be problematic. An ingenious way to enhance penetration in this case as well as generate free radicals in hypoxic tumors is to combine photothermal therapy and thermodynamic therapy. For example, researchers have fabricated an injectable *N*-isopropyl acrylamide hydrogel loaded with NIR-responsive gold nanorods and a free radical source, AIPH, for tumor ablation (**Figure 7**A).[93] The hydrogel itself was prepared by crosslinking of N-isopropyl acrylamide (hydrophobic component) and glycidyl methacrylate modified hyaluronic acid (hydrophilic component) which acts as a biodegradable long-acting system with controlled generation of free radicals. Under NIR irradiation, gold nanorods converted light to heat energy, which simultaneously activated the generation of alkyl radicals from the oxygen-independent AIPH source that attacked hypoxic tumor cells. AIPH is an azo initiator that can decompose rapidly under thermal stimulation and generate free radicals in hypoxic environment. Gold nanoparticles can also be combined with other nanomaterials to treat malignant tumors. For instance, in an *in vivo* experiment, an alginate hydrogel was loaded with NIR-responsive up-conversion lanthanide-gold hybrid nanoparticles that resulted in rapid and complete elimination of bone tumors in mice models.[94] Overall, light-

responsive nanocomposite hydrogels are excellent therapeutic devices that take advantage of photothermal energy to kill tumor cells.

6.3 Progress and Considerations in Designing On-demand Drug Delivery Systems

Prior sections summarized the important recent progress in the area of light-triggered hydrogel-based antimicrobial and tumor ablation therapy. In this section, we continue discussing the potential of light-responsive hydrogels as a platform for on-demand delivery of therapeutic molecules. This can be pharmaceutical drugs, small molecules, growth factors, cytokines, proteins, antibodies, nucleic acids, to name a few. Upon light-exposure, these hydrogels undergo swelling or shrinkage, which alters the pore structure of the material.[95] The altered porous network of the hydrogel can then facilitate the release of drugs. This release mechanism can be treated as an "on-off" switch, where turning the light "on" leads to a burst release of therapeutics. Such "on-off" phenomenon essentially allows for pulsatile release of encapsulated materials and is particularly useful for maximizing therapeutic effects. Moreover, the kinetics of drug release, in this case, can be mathematically simulated using the Ritger-Peppas equation.[49] Here, the amount of drug released follows a power law model, and the equation is effective for light-induced burst release of drugs from hydrogels. This simple mathematical simulation gives light-triggered nanocomposite hydrogels a high degree of control. Due to such temporally and spatially controlled drug release, these nanocomposite hydrogels do not exhibit some of the common downfalls of conventional drug delivery platforms. This strategy of controlled, pulsatile, localized drug delivery by light-triggered hydrogels has led to exciting innovations in recent years, that has the potential to overcome current bottlenecks of drug delivery systems including incomplete and/or untimely release of drug cargoes at the target site, *in vivo* instability of active drug molecules, and the inability to deliver therapeutic compounds simultaneously.[49,96] Recently, researchers have

developed inverse opal hydrogels like PEGDA gels composed of poly(N-isopropyl acrylamide) and gold nanorods that deliver fluorescein isothiocyanate–carboxymethyl–dextran as a drug and visibly changes color as a reporting signal under NIR light.[81] Gold nanorods have excellent photothermal properties owing to their strong surface-enhanced Raman scattering activity. In Raman scattering, a ray of light changes the nanoparticle's vibrational modes, which alters the light frequency and emits energy. This effect can be magnified by using rough metal surfaces to produce a higher scattering of light for drug release.[97,98] Knowing that poly(*N*-isopropyl acrylamide) exhibited a lower critical solution temperature (LCST) of 32 ^{o}C, the authors added *N*,*N*'-Methylenebisacrylamide, a crosslinking agent to the mixture to adjust the LCST of the hydrogel close to the human body temperature. Under NIR irradiation, the gold nanorods heat poly(*N*-isopropyl acrylamide), a thermoresponsive polymer. When this polymer is heated its volume shrinks and squeezes the encapsulated drug out of the carrier. It was reported that the 50% of loaded dextran was released slowly in 8 minutes. The same amount of drug was released in 2 minutes when the NIR power was increased by 2.5 folds. *In vitro* and *in vivo* bone repair studies have utilized NIR to activate a chitosan hydrogel loaded with NIR-responsive graphene oxide to locally deliver teriparatide, a hormone promoting bone regenerating drug, to osteoporotic rats.[99] The osteoporotic rats showed significantly larger new bone area under controlled NIR light compared to the constant release of drugs. Another application of these hydrogels is to provoke the immune system to target tumors. For instance, Shou et al. have fabricated a poly(*N*-isopropyl acrylamide) hydrogel doped with black phosphorus quantum dots to photothermally release zoledronate, a drug that can induce a T-cell mediated anti-tumor response (**Figure 7**B).[100] The antitumor efficacy of zoledronate-loaded nanocomposite hydrogels was investigated by injecting human γδ T cells into immunocompromised mice with the inhibition of human breast cancer cell

invasion to mimic human immune responses. The designed nanocomposite hydrogel with NIR irradiation showed a significant temperature rise compared to the control group in photothermal conversion ability (**Figure 7**C). Comparative analysis of tumor samples after animal euthanasia showed significant tumor size reduction in the NIR-irradiated BPQDs@NIPAM-Zol group (**Figure 7**D, E). These results demonstrated potent tumor growth inhibition when applied with the combination therapy of NIR irradiation.

Another emerging technique for on-demand delivery of drugs involves the use of polymeric microbubble coupled with light-triggered nanoparticles (**Figure 8**A).[101] Polyester-based polybubbles were incorporated with gold nanorods that respond to light stimuli, enabling them to deliver small molecule drugs, antigens, proteins, and peptides upon NIR exposure.[101] In this system, NIR light penetrated deep tissue to heat the nanoparticles to release the anti-tumor drug by modifying the network structure of the polymer. Overall, such well-designed light-triggered polymeric nanocomposites can deliver drugs at targeted sites and desired times with a localized high concentration that can reduce drug consumption (**Figure 8**B).

7. Progess in Developing Nanocomposite Hydrogels with Photosensitizers for Photodynamic Therapy

Photodynamic therapy (PDT) has become an attractive field in anticancer and antibacterial pre-clinical studies for its low systematic toxicity and minimal invasiveness. Photodynamic action involves a two-step treatment method facilitated by light-triggered nanomaterials, photosensitizers, and oxygen, designed to destroy tumors. In the first step, light exposure leads to the production of reactive oxygen species (ROS). In the second step, the generated ROS kill tumor cells by damaging the cellular environment and causing a local inflammation. PDT is usually limited by the low penetrance of light into the deep tissues [102] To solve this problem, Zhang et al.

designed dual light activated hydrogel containing upconversion nanoparticles (UCNPs), a photosensitizer (Rose Bengal), and cyanobacteria (S.7942) for treating tumors.[103] First, a 640 nm laser was irradiated on the system to stimulate oxygen production by cyanobacteria. The generation of oxygen is essential for effective PDT since tumors grow in a hypoxic microenvironment. Then, UCNPs were excited by NIR irradiation to generate visible light (980 nm) because visible light cannot penetrate deep tissue and must be generated internally. Finally, the visible light-activated Rose Bengal released ROS that induced tumor death. Rose Bengal, an FDA-approved photosensitizer for PDT, yields high-energy photon under visible light that converts oxygen from cyanobacteria to ROS. It was observed that tumor size was reduced twice more with irradiation treatment. Another limitation to PDT is the dependence of the process on oxygen to produce ROS. In recent years, alkyl radical-based therapies have shown promising solutions to oxygen-dependency.[104–106]Radicals generated by light are capable of damaging DNA and oxidizing biological molecules such as proteins and lipids. Besides resolving the oxygen-dependency of conventional PDT, they exhibit great performance in accurate targeting of the cancer cells with low toxicity for normal cells. For example in one study, PDT was combined with nitric oxide (NO) gas therapy to increase the efficiency of PDT in killing tumor cells by co-encapsulating photosensitizer indocyanine green (ICG) and NO donor L-arginine (L-Arg) into poly (lactic-glycolic acid) nanoparticles (**Figure 9**A).[107] These nanoparticles were then loaded into a poly (ethylene glycol) based hydrogel that generated ROS instead of heat under NIR light, which led to the apoptosis of cancer cells and oxidation of L-Arg. Upon oxidation, L-Arg generated NO that suppressed the tumor cells' proliferation by damaging extracellular matrices of cancer cells (**Figure 9**B). In conclusion, PDT is a minimally invasive method that uses hydrogels loaded with light-responsive nanoparticles and photosensitizers in cancer treatment. Therefore, PDT can

give patients better clinical outcomes than traditional treatments because they do not cause surgical scarring. Future research should include the development of novel PDTs in bioimaging, where PDT is combined with other types of treatments such as radiation therapy and chemotherapy to better target tumor cells.

8. Progress with use of Nanoparticle-reinforced Hydrogel Network for Theranostic Applications

Light-responsive nanoparticles have gained much attention by transforming hydrogels into a platform for both drug delivery and bioimaging. Various types of nanoparticles have been widely used in bioimaging to passively target tumors through the enhanced permeability of cell membranes at the tumor site without the aid of exogenous targeting ligands.[108,109] Tumor-targeting ligands such as peptides, polymeric NPs, and inorganic NPs can be successfully used for disease diagnosis as tumor-specific probes with high specificity in conjugation with nanoparticles.[110] Presently, such nanoparticles are being combined with hydrogels to create multifunctional devices capable of carrying drugs as well as bioimaging.[111] The incorporation of nanomaterials into hydrogel networks provides structural diversity with biomedical and chemical properties and could lead to promising therapeutic applications.[112] Such nanocomposite hydrogels can successfully support the visualization and characterization of cellular functions in molecular imaging and disease detection in target tissues at the cellular and molecular levels. Therefore, nanomaterial-incorporated hydrogels can be of great advantage in designing more diverse diagnostic and therapeutic directions for diseases such as various types of tumors and viral diseases that are difficult to diagnose.[113–115] Light-triggered nanocomposite hydrogels are a subset of such multifunctional materials that have recently emerged in the field of biomedicine. Li et al. designed a poly(*N*-isopropyl acrylamide) hydrogel loaded with rare-earth nanoparticles for

biological diagnosis of choroidal melanoma (**Figure 10**A, B).[116] Here, the rare-earth nanoparticles, delivered by injection, possessed high NIR luminescence efficiency, confirming successful biomedical imaging (**Figure 10**C, D). Imaging-guided cancer therapy is another technique that utilizes hydrogels contained with multiple nanoparticles. For example, a gelatin hydrogel that incorporated nanographene oxide, and rare-earth UCNPs were used for *in vitro* antitumor treatment, applied by injection.[117] While nanographene oxide converted NIR light to thermal energy for photothermal therapy, luminescent nanoprobes, and UCNPs helped guide and track the treatment *in vivo.* Furthermore, surgical adjuvant therapy by nanomaterials is an interesting imaging-guided approach in tumor treatment and wound healing. Recently, it was discovered that antimicrobial, exfoliated 2D germanene nanosheets embedded in hydrogels provided an excellent platform for imaging-guided chemotherapeutic injectable drug delivery.[118] Under NIR irradiation, these nanosheets showed high-quality fluorescent and photoacoustic imaging features for guided treatment. Such light-responsive nanocomposite hydrogels can help in identifying tumor position and progression in addition to serving as a therapeutic platform.

9. Emerging Approaches and Outlook

Enhanced by nanoparticle-induced functionalities, light-responsive nanocomposite hydrogels are being successfully applied in biomedical, particularly drug delivery-based applications. Advanced scaffolds with contact-free photo-response are contesting with other more traditional drug delivery techniques. However, there are certain challenges of using light-triggered nanocomposite hydrogel that need to be addressed. Near-infrared light has less energy and can activate only selected nanomaterials. Therefore, upconversion nanoparticles that converts near-infrared light to uv/visible light are being employed to enhance the effect of photothermal or photodynamic therapies. However, rigorous studies need to be conducted to ascertain the biocompatibility and

biodegradability of such materials. Additionally, it is beneficial when the nanocomposite hydrogels are responsive to longer wavelength light sources, particularly in the form of near-infrared. The longer wavelength light sources have deeper tissue penetration, and therefore, these nanocomposite hydrogels can be used for deep-tissue applications in addition to topical ones. However, to achieve even greater tissue penetration, current efforts should also focus on the fabrication of NIR II-triggered nanocomposite hydrogels. Despite the challenges, a wide collection of results coming out of various research groups confirm the rising popularity of light-triggered nanocomposite hydrogels. The nanoparticles, incorporated within theese hydrogels, can effectively control the behavior of the polymeric materials by making them responsive to light sources of different wavelengths.[119–121] One major application of these nanocomposite hydrogels involves the manipulation of cell functions to treat potentially fatal diseases. Carrow et al. used two-dimensional molybdenum disulfide nanosheets to control the fate of human stem cells using NIR light irradiation.[122] Recently, NIR-responsive polydopamine nanoparticles were used to control the biological functioning of neural and cardiac cells.[123] Here, the electrical activities of both the cell types were modulated by exposing the cells to polydopamine nanoparticles embedded in collagen foam and subsequently shining near-infrared light on the nanoparticle-foam system. Light-responsive nanoparticles can similarly be embedded within physicochemically and biologically tunable macroporous hydrogel matrices. The macroporous structure of sub-zero temperature-synthesized hydrogels, also called cryogels, can provide superior cell migration capabilities.[124] Neural or cardiac cell modulation with such light-responsive macroporous nanocomposite hydrogels can provide unique solutions to treat neurological or cardiac diseases.

