Hybrid Nanostructures for Biomedical Applications

R. Rajakumari, Abhimanyu Tharayil, Sabu Thomas, and Nandakumar Kalarikkal

Abstract Nanoparticles have great potential in the biomedical field owing to its superior properties. Hybrid nanomaterials can be used to perform both diagnostic and therapeutic function by a single system. These materials will have the synergistic beneficial features of the different nanomaterials incorporated. In this chapter, we have categorised the inorganic/organic hybrid nanomaterials which are being developed in the field of biomedical applications. In addition, summarized the most recently reported hybrid nanomaterials, nanoparticles and nanocomposites with their synthesis methods and physicochemical properties. This chapter will summarize the recent advances in the synthesis, design and applications of hybrid nanomaterials in the biomedical field. The applications especially the imaging, drug delivery and cancer therapeutic applications will be highlighted.

Keywords Medical imaging · Theranostic · Cancer therapy · Liposomes · Nanoparticles

R. Rajakumari · A. Tharayil · S. Thomas (✉) · N. Kalarikkal (✉)
International and Inter-University Centre for Nanoscience and Nanotechnology, Mahatma Gandhi University, Kerala 686560, India
e-mail: sabuchathukulam@yahoo.co.uk

N. Kalarikkal
e-mail: nkkalarikkal@mgu.ac.in

S. Thomas
School of Chemical Sciences, Mahatma Gandhi University, Kerala 686560, India

N. Kalarikkal
School of Pure and Applied Physics, Mahatma Gandhi University, Kerala 686560, India

A. Tharayil · S. Thomas
School of Energy Materials, Mahatma Gandhi University, Kerala 686560, India

K. Upadhyay et al. (eds.), *Hybrid Phosphor Materials*, Engineering Materials,
https://doi.org/10.1007/978-3-030-90506-4_12

1 Introduction

The biomaterials such as polymers, metals, ceramics and composites are used in the biomedical applications for the treatment of various diseases. There are different types of polymers are established in the biomedical field because of its improved biocompatibility and biodegradability. In the biomedical applications, these biomaterials are used in the field of drug delivery, drug targeting, imaging, theranostics. There are several polymer based drug delivery systems which are available commercially and also few are clinically approved for the medicinal use [1–5].

The inorganic biomaterials which are used for the biomedical applications such as minerals, metals, metal oxides, glasses, ceramics and other inorganic components. These type of materials have number of advantages than the organic materials which includes mechanical, thermal, magnetic, optical properties and the porous structures [6]. There are also other class of biomaterials which is called as hybrid biomaterials or functionalised biomaterials which contains a mixture of organic and inorganic materials used for the biomedical applications [7, 8]. The inorganic nanoparticles such as gold, iron oxide nanoparticles, carbon dots, quantum dots etc. is easily dispersible in the water with the organic polymers for the surface modification. This type of hybrid biomaterials are used for the diagnostic and therapeutic purposes. Moreover, this type of hybrid materials leads to prepare a novel therapeutic molecules which can be used for imaging because of the excellent properties of inorganic nanoparticles and the surface modification. For fabricating bone graft materials the hybrid biomaterials were used which contains the inorganic ceramic nanoparticles along with the polymer nanocomposites [9, 10].

These hybrid materials containing the organic polymer and the inorganic materials are used particularly in the manufacturing of pharmaceuticals such as drug delivery carriers, scaffolds for tissue engineering etc., and medical devices such as dental implants, vascular stents etc. The organic/inorganic hybrid biomaterials are classified as nanoparticles and nanocomposites and these materials were prepared by many synthesis methods [11]. The reported methods are complex and difficult to process in an industrial level whereas the current scenario demands simpler, cost effective and also requires reproducibility. In addition, there are also some studies they are in continuous efforts to develop a novel class of hybrid materials by overcoming the drawbacks and limitations of the already existing methods. As it is used for the biomedical applications, it should be used safely by all for the clinical purposes. So, it is very important to use the biocompatible materials and also the *in-vivo* studies are very important to know the pharmacodynamics and pharmacokinetic behaviour of the molecules. Moreover, the interaction studies should be performed with the biological cells, tissues and proteins to understand the complexity and nature of the biomaterials [12, 13].

The hybrid biomaterials containing organic and inorganic nanomaterials were used for the drug delivery applications with different imaging concepts. This approach can also be useful for the theranostic applications for the treatment of various diseases. Therefore, this approach represents a novel strategy for the cancer

immunotherapy with the application of hybrid biomaterials. And also, the very novel artificial intelligence is an emerging technology which can contribute in developing personalised biomaterials with the mixture of polymer and inorganic materials. Thus, multidisciplinary approach by involving experts in various fields from biotechnology, medicine, physics, chemistry, pharmacy professionals are necessary for the clinical development of hybrid nanomaterials [14].

2 Organic/Inorganic Hybrid Nanomaterials

The organic/inorganic hybrid nanomaterials can be divided into two groups based on their interaction between the organic and inorganic moieties. The hybrid materials interacts very strongly by formation of covalent bonds or ionic bonds between the organic and inorganic components. This type of materials comes under type 2 hybrid materials in which they can be used to synthesise new materials from alkoxide, minimises the separation of phases and easier to identify the interface between the organic and inorganic components. The type 1 materials are classified as the hybrid materials which interacts with the organic and inorganic components very weakly by the van der Waals, hydrogen and electrostatic bonds. These type of hybrid materials were divided into hybrid nanoparticles and hybrid nanocomposites. The hybrid nanoparticles consists of organic and inorganic nanoparticles or nanomaterials where the hybrid nanocomposites consists of organic and inorganic components which are larger than or in the micro scale. Based on the bonding strength and the process through which they are formulated, these kind of materials were further divided into two different classes [15, 16].

2.1 Hybrid Nanoparticles

Generally the nanoparticles are in the size range of 1–100 nm which can be of organic or inorganic materials. This category of nanoparticles affords a wide range of opportunities to examine the material properties with respect to the particle size. For the biomedical applications, mostly the metal groups consists of Au, Ag and Cu nanoparticles were used because of their unique optical, catalytic and electrical properties based on their size [17, 18]. This kind of nanoparticles differ completely from the category of nanocomposites or bulk materials which completely depends on their shape, size, distance and the nature. If these nanoparticles has to be used in the bioapplications it is very important that these particles should be completely dispersed in the aqueous phase. They should have very good chemical stability and it also should be devoid of oxidation or sintering (avoidance of degradation process). To make it stable the polymer stabilizers were used in the synthesis of inorganic nanoparticles in which it improves the dispersion in the aqueous phase and thereby improving the

chemical stability. Moreover, these hybrid nanoparticles also improves the processability and biocompatibility of the materials by surface modification process. These kind of nanoparticles have the unique characteristics such as it can behave as both inorganic and organic nanomaterials. Therefore, this type of hybrid nanoparticles could be useful in different kinds of biological applications which also includes imaging, photodynamic therapy. Image assisted delivery, drug delivery applications [19–21].