Another emerging application of light-responsive nanocomposite hydrogel is in the area of 4D cell culture.[125] A 4D cell culture model comprises of a 3D scaffold that is capable of dynamically

altering its properties with time.[126,127] Such models can closely mimic the dynamic environment of native tissues, and light-responsive nanoparticles can enhance the time-dependent behavior of these 4D models. Recently, Zheng et al. prepared a near-infrared light-responsive 4D cell culture model for promoting angiogenesis.[128] Here, an amphiphilic polymer-treated, NIR light-responsive, lanthanide-doped upconversion nanoparticle was incorporated into a polyethylene glycol-based hydrogel. Additionally, a photoreactive cell-adhesive peptide was incorporated in the hydrogel matrix to help with cell adhesion. Upon NIR-irradiation, the nanoparticles converted the NIR-light to UV light, which activated the entrapped cell-adhesive peptide. This phenomenon resulted in enhanced attachment and spreading of Endothelial cells encapsulated within the 3D hydrogel. Furthermore, vascular endothelial growth factor was used as a therapeutic molecule to promote angiogenesis. The NIR-irradiated scaffolds showed promising results, and consequently, similar designs can be exploited to prepare advanced dynamic 3D tissue constructs capable of being photo-activated remotely. Most interestingly, with upconversion nanoparticles, the harmless near-infrared light can be used to modulate 4D scaffolds. Therefore, we can expect more 4D cell culture models being developed with upconversion nanoparticle-supported hydrogels.

Cell-laden light-responsive nanocomposite hydrogels can also be 3D bioprinted to design highly precise patient-specific biomimetic artificial tissue constructs. Cell-laden light-responsive nanocomposite hydrogels can also be 3D bioprinted to design highly precise patient-specific biomimetic artificial tissue constructs. With the help of such designs, 3D bioprinting with nanocomposite hydrogels has emerged as a new technique to address biomedical problems.[129] In combination with cell modulation, 3D bioprinted light-responsive nanocomposite hydrogels hold the potential to revolutionize the field of personalized medicine. Lee et al. used 3D bioprinting to design complex vascularized cardiac tissue with entirely polymeric bioink.[130] Advancing such an

innovative 3D bioprinting technique with light-responsive nanomaterials can lead to the synthesis of highly electrically active nanocomposite hydrogel-based cardiac tissue constructs. However, both cryogels and conventional 3D bioprinted structures are manufactured *ex situ* and require invasive surgical implantation if not applied topically.

Unlike the previous two techniques, *in situ* gelation technique forms amorphous hydrogels. These hydrogels can provide a non-invasive, biocompatible alternative platform for regenerative therapy and for delivering therapeutic molecules. Meng et al. injected on-site, radioactive iodine-labeled copper sulfide nanoparticles encapsulated within polyethylene glycol diacrylate, co-delivered with a thermal initiator to treat breast cancer.[131] Upon NIR-light irradiation, the nanoparticles heated the precursor solution, forming the gel by thermal initiation. Cell-instructive natural polymer-based hydrogels can be used in the future to design highly biomimetic cell-modulating *in situ* light-responsive nanocomposite hydrogels. However, initiator molecules can be toxic, and avoiding them is a better option for biomedical treatments. Recently, Lee et al. showed *in situ* gelation of an initiator-free light-responsive nanocomposite hydrogel system.[132] Here, light-responsive two-dimensional sheets of molybdenum disulfide were conjugated with the thermo-responsive thiolated polymer, poly(*N*-isopropyl acrylamide). The gelation was carried out *in situ* by shining the nanocomposite hydrogel precursor solution with NIR light. The resulting increase in temperature led to the gelation of the polymer-nanoparticle solution.

Besides *in situ* gelation, injectable light-responsive nanocomposite hydrogels can also serve as a non-invasive biomimetic platform. One such injectable hydrogel was produced by supramolecular chemical interactions between polydopamine functionalized gold nanoparticles and the synthetic monomers, *N*-acryloyl glycinamide and [*N*-acryloyl glycinamide-co-acrylamide].[133] This hydrogel precursor was co-polymerized with a photoinitiator to form the gel. Here, the catechol

groups of polydopamine interacted with the amine groups of the polymers through non-covalent interactions to add further physical crosslinking points to the hydrogel and subsequently enhance the mechanical properties of the designed material. A chemotherapeutic drug, doxorubicin, was further loaded into the hydrogel, and NIR light was used to control the release of the drug from this injectable material. Similar ideas can be implemented with natural polymers, avoiding the use of initiators to prepare injectable nanocomposite hydrogels for non-invasive, photothermal, and photodynamic therapies. Entirely physically crosslinked hydrogels could provide a natural, biocompatible alternative to potentially cytotoxic chemically crosslinked hydrogels.[134]

Other than using supramolecular interactions, bio-orthogonal chemistry has also emerged as a promising new approach in the biomedical field.[135] The chemistry involved in such reactions avoids the essential biologically active groups, thereby preserving the bioactivity of the materials under consideration. Bio-orthogonal chemistry should be implemented for preparing light-responsive nanocomposite hydrogels to maintain the bioactivity of both the nanoparticles and the polymers. The properties of the polymers must also be utilized to design unique cell-instructive materials. DNA is one such naturally occurring polymer whose nongenetic and highly tunable physicochemical and biological behavior can be thoroughly exploited in the presence of light-responsive nanoparticles to prepare biologically active scaffolds.[136]

Such biologically active scaffolds are frequently susceptible to bacterial invasion. Currently, photocatalytic degradation of bacteria with light-responsive nanoparticles are being widely tested for fabricating antibacterial hydrogel-based biologically active scaffolds. Traditionally, photothermal therapy with nanomaterials has been studied for combating bacterial invasion. However, this photothermal degradation may be supplemented with photocatalytic degradation for achieving a synergistic bactericidal effect. Metal oxides are commonly used nanomaterials for such

photocatalytic degradation.[137] Recently, Cerium and Erbium-doped TiO_2 nanoparticles were used for the photocatalytic degradation of bacteria.[138] The dopants were used to make the nanoparticle responsive to visible light. Upon irradiation with visible light, the nanoparticle could generate reactive oxygen species. The generated reactive oxygen species is effective in oxidizing organic matter. This affects the bacterial membrane, which leads to the leaking of materials from inside. Finally, this leakage contributes to bacterial degradation. Therefore, these photocatalytic metal oxide nanoparticles can be paired with hydrogels for various biomedical applications.With all these emerging research areas, we anticipate the increasing application of light-responsive nanocomposite hydrogels in diverse biomedical applications.

10. Conclusion

It is clear from the literature that light-responsive nanocomposite hydrogels offer huge potential to be used as smart biomedical material from a clinical standpoint. The synergistic effects of nanoparticles and polymeric hydrogels can play a fundamental role to develop next-generation drug delivery systems. As such, these nanocomposite polymeric materials have drawn much attention in recent years.[120] In this perspective, we have discussed the different fundamental mechanisms by which light can activate nanoparticles. These nanoparticles can then be embedded within hydrogel matrices to modify the functionality of the polymer and provide superior bioactivities. Additionally, we have elaborated on the rheological impact of nanoparticles on hydrogels and discussed their subsequent impact on drug delivery. Finally, we have highlighted the different biomedical applications of these nanocomposite hydrogels and have discussed their emerging approaches. With substantial antibacterial properties, these hydrogels can be implemented in the fight against antibiotic-resistant bacteria. Potential applications of these antibacterial hydrogels include treating wounds[139], acting as coating agents for bacterial

infection-prone implants[140], among others.[1] Furthermore, these remotely-triggered nanocomposite hydrogels can be loaded with therapeutic molecules to thermally ablate tumors, promote bone formation, and in general, act as a vehicle for targeted and pulsatile drug delivery. Alongside drug delivery, these light-triggered nanocomposites can also act as diagnostic bioimaging tools. With these impressive emerging contributions, it should be expected that light-responsive nanocomposite hydrogels will have a bright upcoming decade. However, fundamental research and interdisciplinary studies on understanding cytotoxicity, biodegradability, and long-term effects of nanocomposite hydrogels are required for a timely regulatory approval and commercialization. Active collaboration of material scientists and chemists, together with biologists and clinicians, is highly desired in this context to unlock their full potential for clinical application.

Conflict of Interest

The authors declare no conflict of interest.

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References

[1] P. Lavrador, M. R. Esteves, V. M. Gaspar, J. F. Mano, *Adv. Funct. Mater.* **2021**, *31*, 1.

[2] Marek Grzelczak, L. M. Liz-Marzán, Rafal Klajn, *Chem. Soc. Rev.* **2019**, *48*, 1342.

[3] A. P. Singh, A. Biswas, A. Shukla, P. Maiti, *Signal Transduct. Target. Ther.* **2019**, *4*, 1.

[4] S. Senapati, A. K. Mahanta, S. Kumar, P. Maiti, *Signal Transduct. Target. Ther.* **2018**, *3*, 1.

[5] V. K. Pustovalov, *RSC Adv.* **2016**, *6*, 81266.

[6] W. Zhao, Y. Zhao, Q. Wang, T. Liu, J. Sun, R. Zhang, *Small* **2019**, *15*, 1903060.

[7] Y. Wang, Y. Yang, Y. Shi, H. Song, C. Yu, *Adv. Mater.* **2020**, *32*, 1904106.

[8] C. Hu, F. Zhang, Q. Kong, Y. Lu, B. Zhang, C. Wu, R. Luo, Y. Wang, *Biomacromolecules* **2019**, *20*, 4581.

[9] K. H, C. K, L. S, K. DH, L. H, *Wiley Interdiscip. Rev. Nanomed. Nanobiotechnol.* **2016**, *8*, 23.

[10] Y. Yang, L. Wang, B. Wan, Y. Gu, X. Li, *Front. Bioeng. Biotechnol.* **2019**, *0*, 320.

[11] S. Jia, W.-K. Fong, B. Graham, B. J. Boyd, *Chem. Mater.* **2018**, *30*, 2873.

[12] A. Mandal, J. R. Clegg, A. C. Anselmo, S. Mitragotri, *Bioeng. Transl. Med.* **2020**, *5*, DOI 10.1002/BTM2.10158.

[13] E. Barrett-Catton, M. L. Ross, P. Asuri, *Polymers (Basel).* **2021**, *13*, DOI 10.3390/POLYM13060856.

[14] S. Sharmin, M. M. Rahaman, C. Sarkar, O. Atolani, M. T. Islam, O. S. Adeyemi, *Heliyon* **2021**, *7*, e06456.

[15] L. Zhang, J. Zhang, L. Xu, Z. Zhuang, J. Liu, S. Liu, Y. Wu, A. Gong, M. Zhang, F. Du, *J. Nanobiotechnology* **2021**, *19*, 1.

[16] A. C. Anselmo, Y. Gokarn, S. Mitragotri, *Nat. Rev. Drug Discov. 2018 181* **2018**, *18*, 19.

[17] I. X. Yin, J. Zhang, I. S. Zhao, M. L. Mei, Q. Li, C. H. Chu, **2020**, DOI 10.2147/IJN.S246764.

[18] Z. Yu, L. Gao, K. Chen, W. Zhang, Q. Zhang, Q. Li, K. Hu, *Nanoscale Res. Lett. 2021 161* **2021**, *16*, 1.

[19] Y. S. Zhang, A. Khademhosseini, *Science (80-.).* **2017**, *356*, DOI 10.1126/SCIENCE.AAF3627.

[20] R. Narayanaswamy, V. P. Torchilin, *Molecules* **2019**, *24*, DOI 10.3390/MOLECULES24030603.

[21] H. M, A. A, R. P, *Adv. Drug Deliv. Rev.* **2008**, *60*, 1638.

[22] Ke-Han Shen, Cheng-Hsun Lu, Chih-Yu Kuo, Bo-Yan Li, Yi-Cheun Yeh, *J. Mater. Chem. B* **2021**, *9*, 7100.

[23] D. Barolet, **2008**, DOI 10.1016/j.sder.2008.08.003.

[24] H. P. Lee, A. K. Gaharwar, *Adv. Sci.* **2020**, DOI 10.1002/advs.202000863.

[25] H. Yu, Y. Peng, Y. Yang, Z. Y. Li, *npj Comput. Mater.* **2019**, *5*, 1.

[26] M. L. Brongersma, N. J. Halas, P. Nordlander, *Nat. Nanotechnol.* **2015**, DOI 10.1038/nnano.2014.311.

[27] J. Cunha, T. L. Guo, G. Della Valle, A. N. Koya, R. Proietti Zaccaria, A. Alabastri, *Adv. Opt. Mater.* **2020**, *8*, 2001225.

[28] A. Manjavacas, J. G. Liu, V. Kulkarni, P. Nordlander, *ACS Nano* **2014**, *8*, 7630.

[29] L. V. Besteiro, X. T. Kong, Z. Wang, G. Hartland, A. O. Govorov, *ACS Photonics* **2017**, *4*, 2759.

[30] J. Qiu, W. David Wei, **2011**, DOI 10.1021/jp5042553.

[31] G. W. Luckey, *J. Am. Chem. Soc.* **1957**, *79*, 3299.

[32] H. Lodish, A. Berk, S. L. Zipursky, P. Matsudaira, D. Baltimore, J. Darnell, **2000**.

[33] J. U. Kim, S. Lee, S. J. Kang, T. Il Kim, *Nanoscale* **2018**, *10*, 21555.

[34] A. Streitwieser, *Introduction to Organic Chemistry*, Macmillan, **1992**.

[35] A. Demchenko, *C — J. Carbon Res.* **2019**, *5*, 71.

[36] E. A. Taft, H. R. Philipp, *Optical Properties of Graphite**, **1965**.

[37] G. Liu, J. Xu, K. Wang, **2017**, DOI 10.1016/j.nanoen.2017.09.005.

[38] M. Biyiklioglu, *https://doi.org/10.1142/S1088424620500480* **2021**, *25*, DOI 10.1142/S1088424620500480.

[39] Y. Li, J. Zhang, S. Liu, C. Zhang, C. Chuah, Y. Tang, R. T. K. Kwok, J. W. Y. Lam, H. Ou, D. Ding, B. Z. Tang, *Adv. Funct. Mater.* **2021**, *31*, 2102213.

[40] K. R. Jennings, *Org. Mass Spectrom.* **1991**, *26*, 813.

[41] S. P. Pappas, in *Compr. Polym. Sci. Suppl.*, Elsevier, **1989**, pp. 337–355.

[42] W. R. Zhuang, Y. Wang, P. F. Cui, L. Xing, J. Lee, D. Kim, H. L. Jiang, Y. K. Oh, *J. Control. Release* **2019**, *294*, 311.

[43] Y. Qin, J. Chen, Y. Bi, X. Xu, H. Zhou, J. Gao, Y. Hu, Y. Zhao, Z. Chai, *Acta Biomater.* **2015**, *17*, 201.

[44] B. V. Slaughter, S. S. Khurshid, O. Z. Fisher, A. Khademhosseini, N. A. Peppas, *Adv. Mater.* **2009**, *21*, 3307.

[45] N. A. Peppas, J. Z. Hilt, A. Khademhosseini, R. Langer, *Adv. Mater.* **2006**, *18*, 1345.

[46] S. P. Ravi, Y. Shamiya, A. Chakraborty, C. Elias, A. Paul, *Trends Pharmacol. Sci.* **2021**, *42*, 813.

[47] A. K. Gaharwar, N. A. Peppas, A. Khademhosseini, *Biotechnol. Bioeng.* **2014**, *111*, 441.

[48] R. Song, M. Murphy, C. Li, K. Ting, C. Soo, Z. Zheng, *Drug Des. Devel. Ther.* **2018**, *12*, 3117.

[49] J. Li, D. J. Mooney, *Nat. Rev. Mater.* **2016**, DOI 10.1038/natrevmats.2016.71.

[50] R. Kouser, A. Vashist, M. Zafaryab, M. A. Rizvi, S. Ahmad, *ACS Appl. Bio Mater.* **2018**, *1*, 1810.

[51] C. Dannert, B. T. Stokke, R. S. Dias, *Polym. 2019, Vol. 11, Page 275* **2019**, *11*, 275.

[52] V. G. Muir, J. A. Burdick, *Chem. Rev.* **2020**, DOI 10.1021/ACS.CHEMREV.0C00923.

[53] Q. Xu, S. Zhao, L. Deng, J. Ouyang, M. Wen, K. Zeng, W. Chen, L. Zhang, Y.-N. Liu, *Chem. Commun.* **2019**, *55*, 9471.

[54] Z. Jiang, M. L. Tan, M. Taheri, Q. Yan, T. Tsuzuki, M. G. Gardiner, B. Diggle, L. A. Connal, *Angew. Chemie* **2020**, *132*, 7115.

[55] X. Xu, Z. Huang, Z. Huang, X. Zhang, S. He, X. Sun, Y. Shen, M. Yan, C. Zhao, *ACS Appl. Mater. Interfaces* **2017**, *9*, 20361.

[56] Y. Liu, S. Hsu, *Front. Chem.* **2018**, *0*, 449.

[57] L. Fan, X. Ge, Y. Qian, M. Wei, Z. Zhang, W.-E. Yuan, Y. Ouyang, *Front. Bioeng. Biotechnol.* **2020**, *0*, 654.

[58] S. Talebian, M. Mehrali, N. Taebnia, C. P. Pennisi, F. B. Kadumudi, J. Foroughi, M. Hasany, M. Nikkhah, M. Akbari, G. Orive, A. Dolatshahi-Pirouz, *Adv. Sci.* **2019**, *6*, 1801664.

[59] H. Chen, F. Fei, X. Li, Z. Nie, D. Zhou, L. Liu, J. Zhang, H. Zhang, Z. Fei, T. Xu, *Bioact. Mater.* **2021**, *6*, 3580.

[60] F. Gao, C. Jiao, B. Yu, H. Cong, Y. Shen, *Mater. Chem. Front.* **2021**, *5*, 4912.

[61] J. Zaragoza, S. Fukuoka, M. Kraus, J. Thomin, P. Asuri, *Nanomater. 2018, Vol. 8, Page 882* **2018**, *8*, 882.

[62] J. L. Guo, Y. S. Kim, V. Y. Xie, B. T. Smith, E. Watson, J. Lam, H. A. Pearce, P. S. Engel, A. G. Mikos, *Sci. Adv.* **2019**, *5*, DOI 10.1126/SCIADV.AAW7396/SUPPL_FILE/AAW7396_SM.PDF.

[63] Y. Li, J. Rodrigues, H. Tomás, *Chem. Soc. Rev.* **2012**, *41*, 2193.

[64] C. Liu, X. Guo, C. Ruan, H. Hu, B. P. Jiang, H. Liang, X. C. Shen, *Acta Biomater.* **2019**, *96*, 281.

[65] M. Cao, Y. Wang, X. Hu, H. Gong, R. Li, H. Cox, J. Zhang, T. A. Waigh, H. Xu, J. R. Lu,

Biomacromolecules **2019**, *20*, 3601.

[66] P. K. Pandey, H. Ulla, M. N. Satyanarayan, K. Rawat, A. Gaur, S. Gawali, P. A. Hassan, H. B. Bohidar, *ACS Appl. Nano Mater.* **2020**, *3*, 1289.

[67] J. Rosenblatt, B. Devereux, D. G. Wallace, *Biomaterials* **1992**, *13*, 878.

[68] A. Schiavi, A. Prato, *Polym. Test.* **2017**, *59*, 220.

[69] J. Kerner, A. Dogan, H. von Recum, *Acta Biomater.* **2021**, *130*, 54.

[70] S. Wu, Y. Kondo, M. Kakimoto, B. Yang, H. Yamada, I. Kuwajima, G. Lambard, K. Hongo, Y. Xu, J. Shiomi, C. Schick, J. Morikawa, R. Yoshida, *npj Comput. Mater. 2019 51* **2019**, *5*, 1.

[71] G. C. Loh, H.-C. Lee, X. Y. Tee, P. S. Chow, J. W. Zheng, *J. Chem. Inf. Model.* **2020**, *60*, 1224.

[72] J. Lee, S. J. Oh, S. H. An, W.-D. Kim, S.-H. Kim, *Biofabrication* **2020**, *12*, 035018.

[73] G. Carleo, I. Cirac, K. Cranmer, L. Daudet, M. Schuld, N. Tishby, L. Vogt-Maranto, L. Zdeborová, *Rev. Mod. Phys.* **2019**, *91*, 045002.

[74] N. Lashari, T. Ganat, D. Otchere, S. Kalam, I. Ali, *J. Pet. Sci. Eng.* **2021**, *205*, 108800.

[75] S. C. T. Moorcroft, L. Roach, D. G. Jayne, Z. Y. Ong, Z. Y. Ong, S. D. Evans, *ACS Appl. Mater. Interfaces* **2020**, *12*, 24544.

[76] Z. Hu, X. Liu, L. Jiao, X. Wei, Z. Wang, N. Huang, J. Li, *New J. Chem.* **2021**, DOI 10.1039/D1NJ02088A.

[77] C. Mutalik, D.-Y. Wang, D. I. Krisnawati, A. Jazidie, S. Yougbare, T.-R. Kuo, *Nanomater. 2020, Vol. 10, Page 643* **2020**, *10*, 643.

[78] A. Vashist, A. Kaushik, A. Vashist, R. D. Jayant, A. Tomitaka, S. Ahmad, Y. K. Gupta, M. Nair, *Biomater. Sci.* **2016**, *4*, 1535.

[79] N. M. O. Andoy, K. Jeon, C. T. Kreis, R. M. A. Sullan, *Adv. Funct. Mater.* **2020**, *30*, 2004503.

[80] B. Tao, C. Lin, Z. Yuan, Y. He, M. Chen, K. Li, J. Hu, Y. Yang, Z. Xia, K. Cai, *Chem. Eng. J.* **2021**, *403*, 126182.

[81] L. Z. Liu, X. Y. Sun, Z. Y. Yan, B. F. Ye, *New J. Chem* **2021**, *45*, 7893.

[82] J. Leganés Bayón, A. Sánchez-Migallón, Á. Díaz-Ortiz, C. A. Castillo, I. Ballesteros-Yáñez, S. Merino, E. Vázquez, *Chem. - A Eur. J.* **2020**, *26*, 17069.

[83] M. Wang, H. Zhu, J. Shen, *New J. Chem* **2021**, *45*, 6895.

[84] Z. Fan, X. Dai, Y. Lu, E. Yu, N. Brahmbatt, N. Carter, C. Tchouwou, A. K. Singh, Y. Jones, H. Yu, P. C. Ray, *Mol. Pharm.* **2014**, *11*, 1109.

[85] R. Cui, Q. Wu, J. Wang, X. Zheng, R. Ou, Y. Xu, S. Qu, D. Li, *Front. Bioeng. Biotechnol.* **2021**, *9*, 671.

[86] P. Pan, D. Svirskis, S. W. P. Rees, D. Barker, G. I. N. Waterhouse, Z. Wu, *J. Control. Release* **2021**, *338*, 446.

[87] B. Xia, W. Zhang, H. Tong, J. Li, Z. Chen, J. Shi, *ACS Biomater. Sci. Eng.* **2019**, *5*, 1857.

[88] G. Guedes, S. Wang, F. Fontana, P. Figueiredo, J. Lindén, A. Correia, R. J. B. Pinto, S. Hietala, F. L. Sousa, H. A. Santos, G. Guedes, S. Wang, F. Fontana, P. Figueiredo, A. Correia, H. A. Santos, R. J. B. Pinto, F. L. Sousa, *Adv. Mater.* **2021**, *33*, 2007761.

[89] B. Xia, W. Zhang, J. Shi, J. Li, Z. Chen, Q. Zhang, *J. Appl. Polym. Sci.* **2019**, *136*, DOI 10.1002/app.47443.

[90] Y. Chao, Q. Chen, Z. Liu, *Adv. Funct. Mater.* **2020**, DOI 10.1002/adfm.201902785.

[91] Z. Wu, H. Zhuang, B. Ma, Y. Xiao, B. Koc, Y. Zhu, C. Wu, **2021**, DOI 10.34133/2021/9780943.

[92] L. Ma, Y. Zhou, Z. Zhang, Y. Liu, D. Zhai, H. Zhuang, Q. Li, J. Yuye, C. Wu, J. Chang, *Sci. Adv.* **2020**, *6*, eabb1311.

[93] X. Sun, D. Liu, X. Xu, Y. Shen, Y. Huang, Z. Zeng, M. Xia, C. Zhao, *Asian J. Pharm. Sci.* **2020**, *15*, 713.

[94] B. Liu, X. Gu, Q. Sun, S. Jiang, J. Sun, K. Liu, F. Wang, Y. Wei, *Adv. Funct. Mater.*

2021, *31*, 2010779.

[95] L. Li, J. M. Scheiger, P. A. Levkin, *Adv. Mater.* **2019**, *31*, 1807333.

[96] S. Shah, P. K. Sasmal, K.-B. Lee, *J. Mater. Chem. B. Mater. Biol. Med.* **2014**, *2*, 7685.

[97] M. Moskovits, *Rev. Mod. Phys.* **1985**, *57*, 783.

[98] M. Fleischmann, P. J. Hendra, A. J. McQuillan, *Chem. Phys. Lett.* **1974**, *26*, 163.

[99] X. Wang, W. Guo, L. Li, F. Yu, J. Li, L. Liu, B. Fang, L. Xia, *Chem. Eng. J.* **2021**, *413*, 1385.

[100] X. Shou, Y. Liu, D. Wu, H. Zhang, Y. Zhao, W. Sun, X. Shen, *Chem. Eng. J.* **2021**, *408*, 127349.

[101] S. A. Kumar, J. Good, D. Hendrix, E. Yoo, D. Kim, K. A. Deo, Y.-Y. Jhan, A. K. Gaharwar, C. J. Bishop, *Adv. Funct. Mater.* **2020**, *30*, 2003579.

[102] A. P, B. K, C. KA, F. TH, G. AW, G. SO, H. SM, H. MR, J. A, K. D, K. M, M. J, M. P, N. D, P. J, W. BC, G. J, *CA. Cancer J. Clin.* **2011**, *61*, 250.

[103] X. Zhang, Y. Zhang, C. Zhang, C. Yang, R. Tian, T. Sun, W. Zhang, J. Chang, H. Wang, **2021**, DOI 10.1016/j.colsurfb.2021.111640.

[104] S. Shen, C. Zhu, D. Huo, M. Yang, J. Xue, Y. Xia, *Angew. Chemie* **2017**, *129*, 8927.