2.2 Hybrid Nanocomposites

Generally the nanocomposites are combination of organic and inorganic nanomaterials. This type of nanocomposites consists of homogenous and heterogenous structures of organic and inorganic materials. Each organic and inorganic material domains are in the range of nanometer scale. Because of the synergy between the organic and inorganic nanomaterials they are considered to be the stronger hybrid nanocomposites. The physicochemical properties of the hybrid nanomaterials depend upon their nature and contents of the individual components of the organic and inorganic materials. When compared to the individual organic and inorganic components, the hybrid nanocomposites have very good mechanical and thermal stability. Moreover, the physicochemical properties (magnetic, electrical, redox) of the hybrid nanocomposites were controlled by the inorganic components because of their porous network. These porous nanostructures of the hybrid materials were used as a suitable candidate for the drug delivery applications. In addition, the hybrid nanocomposites as scaffolds can also be used in tissue regeneration and cell therapy. The porous structures of the hybrid nanomaterials are useful for encapsulation of osteoinductive components which stimulate the cells differentiation for the regeneration of tissues. For example, the hydrogels containing organic and inorganic materials that can be used in an extensive range of biomedical applications [22]. The organic and inorganic hybrid nanocomposites are categorised as matrix materials and hydrogels which are explained in detail below.

2.3 Hybrid Nanomaterials

The studies prove that the researches have utilised the both organic and inorganic nanoparticles for the biomedical applications. To achieve the desirable properties, the position, design and arrangement of individual nanoparticles should be controlled to use in the different fields. There are various synthetic methods were used and they are self-assembly, surface modification, physical blending, metal–organic frameworks (MOFs) and *in-situ* deposition. These methods are utilised to obtain the desired physicochemical properties by modifying the surface properties and thereby controlling its arrangement. The surface incompatibility between the polymer materials and

nanoparticles can be overcome by introduction of polymer or small molecules on the surface of the nanoparticles and this process is called as surface modification. This process improves the nanoparticles dispersion in the polymer matrix and also facilitates the modifications in the matrix which is useful for the wide range of applications [23, 24]. There are several methods to control the aligning of nanoparticles with respect to their physicochemical properties. Hence, there are different kinds of hybrid nanoparticles have been formulated to control the arrangements of nanoparticles using metal organic frameworks (MOFs) and self-assembly methods. Likewise there are methods to develop nanocomposites with the polymer matrix for the improvement of mechanical and other physicochemical properties. The nanoparticles should be well dispersed in the polymer matrix with a high stability to get the desired nanocomposites with the well-defined properties [25, 26]. The homogenous hybrid nanocomposites were categorised into two major classes such as physical and chemical. The synthetic methods of preparing hybrid nanocomposites by means of physical means involves solution and melt blending process and chemical process involves the *in-situ* deposition methods.

2.3.1 Hybrid Nanoparticles

The surface properties of the inorganic nanoparticles such as the colloidal stability and biocompatibility were not suitable for the biomedical applications. Because of their high surface area to volume ratio, the inorganic components are susceptible to the formation of agglomerates and aggregates. Thereby these inorganic nanoparticles undergoes a very rapid clearance by the reticuloendothelial system (RES). So to improve the biocompatibility, circulation time and stability of the inorganic nanoparticles, it is very important to modify the physicochemical properties by coating with organic polymers. And also, this section deals with the methods like surface modification, metal organic frameworks (MOFs) and self-assembly for polymers hybridization and stabilise the inorganic nanoparticles [27, 28].

Surface Modification Method

The inorganic nanoparticle surfaces could be improved by two different kinds of methods consists of adsorption (physical) and grafting (chemical) methods (Table 1). The surface modifications by physical methods were attained by the surface adsorption and reaction with the small molecules. And the surface modifications by chemical methods were achieved by the grafting of polymer molecules in which the functional groups acts as a site for chemical bonding (Fig. 1). The most common agent used for the inorganic nanoparticles are the silane coupling agents which has bifunctional groups forms a bridge/bond between the two phases [29]. The silane coupling agent contains R–Si-$(OR)_3$ in which the R = CH_3O–, CH_3CH_2O– acts as an anchor and it reacts with the –OH groups present on the surface of the metal oxides (M) forming a Si–O–M bond. The R forms an alkyl bridge between the functional group

Table 1 Synthesis of hybrid nanomaterials by surface modification method

	Polymer	Inorganic material
Hybrid nanoparticles (surface modification)	APTES, TEOS	$SrAl_2O_4:Eu^{2+}$ [34]
	DSPE-PEG	Fe_3O_4 [35]
	Poly(*N*-isopropyl acrylamide)	AuNPs [36]
	PMAGal-b-(PMAGal-co-PPyMA)	γ-Fe_2O_3 [37]
	Poly(2-(methylsulfonyl)ethyl acrylate)	Fe_3O_4 [38]
	PEG-PEI-Chitosan	Fe_3O_4 [39]
	Aminosilane, PEG	Fe_3O_4 [40]
	Carboxyl methylated PVA	Fe_3O_4 [41]

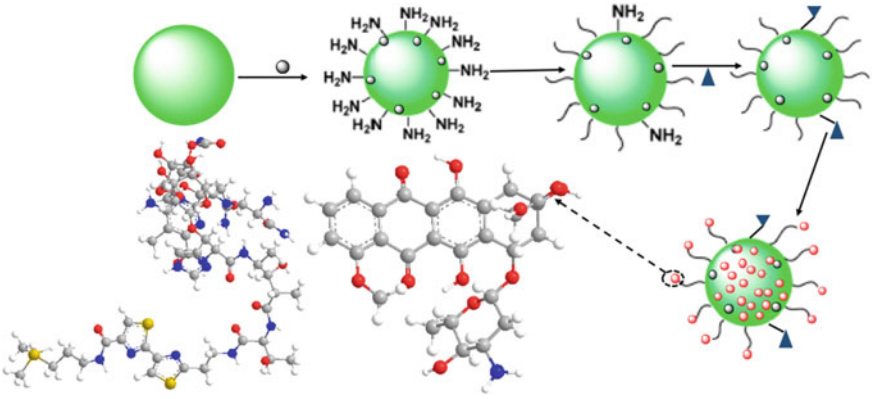

Fig. 1 Surface modification of nanoparticles for biomedical applications (reprinted with permission from MDPI nanomaterials [42])

and the silicon atom through a condensation reaction. The surface modification by the silane molecules undergoes by the four different types and they are (i) the alkoxyl groups should be hydrolysed in the water for the liberation of alcohols and producing a reactive silane molecule, (ii) self-condensation of silanol groups takes place during hydrolysis, (iii) the reactive silane groups were adsorbed by means hydrogen bond formation in the hydroxy groups of the metal oxide surfaces, (iv) and these molecules liberates water during heating then the remaining silane groups condensed with metal oxide groups through the conversion of hydrogen bonds into covalent bonds. Chen et al. prepared a nanoscintillator which is silica coated for the photodynamic therapy. For the synthesis of nanoscintillator, nanoparticles SrAl2O4:Eu^{2+} (SAO) were coated with silane precursors such ad tetra ethyl orthosilicate (TEOS) and aminopropyltriethoxysilane (APTES). These nanoscintillator which are coated with silica have a large number of functional amine group results in positively charged surface [30].