[105] W. Zhang, W. Lin, X. Wang, C. Li, S. Liu, Z. Xie, *ACS Appl. Mater. Interfaces* **2019**, *11*, 278.

[106] S. Goel, C. A. Ferreira, F. Chen, P. A. Ellison, C. M. Siamof, T. E. Barnhart, W. Cai, *Adv. Mater.* **2018**, *30*, 1704367.

[107] Z. Sun, X. Wang, J. Liu, Z. Wang, W. Wang, D. Kong, X. Leng, *Cite This Mol. Pharm.* **2021**, *18*, 928.

[108] S. K. Nune, P. Gunda, P. K. Thallapally, Y. Y. Lin, M. Laird Forrest, C. J. Berkland, *Expert Opin. Drug Deliv.* **2009**, *6*, 1175.

[109] I. Rostami, H. R. Alanagh, Z. Hu, S. H. Shahmoradian, *Int. J. Nanomedicine* **2019**, *14*,

7759.

[110] M. J. Mitchell, M. M. Billingsley, R. M. Haley, M. E. Wechsler, N. A. Peppas, R. Langer, *Nat. Rev. Drug Discov. 2020 202* **2020**, *20*, 101.

[111] A. Sachdev, I. Matai, P. Gopinath, *Colloids Surfaces B Biointerfaces* **2016**, *141*, 242.

[112] F. Wahid, X. J. Zhao, S. R. Jia, H. Bai, C. Zhong, *Compos. Part B Eng.* **2020**, *200*, 108208.

[113] X. Liu, X. Sun, G. Liang, *Biomater. Sci.* **2021**, *9*, 315.

[114] R. Rakhshaei, H. Namazi, H. Hamishehkar, M. Rahimi, *Int. J. Biol. Macromol.* **2020**, *150*, 1121.

[115] X. Chen, J. Zhang, K. Wu, X. Wu, J. Tang, S. Cui, D. Cao, R. Liu, C. Peng, L. Yu, J. Ding, *Small Methods* **2020**, *4*, 2000310.

[116] L. Li, Z. Zeng, Z. Chen, R. Gao, L. Pan, J. Deng, X. Ye, J. Zhang, S. Zhang, C. Mei, J. Yu, Y. Feng, Q. Wang, A. Y. Yu, M. Yang, J. Huang, *ACS Nano* **2020**, *14*, 15403.

[117] P. Li, W. Chen, Y. Yan, B. Chen, Y. Wang, X. Huang, **2019**, DOI 10.1021/acsabm.9b00220.

[118] C. Feng, J. Ouyang, Z. Tang, N. Kong, Y. Liu, L. Y. Fu, X. Ji, T. Xie, O. C. Farokhzad, W. Tao, *Matter* **2020**, *3*, 127.

[119] B. Li, S. Harlepp, V. Gensbittel, C. J. R. Wells, O. Bringel, J. G. Goetz, S. Begin-Colin, M. Tasso, D. Begin, D. Mertz, *Mater. Today Chem.* **2020**, *17*, 100308.

[120] Y. Cao, Y. Cheng, G. Zhao, *Langmuir* **2021**, *37*, 5522.

[121] Y. Chen, S. Kang, J. Yu, Y. Wang, J. Zhu, Z. Hu, *J. Mech. Behav. Biomed. Mater.* **2019**, *92*, 179.

[122] J. K. Carrow, K. A. Singh, M. K. Jaiswal, A. Ramirez, G. Lokhande, A. T. Yeh, T. R. Sarkar, I. Singh, A. K. Gaharwar, *Proc. Natl. Acad. Sci.* **2020**, *117*, 13329.

[123] H. G. Derami, P. Gupta, K.-C. Weng, A. Seth, R. Gupta, J. R. Silva, B. Raman, S. Singamaneni, *Adv. Mater.* **2021**, *33*, 2008809.

[124] A. Memic, T. Colombani, L. J. Eggermont, M. Rezaeeyazdi, J. Steingold, Z. J. Rogers, K. J. Navare, H. S. Mohammed, S. A. Bencherif, *Adv. Ther.* **2019**, *2*, 1800114.

[125] E. R. Ruskowitz, C. A. Deforest, *Nat. Rev. Mater. 2018 32* **2018**, *3*, 1.

[126] A. M. Hilderbrand, E. M. Ovadia, M. S. Rehmann, P. M. Kharkar, C. Guo, A. M. Kloxin, *Curr. Opin. Solid State Mater. Sci.* **2016**, *20*, 212.

[127] T. L. Rapp, C. A. DeForest, *Adv. Healthc. Mater.* **2020**, *9*, 1901553.

[128] Y. Zheng, Z. Chen, Q. Jiang, J. Feng, S. Wu, A. Del Campo, *Nanoscale* **2020**, *12*, 13654.

[129] A. Chakraborty, A. Roy, S. P. Ravi, A. Paul, *Biomater. Sci.* **2021**, DOI 10.1039/D1BM00605C.

[130] S. Lee, E. S. Sani, A. R. Spencer, Y. Guan, A. S. Weiss, N. Annabi, *Adv. Mater.* **2020**, *32*, 2003915.

[131] Z. Meng, Y. Chao, X. Zhou, C. Liang, J. Liu, R. Zhang, L. Cheng, K. Yang, W. Pan, M. Zhu, Z. Liu, *ACS Nano* **2018**, *12*, 9412.

[132] H. P. Lee, G. Lokhande, K. A. Singh, M. K. Jaiswal, S. Rajput, A. K. Gaharwar, *Adv. Mater.* **2021**, *33*, 2101238.

[133] Y. Wu, H. Wang, F. Gao, Z. Xu, F. Dai, W. Liu, *Adv. Funct. Mater.* **2018**, *28*, 1801000.

[134] S. Basu, S. Pacelli, Y. Feng, Q. Lu, J. Wang, A. Paul, *ACS Nano* **2018**, DOI 10.1021/acsnano.8b02434.

[135] S. L. Scinto, D. A. Bilodeau, R. Hincapie, W. Lee, S. S. Nguyen, M. Xu, C. W. am Ende, M. G. Finn, K. Lang, Q. Lin, J. P. Pezacki, J. A. Prescher, M. S. Robillard, J. M. Fox, *Nat. Rev. Methods Prim. 2021 11* **2021**, *1*, 1.

[136] A. Chakraborty, S. P. Ravi, Y. Shamiya, C. Cui, A. Paul, *Chem. Soc. Rev.* **2021**, *50*, 7779.

[137] X. Ge, C. Ren, Y. Ding, G. Chen, X. Lu, K. Wang, F. Ren, M. Yang, Z. Wang, J. Li, X. An, B. Qian, Y. Leng, *Bioact. Mater.* **2019**, *4*, 346.

[138] Y. Ren, Y. Han, Z. Li, X. Liu, S. Zhu, Y. Liang, K. W. K. Yeung, S. Wu, *Bioact. Mater.* **2020**, *5*, 201.

[139] N. Yang, M. Zhu, G. Xu, N. Liu, C. Yu, *J. Mater. Chem. B* **2020**, *8*, 3908.

[140] S. Chandna, N. S. Thakur, R. Kaur, J. Bhaumik, *Biomacromolecules* **2020**, *21*, 3216.

[141] D. Yang, G. Yang, P. Yang, R. Lv, S. Gai, C. Li, F. He, J. Lin, *Adv. Funct. Mater.* **2017**, *27*, 1700371.

[142] S. Clement, W. Chen, A. G. Anwer, E. M. Goldys, *Microchim. Acta 2017 1846* **2017**, *184*, 1765.

[143] J. D. Meyers, Y. Cheng, A.-M. Broome, R. S. Agnes, M. D. Schluchter, S. Margevicius, X. Wang, M. E. Kenney, C. Burda, J. P. Basilion, *Part. Part. Syst. Charact.* **2015**, *32*, 448.

[144] J. Yu, C.-H. Hsu, C.-C. Huang, P.-Y. Chang, *ACS Appl. Mater. Interfaces* **2014**, *7*, 432.

[145] S. Maity, K. A. Kozek, W.-C. Wu, J. B. Tracy, J. R. Bochinski, L. I. Clarke, *Part. Part. Syst. Charact.* **2013**, *30*, 193.

[146] E. Lengert, B. Parakhonskiy, D. Khalenkow, A. Zečić, M. Vangheel, J. M. M. Moreno, B. P. Braeckman, A. G. Skirtach, *Nanoscale* **2018**, *10*, 17249.

[147] X. Tan, J. Wang, X. Pang, L. Liu, Q. Sun, Q. You, F. Tan, N. Li, *ACS Appl. Mater. Interfaces* **2016**, *8*, 34991.

[148] S. Rinaldi, L. Tarpani, L. Latterini, *J. Nanomater.* **2016**, *2016*, DOI 10.1155/2016/7510563.

[149] C. A. S. Ballesteros, J. C. Bernardi, D. S. Correa, V. Zucolotto, *ACS Appl. Bio Mater.* **2019**, *2*, 644.

[150] H. Chen, L. Xiao, Y. Anraku, P. Mi, X. Liu, H. Cabral, A. Inoue, T. Nomoto, A. Kishimura, N. Nishiyama, K. Kataoka, *J. Am. Chem. Soc.* **2013**, *136*, 157.

[151] X. Huang, S. Tang, X. Mu, Y. Dai, G. Chen, Z. Zhou, F. Ruan, Z. Yang, N. Zheng, *Nat. Nanotechnol.* **2011**, *6*, 28.

[152] Y. Wang, Y. Deng, H. Luo, A. Zhu, H. Ke, H. Yang, H. Chen, *ACS Nano* **2017**, *11*, 12134.

[153] K. Deng, Y. Chen, C. Li, X. Deng, Z. Hou, Z. Cheng, Y. Han, B. Xing, J. Lin, *J. Mater.*

Chem. B **2017**, *5*, 1803.

[154] B. P. Nowak, B. J. Ravoo, *Faraday Discuss.* **2019**, *219*, 220.

[155] H. Zhang, S. Zheng, C. Chen, D. Zhang, *RSC Adv.* **2021**, *11*, 6367.

[156] Y. Zhu, Q. Zeng, Q. Zhang, K. Li, X. Shi, F. Liang, D. Han, *Nanoscale* **2020**, DOI 10.1039/d0nr01736a.

[157] T. Kuroda, H. Onoe, *Proc. IEEE Int. Conf. Micro Electro Mech. Syst.* **2020**, *2020-January*, 540.

[158] H. Kosuge, S. P. Sherlock, T. Kitagawa, R. Dash, J. T. Robinson, H. Dai, M. V. McConnell, *J. Am. Hear. Assoc. Cardiovasc. Cerebrovasc. Dis.* **2012**, *1*, DOI 10.1161/JAHA.112.002568.

[159] P. Chakravarty, R. Marches, N. S. Zimmerman, A. D.-E. Swafford, P. Bajaj, I. H. Musselman, P. Pantano, R. K. Draper, E. S. Vitetta, *Proc. Natl. Acad. Sci.* **2008**, *105*, 8697.

[160] Y. Wei, Q. Zeng, M. Wang, J. Huang, X. Guo, L. Wang, *Biosens. Bioelectron.* **2019**, *131*, 156.

[161] W. Liu, X. Zhang, L. Zhou, L. Shang, Z. Su, *J. Colloid Interface Sci.* **2019**, *536*, 160.

[162] R. Kurapati, A. M. Raichur, *Chem. Commun.* **2012**, *49*, 734.

[163] S. Huang, H. Liu, K. Liao, Q. Hu, R. Guo, K. Deng, *ACS Appl. Mater. Interfaces* **2020**, *12*, 28952.

[164] P. Yuan, T. Yang, T. Liu, X. Yu, Y. Bai, Y. Zhang, X. Chen, *Biomaterials* **2020**, *262*, 120357.

[165] H. Lee, S. Kim, C. Ryu, J. Y. Lee, *ACS Biomater. Sci. Eng.* **2020**, *6*, 1931.

[166] M. Qiu, D. Wang, W. Liang, L. Liu, Y. Zhang, X. Chen, D. K. Sang, C. Xing, Z. Li, B. Dong, F. Xing, D. Fan, S. Bao, H. Zhang, Y. Cao, *Proc. Natl. Acad. Sci. U. S. A.* **2018**, DOI 10.1073/pnas.1714421115.

[167] K. N. Kim, K. S. Oh, J. Shim, I. R. Schlaepfer, S. D. Karam, J.-J. Lee, *Polymers (Basel).*

2021, *13*, 1.

[168] Y.-F. Ding, C. H. T. Kwong, S. Li, Y.-T. Pan, J. Wei, L.-H. Wang, G. S. P. Mok, R. Wang, *Biomater. Sci.* **2021**, *9*, 3804.

[169] L. Han, Y. Zhang, X. Lu, K. Wang, Z. Wang, H. Zhang, *ACS Appl. Mater. Interfaces* **2016**, *8*, 29088.

[170] L. Y. Xia, X. Zhang, M. Cao, Z. Chen, F. G. Wu, *Biomacromolecules* **2017**, *18*, 3073.

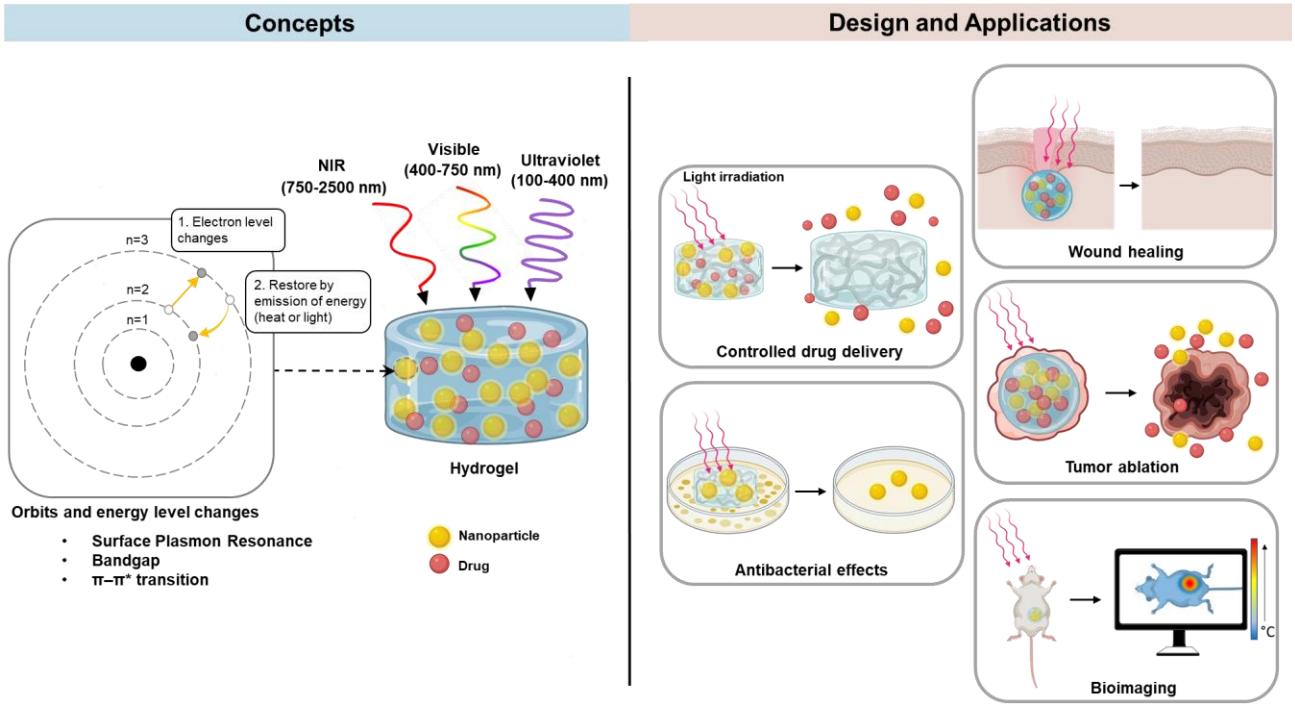

Figure 1. Concepts and designs to prepare light-responsive nanocomposite hydrogel-based systems for diverse biomedical applications. Light-responsive nanocomposite polymeric hydrogels absorb energy by various light stimuli (NIR, Visible, and Ultraviolet). This absorbance of energy drives the electrons in the nanoparticles to higher energy orbits. Subsequently, when the electrons return to their ground state, the nanoparticles dissipate energy in the form of heat or long wavelength (light). This heat dissipation deforms the hydrogels, releasing the encapsulated drug molecules. Light-responsive polymeric nanocomposite hydrogels are emerging as promising advanced materials for non-invasive, tunable, and effective treatment for a wide range of biomedical applications, including controlled drug delivery, antibacterial drug discovery, wound healing, tumor ablation, and bioimaging.

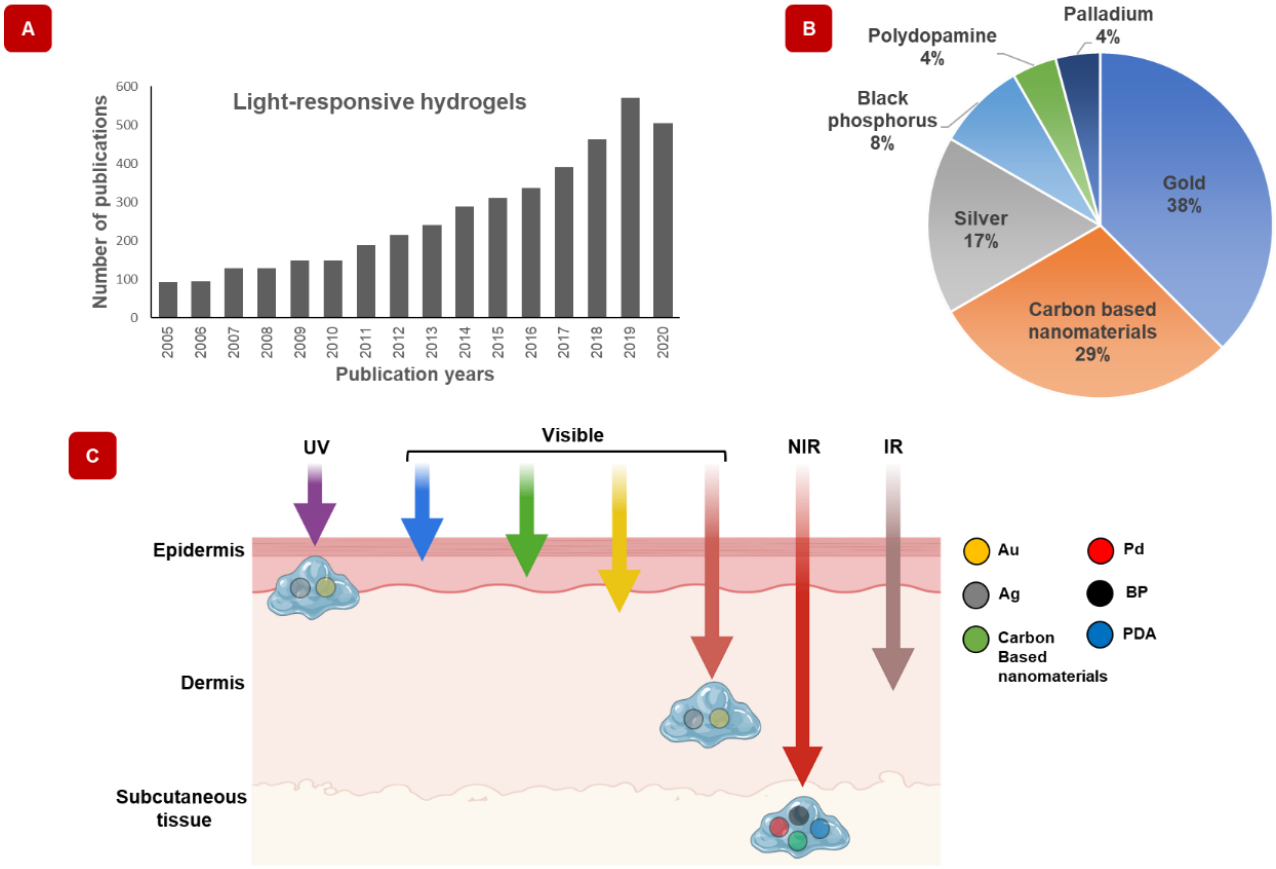

Figure 2. Publication trend of light-responsive nanocomposite hydrogels and depth of implementation based on light penetration. A) Number of publications in light-responsive hydrogels from 2005 to 2020. The literature information was obtained from Web of Science with the keywords, "light responsive", "photoresponsive", and "hydrogel". B) Percentage distribution of different types of nanoparticles to prepare light-responsive polymeric nanocomposite hydrogels in 2020. The data was obtained from Web of Science by using the keywords, "[type, eg. gold] nanoparticle", "hydrogel", and "light". C) The depth of penetration of light in skin depends on the wavelength of light. UV, visible, and IR lights have small penetration depths, usually in the order of 1 mm. In contrast, NIR light has longer penetration depth, and can reach up to 3 mm. As a result, nanocomposite hydrogels sensitive to a certain wavelength of light must be designed based on the location of application.

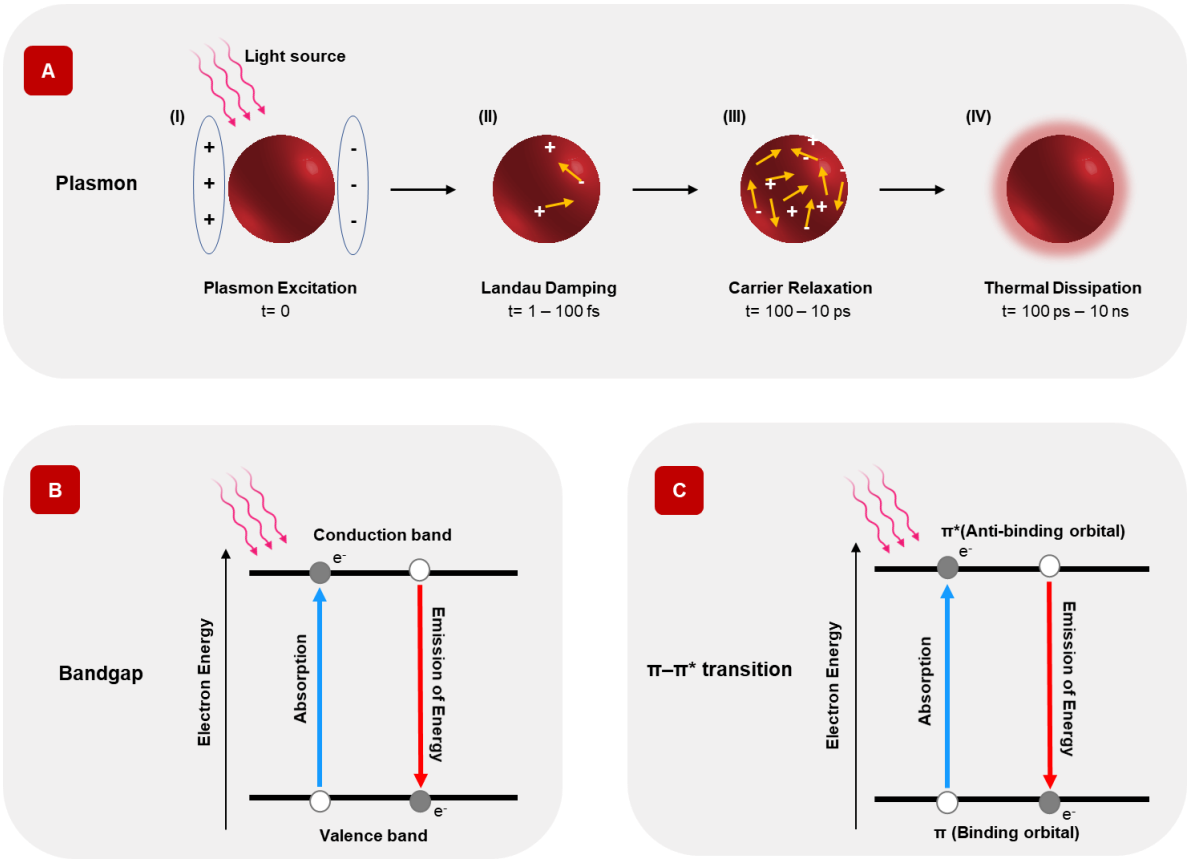

Figure 3. Mechanisms by which light interacts with nanoparticles. A) Surface Plasmon Resonance (SPR): Photoexcitation and relaxation of metal nanoparticles. Resonant oscillations occurs when conduction electrons of a dielectric material is stimulated by light. (I) Plasmon excitation: metal nanoparticles are excited by light stimulation. (II) Landau damping: energy exchange occurs due to electron-electron interactions. (III) Carrier relaxation: hot carriers redistribute energy by the electron-electron scattering process. (IV) Thermal dissipation: heat is transferred through thermal conduction around the metal nanoparticles. B) Bandgap: When an electron is stimulated by light, it moves from the valence band to the conduction band and is subsequently restored through energy release (light or heat). C) π–π* transition: After excitation by light, electrons move from a π-bonding orbital to an antibonding π orbital* and is then restored through energy release.