Table 2 Synthesis of hybrid nanoparticles by self-assembly

	Polymer	Inorganic material
Hybrid nanoparticles (self-assembly)	Diethylene glycol Tetra thiafulvalene	AuNPs [39]
	PEG-PBLA-Ce6	Fe_3O_4 [8]
	Gd-DTTA, polystyrenesulfonate	$[Ru(bpy)_3]Cl_2$ [48]
	NH_2–Leu–Aib–Tyr–OMe peptide	AuNPs[49]
	Diethylene glycol dioxynaphthalene	AuNPs [50]

Chemical method is another approach for the surface modification of nanoparticles. It includes the grafting of polymers to the surface that improves the functional characteristics and modifies the surface morphology of the inorganic nanoparticles [31]. There are two methods for chemical grafting and the first one is that it links the polymers with the surface of the inorganic nanoparticle. This process tends to low grafting density because of the reactivity of the functionalised polymer chains. The second approach is that to increase the grafting density the surface initiated polymerisation process is involved. This process includes radical, cationic, anionic polymerisation methods which involves the distribution of the functionalised grafted polymers from the nanoparticle surface. The monomers which are polymerised from the inorganic nanoparticle surface in the grafting method. They will easily penetrate the aggregated nanoparticles which reacts on the activated surface on the polymer because of its low molecular weight. The density and the thickness of the polymer could be controlled by the rate of polymerisation and the nature of monomer. In a study they have grafted poly (2-(methylsulfonyl) ethyl acrylate) using 12-(2-bromoisobutyramido) dodecanoic acid on the surface of superparamagnetic iron oxide nanoparticles through the polymerisation reaction [32, 33].

Self-Assembly

This method involves the controlling of accumulation of inorganic nanoparticles by improving their properties in a controlled way (Table 2). The nanoparticles or other distinct constituents in which they unite together via directly or indirectly through the specific interactions [43, 44]. The block copolymers play an important role in self-assembly of nanoparticles because ABA triblock chemical structures along with the nanoparticles provides well-defined interactions. Through the specific interactions these block copolymers self-assemble into the ordered nanostructures. Those specific interactions occurs by the block copolymers and they are dipole–dipole, covalent, non-covalent, steric hindrance, columbic attraction or repulsion. Balancing the hydrophilic and lipophilic balance (HLB) of the block copolymer has a great influence on the self-assembly of nanoparticles. Moreover, by controlling the HLB of the block copolymer, the morphology of the self-assembled nanoparticles can be maintained. In addition to the block copolymers, the inorganic nanoparticles

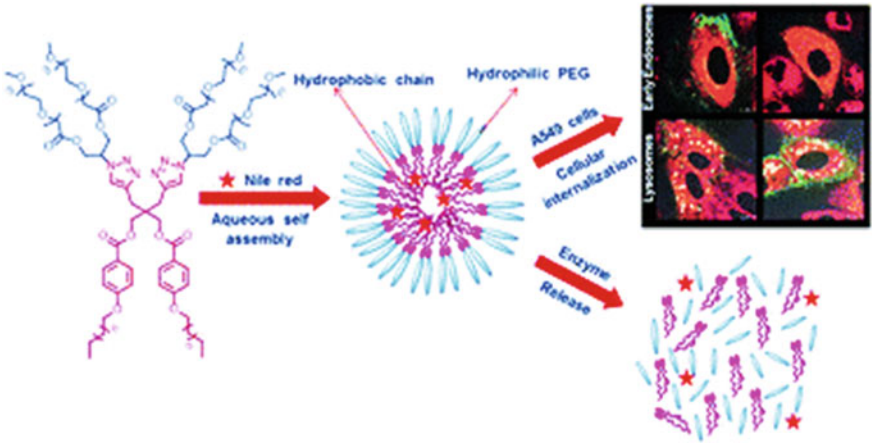

Fig. 2 Self-assembly nanomaterials for biomedical applications (reprinted with permission from RSC advances [51])

are also used for the functionalization or as the templates to provide stable self-assembled nanostructures. Mostly, the magnetic nanoparticles were combined with the block copolymers to produce a well-defined nanostructures. In a report, they have used pH sensitive magnetic nanoparticles (PMNs) as a functionalising agent on the block copolymers to obtain a self-assembled iron oxide nanoparticles. PMNs exhibited improved imaging for targeting the cancer cells through the self-assembly of iron oxide nanoparticles. This is because of the selective targeting ability of the PMNs which also showed photodynamic activity which kills and prevent the growth of cancer cells (Fig. 2) [45–47].

Metal–Organic Frameworks (MOFs)

The MOFs has the ability to protect the active moieties from degradation and also it improves the drug loading efficiency. Because of their even porosity, it has a good pore volume and shell surface to increase the drug loading capacity. And also, the metals are connected by the strong coordination bonds with the multidentate organic ligands which results in the high mechanical and thermal stability [52]. There are various functional materials such as graphene based materials, carbon nanotubes, quantum dots, metal nanoparticles and biomolecules were combined to form the hybrid nanomaterials (Table 3). So, it will be easy for the drug molecules in which it can be loaded in the MOFs which acts as a drug carriers to target the disease region and also it improves the stability. This leads to the commercialisation of few nanodrugs such as Abraxane, Ambisome and Doxil [53, 54]. In addition, MOFs can be attained by the single-component nanostructures with good physicochemical properties, intriguing morphological structures, improved BET (Brunauer–Emmett–Teller) surfaces and high porosity. Moreover, the fabrication methods for the MOFs