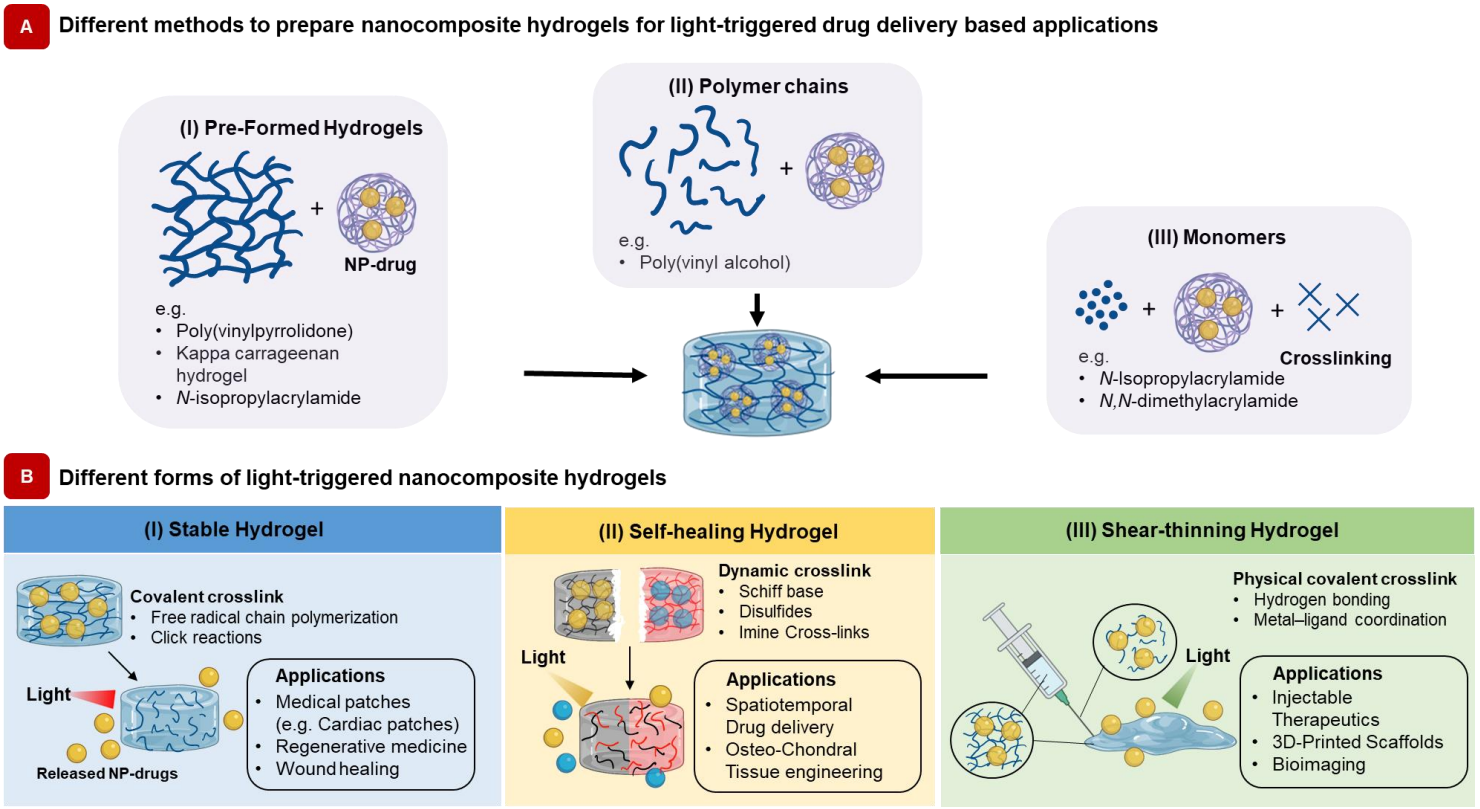

Figure 4. Schemes for preparing light-triggered nanocomposite hydrogels and different physico-chemical forms that can be fabricated using these methods. A) Different methods to prepare light-triggered nanocomposite hydrogels for drug delivery-based applications. Methods: (I) Addition of drug-conjugated nanoparticles (NPs) to pre-formed hydrogel, (II) Drug-conjugated NPs are added to the pre-polymer solutions, followed by physical/chemical crosslinking to form the final hydrogel product, (III) Drug-conjugated NPs are dispersed in a monomeric solution (containing suitable crosslinkers), followed by crosslinking to form the desired hydrogel. B) Different physico-chemical forms of light-triggered nanocomposite hydrogels. Forms: (I) Stable nanocomposite hydrogels, (II) Self-healing nanocomposite hydrogels, and (III) Injectable nanocomposite hydrogel for light-triggered drug release. Upon light-irradiation, the polymeric networks of these three types of hydrogels undergo rapid change, leading to the release of bound therapeutic molecules.

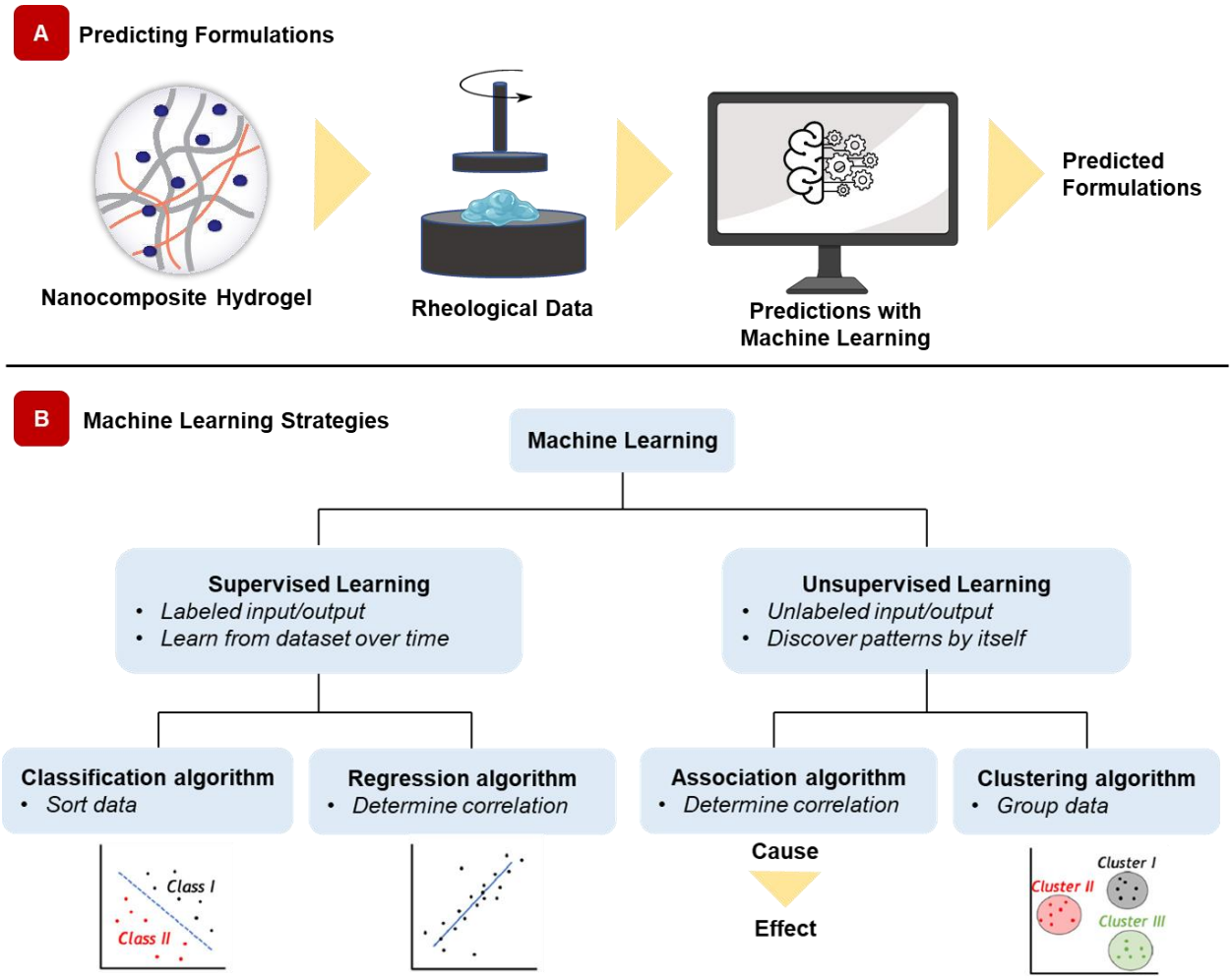

Figure 5. Using machine learning to predict rheological properties of nanocomposite hydrogels. (A) A general scheme for optimizing hydrogel formulations using machine learning has been shown here. Rheological information of nanocomposite hydrogels must first be experimentally collected or obtained from literature. The gathered information is then fed to a machine learning-based algorithm. A robust algorithm predicts the properties of different compositions and helps with optimizing hydrogel formulation.[69] (B) The different types of machine learning algorithms along with their salient features have been listed here. Adapted and reproduced with permission.[72] Copyright 2021, Elsevier.

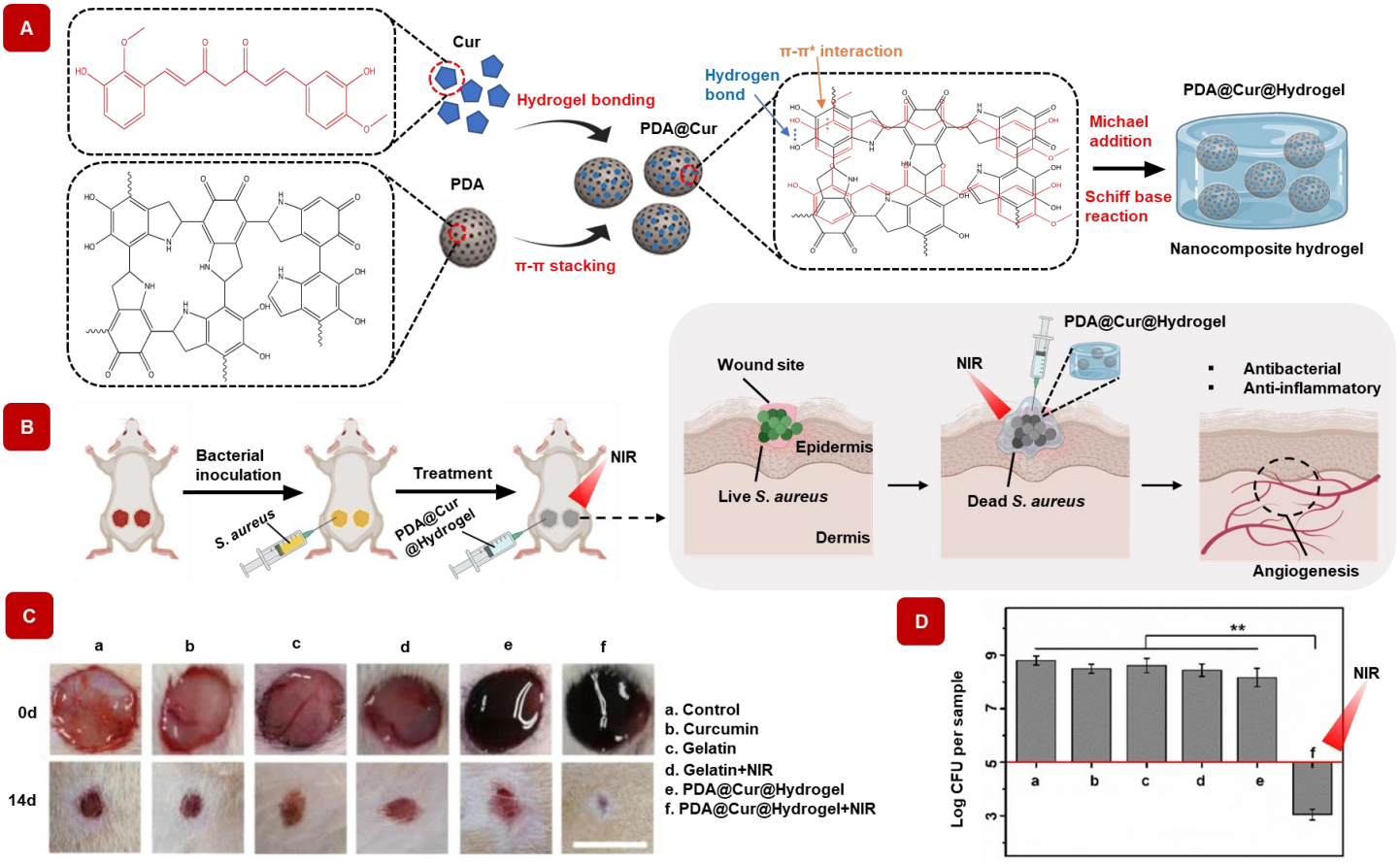

Figure 6. Antibacterial activity of light-responsive nanocomposite hydrogels. A) Schematic of the synthetic route of the PDA@Cur@hydrogel. Photoreactive PDAs were loaded with curcumin (Cur) via π–π stacks and/or hydrogen bonding interactions to form PDA@Cur. PDA@Cur was integrated with polymers to produce PDA@Cur@hydrogels via Schiff base and/or Michael addition reaction. B) Schematic diagram of healing of skin damage in mice infected with bacteria (*S. aureus*). As an antioxidant, Cur is released from the PDA@Cur@hydrogel under NIR irradiation (808 nm) with on-demand release properties, allowing it to be applied in therapies such as cancer treatment, wound healing, and orthopedics. In addition, NIR irradiation can generate local heat to inhibit the activity of bacteria such as E. coli and Staphylococcus aureus (*S. aureus*) by photothermal reaction of PDA. This PDA@Cur@hydrogel not only has antibacterial activities but also shows anti-inflammatory and angiogenenic properties, making it a promising biomaterial for wound healing applications. C) Bacterial site defects on the skin of rats were visually observed on days 0 and 14 for each group (a. control b. curcumin c. gelatin d. gel+NIR e. PDA@Cur@Hydrogel f. PDA@Cur@Hydrogel+NIR), scale bar: 1 cm. A substantial reduction in wound site can be visually observed for the designed nanocomposite hydrogel under NIR light exposure. D) Graph demonstrates a significant decrease in the bacterial count for the designed nanocomposite hydrogels under NIR irradiation. Adapted and reproduced with permission.[80] Copyright 2021, Elsevier.