Table 3 Synthesis of hybrid nanomaterials by MOFs method

	Polymer	Inorganic material
Hybrid nanoparticles (metal organic frameworks (MOFs))	Terephthalic acid, 1,3,5-tris(4-carboxyphenyl)benzene	Zn_4O cluster [63]
	BTC	Fe_3O trimer [64]
	Naphthalene-2,6-dicarboxylic acid	Zinc nitrate [65]
	Lipoic acid, PEG	Zirconium nodes, AuNPs
	AzTPDC	Zinc nitrate [66]
	2-methylimidazole	Zinc nitrate [67]
	Amino-TPDC	$Zrcl_4$ [68]

include solution, diffusion and hydrothermal techniques [55]. The solution method is the most widely used method in which it contains organic ligands, metal elements and other materials in a solvent were stirred at a specified time and temperature. The purification process involves the filtration method in which the solvent is evaporated and whereas the diffusion method involves the long reaction process under mild condition which can be of liquid, gas or gel diffusion. Firstly, the gel diffusion method is a process in which the organic ligands are dispersed in the gel containing metal ion solution which forms a crystals of MOFs. Secondly, in the liquid diffusion process the organic ligands are dissolved in the solvent containing metal ions to form MOF crystals. Thirdly, the gas diffusion involves the process of mixing metal ion with the volatile organic ligand solution to form MOFs. An another method of preparing MOFs is the hydrothermal method in which it can be obtained by involving the organic ligands, metal ions, solvents and the other required materials in the polytetrafluoroethylene liner. These materials are kept in the high temperature reactor for the initiation of reaction process to form MOFs [56–59]. In a study, they have used an autophagy inhibitor 3-methyladenine (MA) in the MOFs (zeolitic imidazole framework) which has high drug loading capacity and they found that it has a strong anticancer activity. The MOFs have high encapsulating efficiency, particles with uniform size and shape, exceptional biocompatibility and high stability. Furthermore, the MA-ZIF exhibits strong anticancer effect by inhibiting the autophagy in the tumour bearing mice and also delivers the drug in a controlled manner with improved permeability. In addition, because of the improved permeability and retention, the active molecule accumulates in the tumour tissue more than normal because of the angiogenesis in the tumour tissue (Fig. 3) [60–62].

2.4 Hybrid Nanocomposites

The hybrid nanocomposites are intended to increase the optical, magnetic, electrical, rheological and mechanical properties. In this type of nanocomposites, the inorganic nanoparticles such as metal and metal oxides were incorporated in the polymer

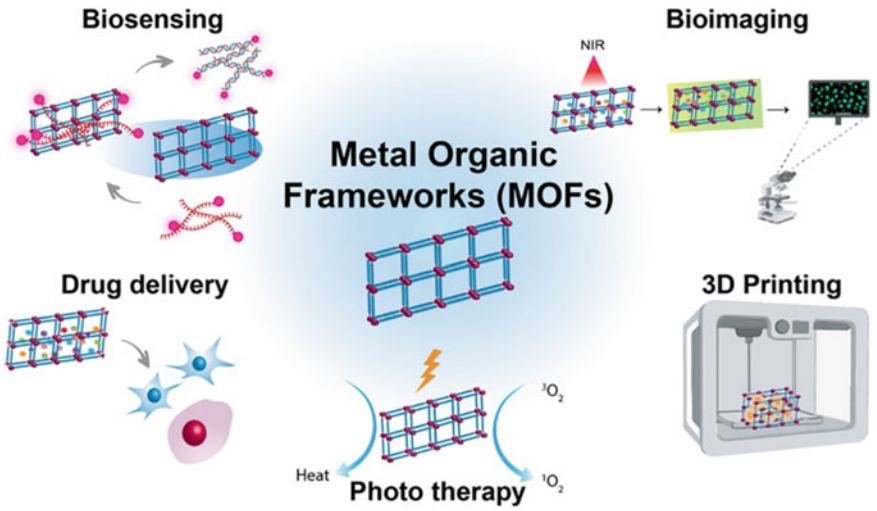

Fig. 3 Biomedical applications of MOFs (reprinted with permission from Wiley Interdisciplinary Reviews: Nanomedicine and Nanobiotechnology [69])

matrices. The only disadvantage in this type of hybrid nanocomposites is that it undergoes agglomeration if there is any inadequate distribution of nanoparticles in the polymer matrices. And also, this may leads to affect the physico chemical properties of the nanocomposites. Therefore, to increase the dispersion behaviour, the surface modification process is followed to create a strong repulsion between the nanoparticles on the polymer matrices. There are different methods were developed to get a well-defined characteristics to obtain an improved physico chemical properties [29].

2.4.1 Physical Blending

The conventional method for the preparation of hybrid nanocomposites is physical blending and this consists of solution and melt blending. Solution blending involves the direct mixing of polymer and inorganic nanoparticles in the solvent [29]. Then the hybrid nanocomposites is obtained by precipitation, filtration and removal of solvents. The main disadvantage of the solution blending method is that identifying a suitable solvent, its removal and the toxicity of the solvents. In a study, they have prepared polystyrene-zinc oxide nanocomposites by solution blending method and then they were casted as film. Firstly, the ZnO nanoparticles dissolved in the dimethylacetamide and polystyrene with vigorous stirring. After mixing, the obtained polystyrene-zinc oxide mixture were casted into films at 90 °C to get the nanocomposite film. This technique evenly distribute the ZnO nanoparticles in the polymer matrix and it also has improved stability [70].

Table 4 Synthesis of hybrid nanomaterials by physical blending method

	Polymer	Inorganic material
Hybrid nanoparticles (physical blending)	PMMA, PVPh	POSS [73]
	Polydopamine	AuNR [74]
	PS	ZnO [70]
	PP	SiO_2 [72]
	Polybenzoxazine	POSS [75]
	OBT, OBA	POSS [76]

2.4.2 Melt Blending

This technique is a very simple, cost-effective method which effectively removes the toxic solvents. In this method, the inorganic nanoparticles are dispersed in the polymer which is melted by the extrusion technology [71]. Because of the high viscosity of the polymers, it's difficult to regulate the dispersion of inorganic nanoparticles in the polymer matrix. In a study they have used polypropylene incorporated with nano silica by melt blending method with the addition of maleic anhydride which forms an amino functionalised polypropylene silica nanoparticles (Table 4). The grafting was done by condensation method by the incorporating maleic anhydride functionalised polypropylene and amino functionalised silicon dioxide. Then these blended mixture is dispersed in the polypropylene matrix using Haake Polylab at 140 °C which is refluxed with xylene and completed the blending at 200 °C. The rheological results proved that it increased the melt strength of polypropylene [72].