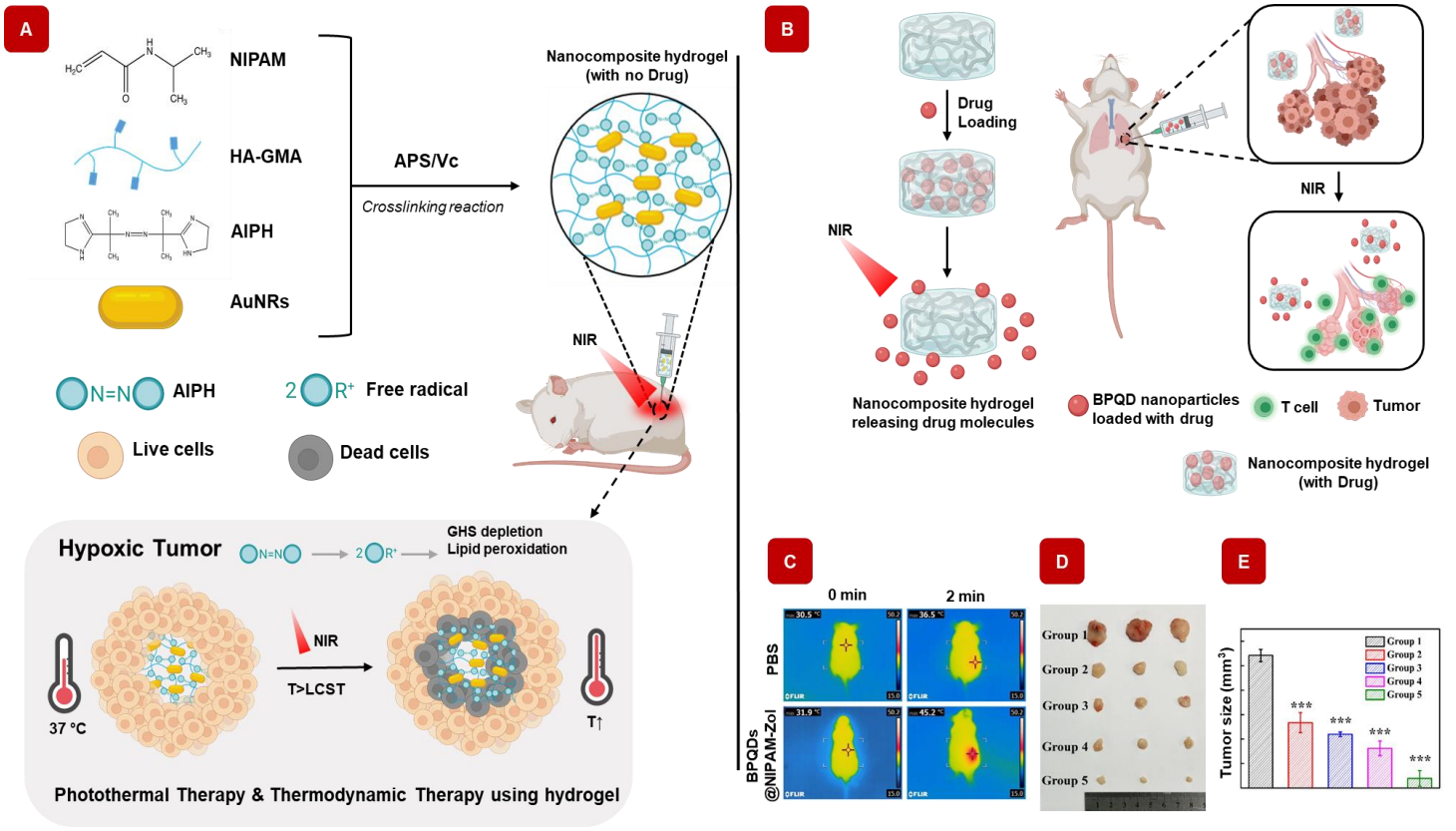

Figure 7. Photothermal therapy and drug delivery-based application of light-responsive nanocomposite hydrogels. A) Schematic shows photothermal and thermodynamic therapy for the treatment of hypoxic tumors in hydrogels composed of hydrophilic glycidyl methacrylate modified hyaluronic acid (HA-GMA) and hydrophobic *N*-isopropyl acrylamide (NIPAM) mixed with 2,2'-Azobis[2-(2-imidazalin-2-yl)propane]dihydrochlaride (AIPH) and gold nanorods (AuNR). The designed nanocomposite hydrogel can generate PTT and free radicals under hypoxic conditions upon NIR laser irradiation. Heat-induced contraction of the hydrogel can accelerate the production of free radicals to achieve controlled drug release that inhibits tumor growth. B) Display exhibits the components and functions of NIR-responsive hydrogels for drug delivery. In this system, an antitumor drug called zoledronate was loaded onto a poly(*N*-isopropyl acrylamide) hydrogel doped with black phosphorus quantum dots (BPQDs). When BPQDs are irradiated with NIR, the nanoparticles are heated to cause photothermal emission of the drug, which is targeted to treat cancer by triggering an anti-tumor response of the immune system (T cells). C) The thermal images show the *in vivo* photothermal conversion effect of the BPQDs@NIPAM-Zol hydrogel compared to the control, PBS. The mice were given intratumoral injection of the nanocomposite hydrogel and subsequently exposed to NIR irradiation (1.24 W for 2 min). The photothermal conversion with the nanocomposite hydrogel was then imaged using a thermal camera. After NIR irradiation, the temperature increase in the PBS group was only 6 °C, whereas the temperature increases in the BPQDs@NIPAM-Zol hydrogel treated group reached 12 °C, indicating a significant temperature rise for the nanocomposite hydrogel. D) Tumor images with different treatment groups were collected. (Group 1: PBS treated, Group 2: γδ T cells treated, Group 3: γδ T cells + Zol treated, Group 4: γδ T cells + BPQDs@hydrogel-Zol treated, Group 5: γδ T cells + BPQDs@hydrogel-Zol + NIR treated) E) Graph showing tumor size of respective treatment groups. (***$p < 0.001$). The light-responsive nanocomposite hydrogel studied here showed significant reduction in tumor. Adapted with permission.[100] Copyright 2021, Elsevier.

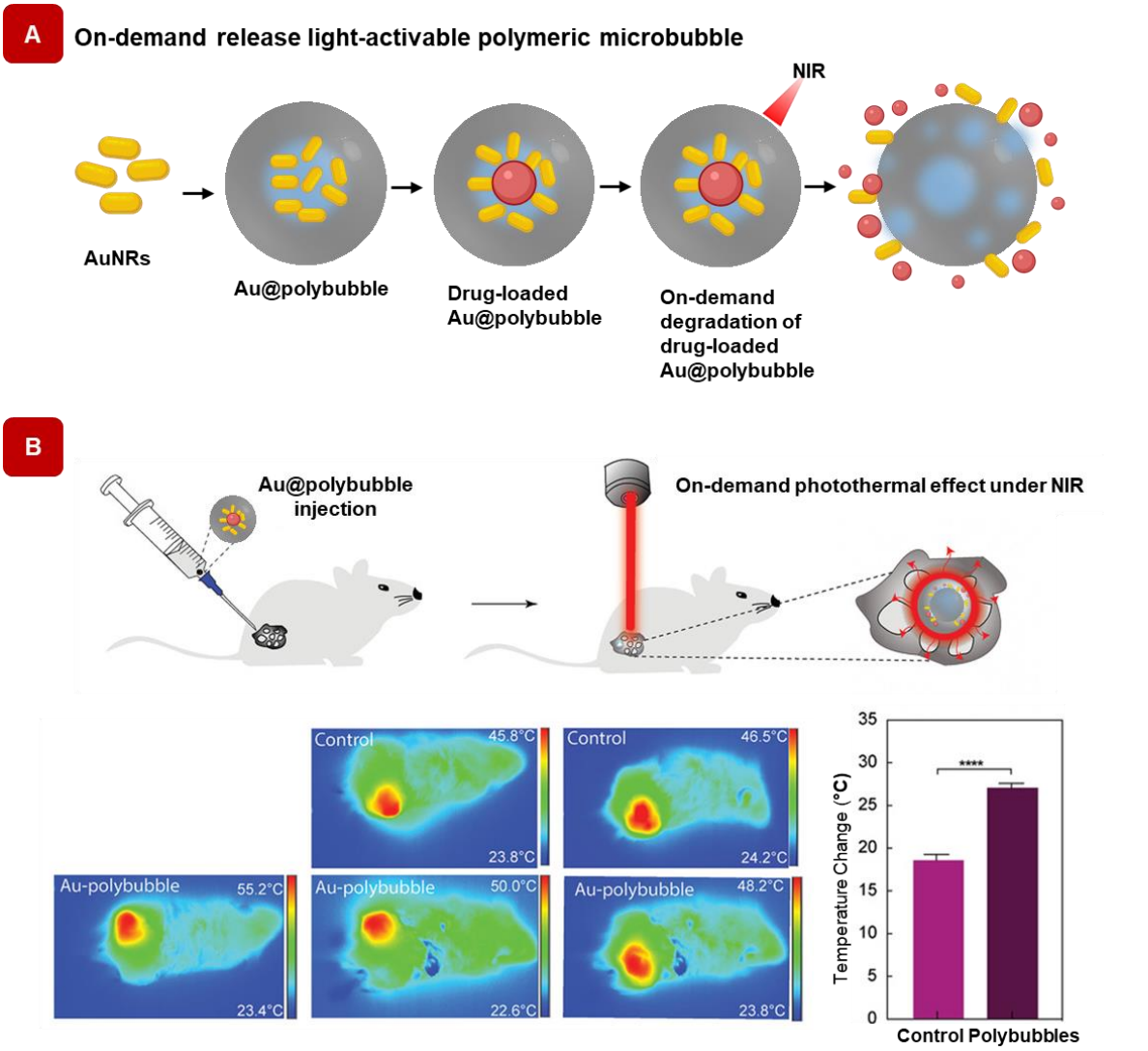

Figure 8. Application of drug delivery using light-activable polymeric microbubble. A) Formation and characterization of the light-activable polymeric bubble. The polymeric bubble is built using a phase separation approach in which the cargo dissolved in an aqueous phase is injected into a polymer "bubble" in the organic phase. Polymeric microbubble is a polyester-based, injectable platform with a UV-cured polymer shell covering the cargo in the center. This technology can ensure cargo stability by limiting organic solvent exposure and can accurately achieve predefined and on-demand drug release. By incorporating light-responsive AuNRs in polymeric microbubbles, they can be activated upon NIR stimulation. B) Observation of *in vivo* laser activation of AuNR-polymeric microbubbles upon injection into melanoma tumors in Balb-C mice. A temperature increases of 8 ± 1 °C was confirmed after *in vivo* NIR laser activation of AuNR-polymeric microbubbles (n = 3). ****p < 0.0001, t-test. Adapted and reproduced with permission.[101] Copyright 2020, John Wiley & Sons.

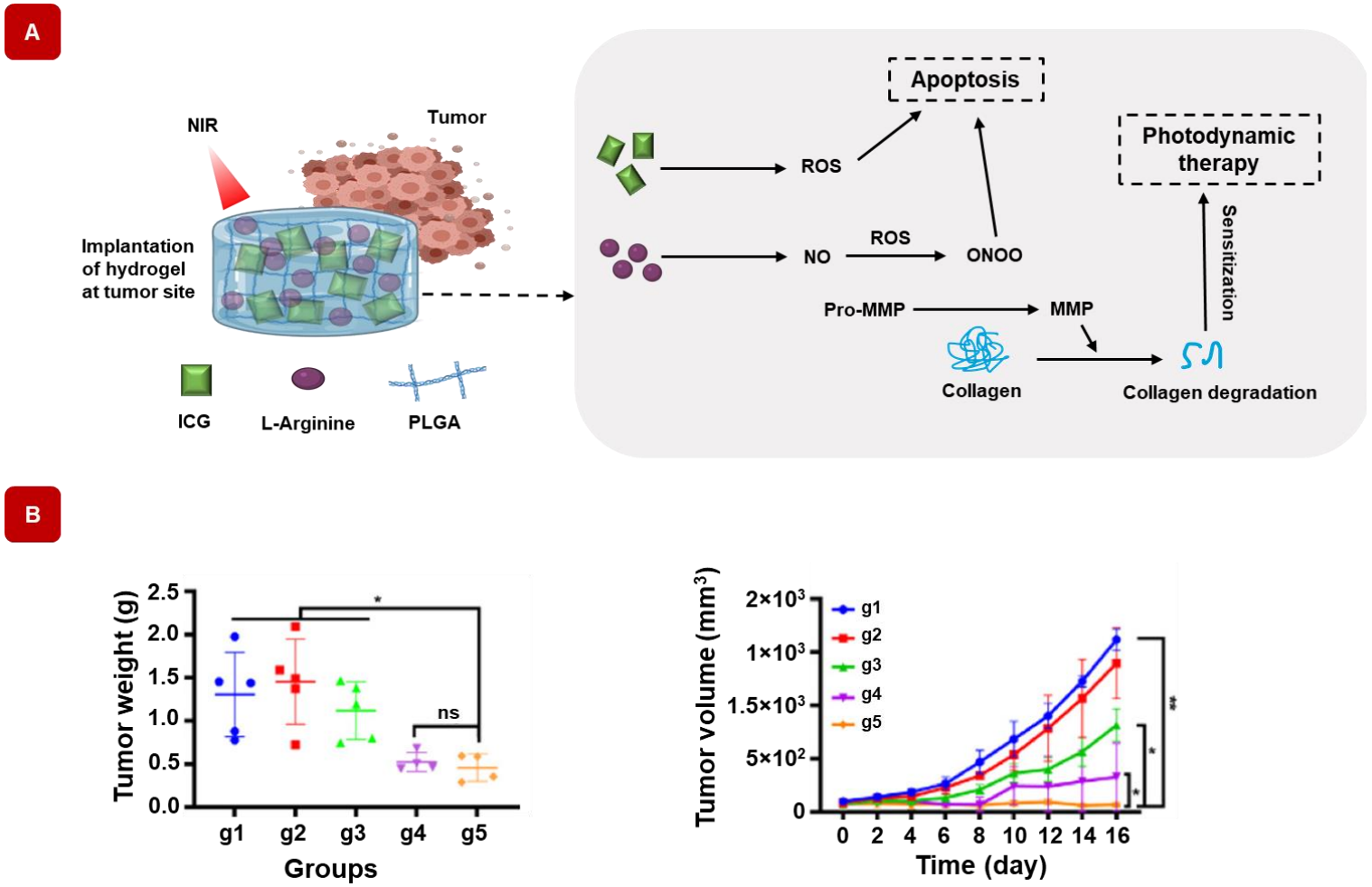

Figure 9. Photodynamic therapy of light-responsive nanocomposite hydrogels. A) The preparation and function of hydrogels in photodynamic therapy to combat tumors have been depicted. Hydrogels were fabricated using poly(ε-caprolactone)-poly(ethylene glycol)-poly(ε-caprolactone) (PCL-PEG-PCL). In this nanocomposite hydrogel, poly(lactic acid-glycolic acid) nanoparticles were loaded with the photosensitizer indocyanine green (ICG) and the nitric oxide (NO) donor L-arginine (L-Arg). Upon NIR irradiation, ICG generated reactive oxygen species (ROS) without the photothermal effect causing apoptosis of cancer cells. This reaction further oxidized L-Arg to produce NO, which inhibits tumor cell proliferation. B) Graphs showing the tumor weight and volume in different groups. Tumor weights were measured on day 16 of treatment. The results confirmed that the designed nanocomposite hydrogel which is group g5 effectively treats tumor (g1: control; g2: PLGA@l-Arg/Gel + Laser; g3: PLGA@ICG/Gel + Laser; g4: PLGA@ICG@l-Arg + Laser; g5: PLGA@ICG@l-Arg/Gel + Laser). Adatped with permission.[107] Copyright 2021, American Chemical Society.