2.4.3 *In-Situ* Deposition

The *in-situ* deposition technique is one of the simple and effective method for dispersing the inorganic nanoparticles in the polymer matrix (Table 5). In this method the nanoparticles are uniformly distributed inside the polymer matrices and this method does not involves the usage of solvents [71]. Firstly, the inorganic nanoparticles are mixed with the monomer and this mixture is incorporated into the polymers through the liquid or the gas phase. The *in-situ* deposition method are prepared by

Table 5 Synthesis of hybrid nanomaterials by *in-situ* deposition method

	Polymer	Inorganic material
Hybrid nanoparticles (*in-situ* deposition)	Polylactic acid	AgNPs, GO [78]
	Polyaniline	MnO_2, Cr_2O_3 [79]
	Polypyrrole, Polyaniline	Fe_3O_4 [80]
	BisGMA-TEGDMA resin mixture	Silver 2-ethylhexanoate [77]
	Polyindole, PVA	$ZnFe_2O_4$ [81]

the methods such as stirring, ultrasonication and UV curing (photo initiation) which contains the blend of inorganic nanoparticles with the monomers. In addition, the hybrid nanocomposites or the polymer which cannot be processed under the melt mixing or the solution method can be fabricated by the *in-situ* deposition method [29]. In a study by Cheng et al., the preparation method involves the mixing of crosslinked dimethacrylate and silver nanoparticles through the photo initiated free radical polymerisation. The silver 2 ethyl hexanoate is mixed with the resin mixture BisGMA-TEGDMA (bisphenol A glycerolate methacrylate-triethylene glycol dimethacrylate) and this mixture undergoes photo polymerisation reaction using visible light. The X-ray photoelectron spectroscopy (XPS) and the morphological analysis proved that the silver nanoparticles are dispersed on the surface of the polymer matrix [77].

3 Biomedical Applications

3.1 Detection and Treatment of Cancer

Hybrid nanoparticles contain two or more different materials in the nanometer dimension, which will have the advantages of both individual nanoparticles (Table 6). In the medical field it is believed that this material will have superior properties of individual nanoparticles and is very useful in cancer detection and treatment [82, 83]. Many nanoparticles are manufactured which have the ability to circulate in the blood stream and detect cancer causing tumors [83]. Nanoparticles are used as a drug delivery agent as it can carry comparatively higher drug loads and deliver at targeted tumor sites [84]. Liposomes based on lipid bi layer have high load carrying capability combined with minimum toxicity [85]. Similarly the inorganic mesoporous silica nanoparticles were used and were proven to have targeted drug delivery properties [86]. Nanoparticles can also be engineered to produce thermal energy from optical or radio frequency sources and can be used in photothermal therapy to destroy malignant tumors (Fig. 4) [87]. The nanoparticles produce outstanding results in the treatment of cancer, but the single functionality limits their use; as a result a synergistic multi component system is required to detect, monitor and treat malignancies that arises [88, 89]. This is where the hybrid systems come into play where multiple nanostructures and components are integrated into a single component to form a therapeutic and diagnostic system commonly referred to as theranostic device [90–93].

The functional nanostructures which are used as a contrast agent, fluorescence imaging etc. are incorporated onto the surface to the another inner compartment of another structural nanocomponents[94]. These structural nanocomponents could be a polymer, liposome, micelle etc. that serve as a drug carrier or components like gold nanoparticles that can be used in photothermal therapy [95, 96]. These hybrid nanostructures when administered intravenously should circulate in the blood stream for more than two hours and have the ability to be readily filtered out by the

Table 6 Hybrid nanostructure based systems for theranostic applications

Nanocomponent	Functional nanocomponents	Function	Target cells/area	Referencess
Phospholipid liposome	Gold NP	Plasmonic investigation, optical imaging	Jurkat cells	[144, 145]
DSPC/DPPC phospholipid liposome calcein drug	Gold NP	Light triggered drug release	ARPE 19 cells	[146]
Phospholipid liposome [6-carboxyfluorescein drug]	Gold NP	Photothermal drug release	NA	[147]
Phospholipid liposome [xylenol orange sodium salt drug]	Superparamagnetic iron oxide nanodots	Ultra sound triggered MRI	NA	[148]
Bilayer decorated magneto liposomes	Hydrophobic superparamagnetic iron oxide nanoparticle	NP heating using AC electromagnetic fields		[149]
PEGylated liposome JPM 565	Ferrimagnetic iron oxide	Non-invasive drug delivery	MMTV-PyMT tumour	[150]
Phospholipid liposome	Quantum dot	Optical imaging	A549 lung cells	[151]
Phospholipid liposome doxorubicin	NA	NA	MCF-7/HER 2 cells	[152]
Polybutyl cyanoacrylate microbubbles/paclitaxel	Iron oxide nanoparticles	Magnetic resonance and ultrasound imaging	MLS human epithelial ovarian cancer cells	[153]
MAL-PEG-PLA block MPEG-PLA/doxorubicin	Superparamagnetic iron oxide nanoparticles	Magnetic resonance imaging	SLK cells, Avβ3 integrins	[154]
Phospholipid micelle	Oleic acid coated magnetic nanocrystal		MKN-74	[155]
PEG-PAsp(DIP)-CA/Paclitaxel	Quantum dot	Optical imaging	Bel 7402 human carcinoma cells	[156]
PEG-phospholipid micelle	Magnetic nanoparticle, TOP coated quantum dot	Optical and magentic resonance imaging	MDA-MB-435 human cancer cells	[157]
PS(16)-b-PAA(10)/doxorubicin	Magnetic nanocrystal	Optical imaging	4T1 cancer cells	[158]
Adenovirus	MnMEIO magnetic nanoparticle	Gene delivery	CAR positive cells	[104]
HIV-1	DNA-Au nanoparticles	Photothermal imaging	NA	[159]

(continued)

Table 6 (continued)

Nanocomponent	Functional nanocomponents	Function	Target cells/area	Referencess
PLGA/methotrexate	RGD attached gold nanoparticles	Photothermal healing	A 431 carcinoma cells	[160]
PS-PLGA/paclitaxel	QD and Iron oxide nanoparticles	Optical and magnetic resonance imaging	LNCaP prostrate cancer cells	[161]
Magnetic gold nanoshells and PEG linker	Iron oxide nanoparticles	Magnetic resonance imaging	SKBR3 and H520 cells	[162]
SWNT/cisplatin	Quantum dots	Optical imaging	EGFR antibody	[163, 164]