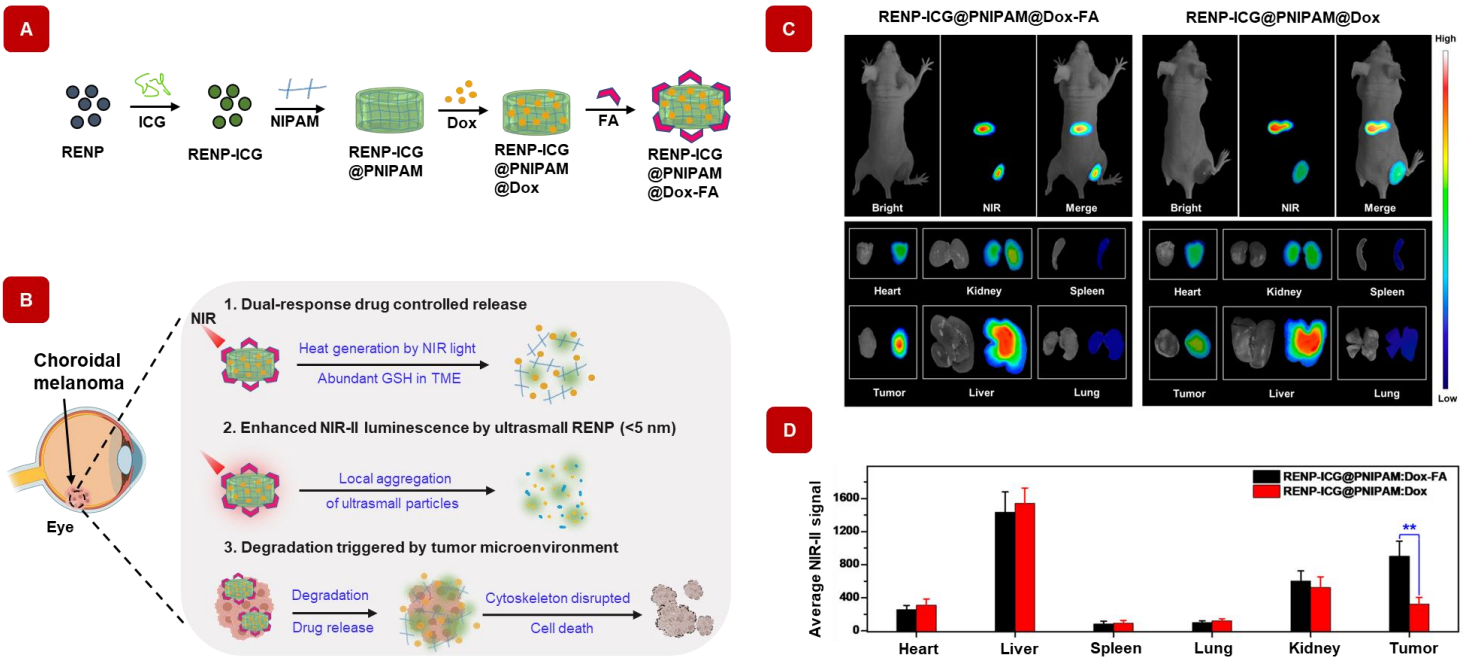

Figure 10. Dual-responsive drug release and bioimaging platform using light-responsive nanocomposite hydrogels. A) Diagram displays the chemical composition of the nanocomposite hydrogel. Indocyanine green (ICG) and folic acid (FA) were added to improve photothermal therapy and targeted drug delivery. Nanocomposite hydrogel (RENP-ICG@pNIPAM@Dox-FA) with ultra-small (<5 nm) rare-earth nanoparticles (RENPs) were used to image tumor site by enhanced NIR-II luminescence. The nanoparticles were used to improve the delivery of the drug doxorubicin (Dox), which was electrostatically loaded onto the light-responsive nanocomposite hydrogel for treating choroidal melanoma. B) Schematic illustration of the synthesis of dual-responsive nanocomposite hydrogel and their application in chemo-photothermal therapy for choroidal melanoma. Diagram also shows the degradation reaction of crosslinked Poly(*N*-isopropylacrylamide) (pNIPAM) hydrogels under the tumor microenvironment. The illustration displays the mechanism of release of Dox from the degradation reaction of crosslinked pNIPAM hydrogels in the tumor microenvironment with chemo-photothermal therapy for choroidal melanoma. NIR irradiation revealed that RENP was incorporated into a dual-reacting pNIPAM hydrogel capable of releasing drugs in a controlled manner in response to thermal energy and glutathione in the tumor microenvironment. C) NIR-II imaging of organs after injection of RENP-ICG@pNIPAM:Dox-FA and RENP-ICG@pNIPAM:Dox nanocomposites (10 mg/kg) into BALB/c nude mice. From the light intensity at tumor site, it was concluded that the inclusion of FA enhanced the targeting ability of the delivery vehicle. D) The light intensity was then quantified and has been displayed in this graph. The graph further proves enhanced imaging capability of the designed nanocomposite hydrogel. Adapted and reproduced with permission.[111] Copyright 2020, American Chemical Society.

Table 1. Light-triggered nanoparticle (NP)/hydrogel composites for therapeutic and diagnostic applications.

Phenomenon	NP	Conjugation	Polymeric hydrogels	Wavelength/Irradiation time	Applications	Refs
Plasmon Surface Resonance	Au	BP@Au@Fe_3O_4	Polyetherimide	980, 808, 650 nm/10 min	Photothermal therapy	[141]
		Methylene blue@Au@A9 RNA aptamer@thiolated polyethylene glycol (HS-PEG)	HS-PEG	785 nm/10 min	Combinational photothermal, thermodynamic therapy	[84]
		Gold nanorods@2,2′-Azobis[2-(2-imidazalin-2-yl)propane] dihydrochlaride (AIPH)@Hydrogel	*N*-isopropyl acrylamide (NIPAM) and hyaluronic acid (HA-GMA)	785 nm/10 min	Combinational photothermal, thermodynamic therapy	[93]
		Verteporfin (VP) conjugated to gold nanoparticles	SH-PEG and SH-PEG-NH_2	690 nm/30 min	Bioimaging, photodynamic therapy	[142]
		EGF_{pep}@AuNP@Pc4	PEG	672 nm	Photodynamic therapy	[143]
		Au@polymer@MB-Tf NPs	Polystyrene-*alt*-maleic acid (PSMA)	660 nm/4 min	Photodynamic therapy	[144]
		Gold nanorods (GNRs)@Polymer	Polymer nanofibers	808 nm/10 min	Photothermal therapy	[145]

	Ag	AgNP@alginate hydrogel shells	Alginate hydrogel shells	785 nm/10 s	Drug delivery	[146]
		Indocyanine Green-Loaded AgNP@Polyaniline Core	Polyaniline shell	704 nm/15 min	Bioimaging	[147]
		Silver nanocrystals@ poly(vinylpyrrolidone) (PVP)	PVP oligomers	405 nm/45 min	Optical imaging	[148]
		AgNP@nanogel	Chitosan	405 nm/every 30 s during 600 s	Antibacterial effects	[149]
	Al	Al(III) phthalocyanine chloride disulfonic acid@polyion complex vesicles	PEG	680 nm/5 min	Photodynamic therapy	[150]
	Pd	Pd nanosheets@PVP	PVP	826-1068 nm/30 min	Photothermal therapy	[151]
	Se	Selenium-inserted copolymer	PEG	650–900 nm/5 min	Photothermal therapy	[152]
Bandgap	Ferrite	$MnFe_2O_4$NP@Phospholipid monolayer (DSPE-PEG_{2000}-NH_2)	PEG	808 nm/5 min	Bioimaging, phtodynamic, and photothermal therapy	[153]

		$CoFe_2O_4$@Nap-GFFYS-AAP	Arylazopyrazole (AAP) modified pentapeptide gelator Nap-GFFYS	365-520 nm/over three fully reversible cycles	Tissue engineering	[154]
	Graphene	Graphene @*N*-acryloyl glycinamide (NAGA)	NAGA	808 nm/5 s with four cycles	Photothermal therapy, wound healing	[155]
		Graphene aerogel and a poly(*N*-isopropylacrylamide) hydrogel with incorporated polydopamine NP	Poly(*N*-isopropylacrylamide)	808 nm/3 min	Drug release	[156]
	Carbon nanotubes	Single-walled carbon nanotubes (SWCNT)@ pNIPAM	pNIPAM hydrogel	780 nm/1 min	Intravascular surgery	[157]
		SWCNT@phospholipid–polyethylene glycol (PL-PEG)	PL-PEG	808 nm/2 min	Near-Infrared Imaging, photothermal Ablation	[158]
		mAb@CNT@1,2-distearoyl-sn-glycero-3-phosphoethanolamine-*N*-[biotinyl(polyethylene glycol) 2000] [DSPE-PEG(2000)-biotin]	PEG	805-811 nm/7 min	Tumor ablation	[159]

	Graphene oxide (GO)	GO@polyaniline@ pNIPAM	pNIPAM hydrogel	808 nm/30 s	Biosensing, photothermal therapy	[160]
		Carboxymethyl chitosan-functionalized reduced graphene oxide@aldehyde functionalized PEG	PEG	808 nm/8 min	Photothermal therapy, drug delivery	[161]
		GO@poly(allylamine hydrochloride)	Poly(allylamine hydrochloride)	800-1200 nm/15 s to 30 s	Drug delivery	[162]
		GO@β-cyclodextrin @GelMA@dopamine	Methacrylate-modified gelatin (GelMA)	808 nm/10 min	Antibacterial effects	[163]
		GO@DOX-MSNs-PE@Fe_3O_4@PNAGA hydrogel	poly(*N*-acryloyl glycinamide) (PNAGA)	808 nm/one pulse a day upto 21 d	Tumor ablation	[164]
		GO@PEG	PEG	532, 785, 980 nm/20 min	Photothermal therapy	[165]
	Black phosphorus (BP)	BP@Hydrogel	Polyethylene glycol–amine (PEG-NH_2)	808 nm/5 min	Drug delivery	[166]
π-π* transition	Micellar NP	Diazonaphthoquinone @doxetaxel@micellar NP	Poly(ethylene glycol)-block-poly(l-lysine trifluoroacetate) (PEG-PLL)	365 nm/10 min	Drug delivery	[167]

	GO	GO@cucurbit[7]uril (CB[7])	PEG	808, 660 nm/each 10 min	Photothermal therapy, Photodynamic therapy	[168]
	PDA	PDA@pNIPAM	pNIPAM Hydrogels	808 nm/1 min	Wound healing	[169]
	Organic Photosensitizer	TMPyP@Hydrogel	Glycol chitosan and dibenzaldehyde-terminated telechelic PEG	532 nm/5 min	Bioimaging, Photodynimic therapy	[170]

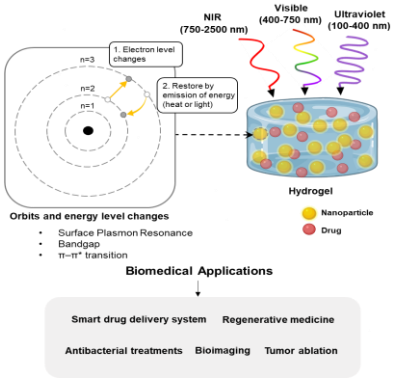

Table of Contents. Light-responsive nanocomposite polymeric hydrogels can be activated by absorbing light. Electrons of light-responsive nanoparticles in the hydrogel are moved to higher energy orbits by light stimulation. As the electrons return to their ground state, the nanoparticles release energy in the form of heat or long wavelength light. This heat dissipation can be further used for diverse biomedical applications.