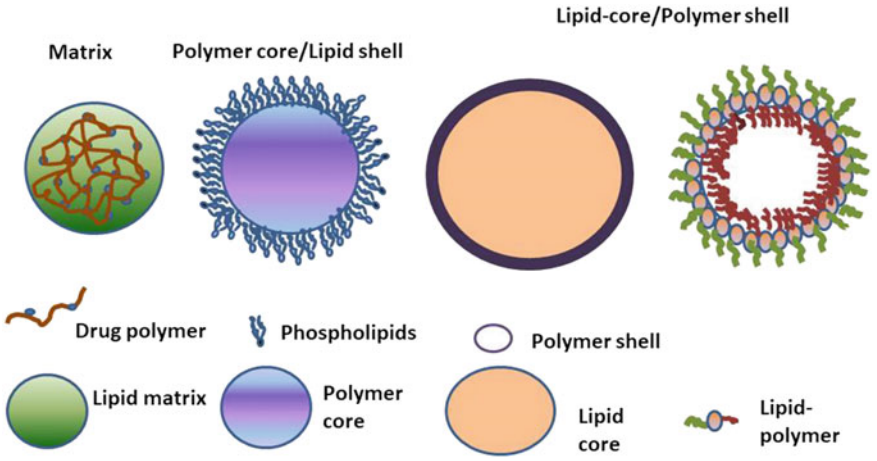

Fig. 4 Polymer-Lipid hybrid nanocarrier system showing the monolithic polymer matrix and the core shell type (redrawn from [143])

liver and kidneys [97]. The theranostic agents provide both diagnosis and treatment with the same material. A hybrid nanoparticle composite of doxorubicin and calcium carbonate hybrid nanoparticles were used for chemotherapy and cancer related imaging applications [98]. The enhanced permeability and retention effect causes the nanomaterial to selectively attach to the tumor tissues [99]. In the *in-vivo* studies the hybrid nanomaterial composites showed excellent anticancer properties. Antigens were encapsulated inside nanoparticles and delivered to improve the B and T cell responses. These materials can directly act on antigen presenting cells thereby triggering the activation of antigen specific T cells [100].

A uniform core shell spherical nanoparticles made of bovine serum albumin and polymethylmethacrylate core was made. This protein hydrophobic polymer conjugate functions as a drug delivery agent and possess additional features owing to their amphiphilic molecular structures and island growth. In the *in-vivo* studies camptothecin encapsulated BSA/PMMA nanohybrid material showed enhanced anti tumor activity [101]. Kang et al. prepared gold nanoparticle based vaccines where conjugated with a recombinant ovalbumin for the analysis of CD^{8+} T cell response and delivery into lymph nodes [102]. The *in-vivo* mice study showed remarkable tumor inhibition properties and a higher interferon gamma production. The study also showed the importance of nanoparticle size in the therapeutical applications. In another study, Zhang et al. constructed a novel mannose targeting LPNP vaccine system based on a biodegradable polymer PCL-PEG-PCL and cationic lipid DOTAP for the delivery of an antigen and a toll like receptor (TLR 7/8). The vaccine had a hydrophobic inner core of PCL-PEG-PCL with imiquimod, a lipid layer, a cationic DOTAP lipid and a mannose targeting moiety. The vaccine delivery with Monophosphoryl lipid A (MPLA) and imiquimod (IMQ) with a hybrid nanoparticle system showed promising antigen delivery [103].

Yong Min Huh et al. developed adenovirus based hybridised magnetic nanoparticle system based on manganese doped iron oxide that had the capabilities of targeted infection and magnetic resonance imaging. The adenovirus was selected as it showed specificity to the cells with overexpression of coxsackievirus receptor and outstanding gene delivery capability [104]. Polydopamine coated nano star shaped gold nanoparticles showed improved photothermal efficiency. When doxorubicin were administered along with polydopamine coated gold nanoparticle the material showed remarkable antitumor immune response. The *in-vivo* studies also showed a long term anti tumor immunity response [105]. In another study by Wu et al. gold nanoflowers with Chlorin e6 and a polydopamine coating was used in the photothermal therapy applications. The material showed lower cytotoxicity and phototoxicity and had a combined effect for killing cancer cells [106]. A poly (ethylene glycol)/ poly (ethylene imine) co grafted iron nanoparticles were prepared and shown to have improved tumor resistance. This magnetic hyperthermia based material produced tumor associated antigens and elicited anti tumor immune response [107].

Photosensitizers used in the non-invasive photodynamic therapy has low selectivity for tumors and also aggregates under physiological conditions [108]. Lanthanide ion doped upconversion nanoparticles acts as a transducer by up converting absorbed near infra-red light to the high energy visible light. A highly efficient NIR-triggered PDT system based on $LiYF_4$: Yb/Er upconversion nanoparticles were coupled with a photosensitizer of a β-carboxyphthalocyanine zinc (ZnPc-COOH) molecule by a direct electrostatic interaction, which produced singlet oxygen ($^1O_2$). This helps in the deep tissue penetration of visible light to treat deep tumors. The infra-red photons absorbed by lanthanide ions in a host lattice produces high energy photon [109]. Nano scintillated ionizing radiation was used which overcame the issue of low skin penetration depth in the photodynamic therapy [110]. The ionizing X-rays showed tissue penetration which was multiple times deeper than

infrared radiations. The interaction of high energy X ray photons with nano scintillator occurs through a cascading of photo electric effect and Compton scattering that generates many electron hole pairs [111]. This trapping of electron and hole creates luminescence and leads to the production of $^1O_2$ which is cytotoxic in nature [112]. The microenvironment of the tumor plays a big role in the efficacy of the photodynamic therapy as a low oxygen microenvironment increase tumor metasis and promote resistance to chemotherapy [113, 114].

Perfluorocarbon based oxygen nanoparticles were delivered to improve the hypoxic tumor microenvironment even though the efficiency is quite less as the oxygen quantity is less [115]. Human serum albumin, chlorin e6, and manganese di oxide nanoparticles (HSA-MnO_2-Ce6) were prepared to overcome tumor related hypoxia and treat bladder cancer by a photodynamic therapy. Manganese dioxide nanoparticles reacted with hydrogen peroxide improved the PDT efficiency by the production of O_2. These were performed in an *in-vivo* mouse experiment and showed good PDT efficiency [116]. Hyperthermia is another factor that causes destruction of cancer cells [117]. The thermal gradient that develops will be maximum at the body surface and reduces as it penetrates the tissues. Indocyanine green (ICG) dye in combination with a nanocarrier is used to improve its photothermal efficiency. These was shown in an *in-vivo* study when the ICG nanohybrid particles targeted large tumor particles. An Indocyanine green, 1,2 distearoyl-sn-glycero-3-phosphethanolamine-*N*-[methoxy (polyethylene glycol) coated iron oxide nanoparticles were constructed for dual modal imaging as a theranostic agent. The hybrid material showed excellent photostability and temperature increment upon treatment with NIR laser [118].

A gene editing nanohybrid system prepared by Mout et al. had a CRISPR/Cas9-ribonucleoprotein with cationic arginine gold nanoparticle based system. The system showed an improved cytoplasmic delivery for the gene editing system [119]. A nanohybrid containing PEGylated triangular gold nanoparticles conjugated with a peptide P_{75} was prepared (TGN-PEG-P_{75}). The system had an affinity towards epidermal growth factor receptor and is overexpressed in non-small cell lung cancer (NSCLC) cells due to the interaction between anti-epidermal growth factor receptor (EGFR) and the peptide. The material behaved as an efficient theranostic device showing visual guidance and inhibition of the NSCLC cells by the photothermal therapy effect [120]. A 3D bioprinting method was adopted to produce nanohybrids of PEGDA, laponite and hydroxyapatite. The material was intended for usage as a bone scaffold [121]. A nanocomposite scaffold made of 3D printed porous calcium phosphate polylactic acid conjugated with human bone morphogenetic protein-2 (rhBMP-2) showed delivery of both rhBMP-2 and calcium ions and promoted differentiation of stem cells [122].

In another study functionalized graphene oxide (GO) nanosheets that has angiogenic genes incorporated into GelMA hydrogel showed good revascularization in the diseased heart [123]. Also, graphene oxide and reduced graphene oxide embedded PEG/PA hydrogel showed good chondrogenesis and adipogenesis [124]. Liu et al. prepared crosslinked functionalized graphene oxide acrylate (Goa) with CNT and poly (ethylene glycol) acrylate with oligo (polyethylene glycol) fumarate

hydrogel. The material showed excellent biocompatibility as enhanced proliferation and spreading of PC12 cells were observed on the conducting hydrogels [125]. Gold nanoparticles embedded in GelMA to form hybrid nanostructures and showed improved cell matrix adhesion. The amount of gold nanoparticles decides the proliferation and osteogenic differentiation of the stem cells [126].

A hybrid nanostructure based scaffold made of PLGA/$Mg(OH)_2$ showed good anti-inflammatory properties. In the *in-vivo* study using a mouse model the hybrid material showed regeneration of renal glomerular tissue and had a very low inflammatory response [127]. Starch modified hyperbranched polyurethane with carbon dot silver nanomaterials based hybrid structures shows improved thermal, mechanical properties along with high biocompatibility and infection resistance [128]. Owing to these features the material can be used as a material for self-expandable stents. A vascular stent made of cobalt-chromium, Sirolimus loaded PLGA with a surface modified coating of $Mg(OH)_2$ nanoparticles showed less inflammatory response by in stent restenosis as part of intimal hyperplasia [129]. Improving the endothelialisation is one of the most sought after way to improve the efficiency of the vascular stent implantation [130]. A collagen/gold nanocomposite material showed excellent biomechanical and thermal properties [131]. The *in-vivo* studies in a rat model showed excellent vascular regeneration, higher antifibrotic ability and anti-inflammatory responses. A polyhedral oligomeric silsesquioxane poly (carbonate-urea) urethane nanocomposite was attached with anti CD34 antibodies to improve endothelialisation by capturing the endothelial progenitor cells. Thus this material can be used as an ideal coating for catheter stents due to its superior biocompatibility and biophysical properties [132].

Naturally occurring viral nanoparticles like cowpea mosaic virus and bacteriophage Qβ particles were linked with C60 fullerenes to improve their solubility. The bio conjugation was realised by a click chemistry involving poly (ethylene glycol) modified propargyl-O-PEG C60 units. This material had the potential to be used in photo activated tumor therapy applications [133]. A nanohybrid system comprising of a hydrophobic PLGA core loaded with fluorescent quantum dots and with a positive charged glycol chitosan shell. The loaded DNA was released as the pH of the system changes. An *in-vivo* study using a mouse model confirmed the transfection of DNA into the Langerhans cells present on the skin surface [134]. A treatment device for Rheumatoid arthritis was developed by making a methotrexate drug loaded PLGA with RGD conjugated gold half shell nanoparticles. The developed nanohybrid was injected into an arthritic mouse and the nanoparticles selectively adhered at the inflammation sites. The drug was delivered by a photothermal method after being exposed by near infrared radiation (NIR). The nanohybrid material showed excellent therapeutic efficiency even when smaller dosage of drug is used [135]. A ferromagnetic iron oxide nanoparticle prepared using saline crystal hydrate were encapsulated in a steric stable PEGylated liposome. The intracellular delivery of the targeted ferri liposome in an *in-vivo* mice mammary tumor cell was observed with a significant reduction in tumor growth [136]. A dumbbell like gold-iron oxide hybrid nanoparticles were prepared and coupled with Herceptin and platin complex. These material could be used as potential nanocarriers for theranostic applications [137].

In a study by Zhu et al. a bifunctional iron oxide silver ^{125}I heterodimers were prepared to be used as imaging modules. The $Fe_3O_4/Ag/^{125}I$ heterostructured radionuclide nanoparticles showed high radiolabeling combined with a low cell toxicity, where ^{125}I served as the contrast agent. The SPECT images of mice *in-vivo* study showed the nanoparticles were taken readily by liver and spleen [138]. An Ag–Fe_3O_4 heterodimer nanocomposite heterodimer system was prepared where nanocrystal sizes could be varied by the synthesis conditions. This material has the advantage for simultaneous two photon fluorescence imaging and magnetic manipulation [139]. A multimodal contrast agent's i.e. thiol modified gold nanocages and iron oxide nanoparticles were prepared for simultaneous T_1–T_2 contrast imaging. The prepared hybrid nanoparticles showed excellent biocompatibility with very less aggregation and has good contrast properties [140].

Li etc. prepared gold coated iron oxide nanoroses which can be used in optical imaging, magnetic resonance imaging, photothermal therapy, chemotherapy and aptamer based targeting. The anticancer drug doxorubicin is integrated with nanoroses and is released due to a rise in temperature when near infrared light is absorbed by the gold shell. The aptamers present on the surface provides efficient and selective drug delivery and imaging with high specificity [141]. A theranostic device made of Polystyrene which was embedded with superparamagnetic iron oxide nanoparticles and the drug paclitaxel was loaded in a poly (lactic-co-glycolic acid). The targeting was by conjugating nanocarriers with anti-prostrate specific membrane antigen. The detection studies and the nanocarrier binding activity was carried out in the LNCaP prostrate cancer cells. This material has the advantage of dual modality within the same nanosystem for cancer diagnosis and chemotherapy [142].

4 Conclusions and Clinical Prospects

The hybrid nanoparticle based systems have made significant development in the field of biomedical applications especially cancer therapy. These hybrid nanoparticles show significant function in *in-vitro* based studies, but once testing is done inside the body environment the behaviour of these materials change. Inside the dynamic body environment the nanoparticles interact with many cells, tissues, proteins and majority of them are cleared out from the body before reaching the targeted site. It requires careful engineering of the chemical and surface properties to improve the efficiency and residence time of these materials. The hybrid nanomaterials will have a combined size larger than individual nanomaterials and are designed in such a way so that they can accumulate preferentially at the tumor sites due to the enhanced permeation and retention (EPR) effect. The biggest challenge is that all the components of the hybrid system should work in tandem and coherently to achieve the desired biomedical function. All the materials individually and together should not elicit any adverse reactions and cause an immunological response. Thus it is imperative to have reliable and biocompatible material and the design and its *in-vivo* behaviour should be given considerable weightage.

References

1. Qiu, L.Y., Bae, Y.H.: Polymer architecture and drug delivery. Pharm. Res. **23**, 1–30 (2006)
2. Huebsch, N., Mooney, D.J.: Inspiration and application in the evolution of biomaterials. Nature **462**, 426–432 (2009)
3. Bobo, D., Robinson, K.J., Islam, J., Thurecht, K.J., Corrie, S.R.: Nanoparticle-based medicines: a review of FDA-approved materials and clinical trials to date. Pharm. Res. **33**, 2373–2387 (2016)
4. Allen, T.M., Cullis, P.R.: Drug delivery systems: entering the mainstream. Science **303**(80), 1818–1822 (2004)
5. Ramakrishna, S., Mayer, J., Wintermantel, E., Leong, K.W.: Biomedical applications of polymer-composite materials: a review. Compos. Sci. Technol. **61**, 1189–1224 (2001)
6. Nicole, L., Rozes, L., Sanchez, C.: Integrative approaches to hybrid multifunctional materials: from multidisciplinary research to applied technologies. Adv. Mater. **22**, 3208–3214 (2010)
7. Mir, S.H., Nagahara, L.A., Thundat, T., Mokarian-Tabari, P., Furukawa, H., Khosla, A.: Organic-inorganic hybrid functional materials: an integrated platform for applied technologies. J. Electrochem. Soc. **165**, B3137 (2018)
8. Ling, D., Park, W., Park, Y.I., Lee, N., Li, F., Song, C., et al.: Multiple-interaction ligands inspired by mussel adhesive protein: synthesis of highly stable and biocompatible nanoparticles. Angew. Chemie. Int. Ed. **50**, 11360–11365 (2011)
9. Liu, H., Webster, T.J.: Mechanical properties of dispersed ceramic nanoparticles in polymer composites for orthopedic applications. Int. J. Nanomed. **5**, 299 (2010)
10. Hong, Z., Reis, R.L., Mano, J.F.: Preparation and *in-vitro* characterization of scaffolds of poly (L-lactic acid) containing bioactive glass ceramic nanoparticles. Acta Biomater. **4**, 1297–1306 (2008)
11. Ates, B., Koytepe, S., Balcioglu, S., Ulu, A., Gurses, C.: Biomedical Applications of Hybrid Polymer Composite Materials. Elsevier Ltd (2017). https://doi.org/10.1016/B978-0-08-100785-3.00012-7
12. Tsuru, K., Hayakawa, S., Osaka, A.: Medical Applications of Hybrid Materials. Weinheim. Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim (2007)
13. Sanchez, C., Shea, K.J., Kitagawa, S.: Medical applications of organic–inorganic hybrid materials within the field of silica-based bioceramics. Chem. Soc. Rev. **40**, 596–607 (2011). https://doi.org/10.1039/c0cs00025f
14. Chimene, D., Alge, D.L., Gaharwar, A.K.: Two-dimensional nanomaterials for biomedical applications: emerging trends and future prospects. Adv. Mater. **27**, 7261–7284 (2015)
15. Adnan, M.M., Dalod, A.R.M., Balci, M.H., Glaum, J., Einarsrud, M.-A.: *In-situ* synthesis of hybrid inorganic–polymer nanocomposites. Polymers (Basel) **10**, 1129 (2018)
16. Sanchez, C., Ribot, F., Lebeau, B.: Molecular design of hybrid organic-inorganic nanocomposites synthesized via sol-gel chemistry. J. Mater. Chem. **9**, 35–44 (1999)
17. Daniel, M.-C., Astruc, D.: Gold nanoparticles: assembly, supramolecular chemistry, quantum-size-related properties, and applications toward biology, catalysis, and nanotechnology. Chem. Rev. **104**, 293–346 (2004)
18. Magdolenova, Z., Collins, A., Kumar, A., Dhawan, A., Stone, V., Dusinska, M.: Mechanisms of genotoxicity. A review of *in-vitro* and *in-vivo* studies with engineered nanoparticles. Nanotoxicology **8**, 233–278 (2014)
19. Kelly, K.L., Coronado, E., Zhao, L.L., Schatz, G.C.: The optical properties of metal nanoparticles: the influence of size, shape, and dielectric environment (2003)
20. El-Sayed, M.A.: Small is different: shape-, size-, and composition-dependent properties of some colloidal semiconductor nanocrystals. Acc. Chem. Res. **37**, 326–333 (2004)
21. Zhao, N., Yan, L., Zhao, X., Chen, X., Li, A., Zheng, D., et al.: Versatile types of organic/inorganic nanohybrids: from strategic design to biomedical applications. Chem. Rev. **119**, 1666–1762 (2018)
22. Vallet-Regí, M., Colilla, M., González, B.: Medical applications of organic–inorganic hybrid materials within the field of silica-based bioceramics. Chem. Soc. Rev. **40**, 596–607 (2011)

23. Oun, A.A., Shankar, S., Rhim, J.-W.: Multifunctional nanocellulose/metal and metal oxide nanoparticle hybrid nanomaterials. Crit. Rev. Food Sci. Nutr. **60**, 435–460 (2020)
24. Liu, X., Zhang, Q., Knoll, W., Liedberg, B., Wang, Y.: Rational design of functional peptide-gold hybrid nanomaterials for molecular interactions. Adv. Mater. **32**, 2000866 (2020)
25. Makvandi, P., Wang, C., Zare, E.N., Borzacchiello, A., Niu, L., Tay, F.R.: Metal-based nanomaterials in biomedical applications: Antimicrobial activity and cytotoxicity aspects. Adv. Funct. Mater. 1910021 (2020)
26. Park, W., Shin, H., Choi, B., Rhim, W.-K., Na, K., Han, D.K.: Advanced hybrid nanomaterials for biomedical applications. Prog. Mater. Sci. 100686 (2020)
27. Xiao, M.-C., Chou, Y.-H., Hung, Y.-N., Hu, S.-H., Chiang, W.-H.: Hybrid polymeric nanoparticles with high zoledronic acid payload and proton sponge-triggered rapid drug release for anticancer applications. Mater. Sci. Eng. C **116**, 111277 (2020)
28. Pieretti, J.C., Rolim, W.R., Ferreira, F.F., Lombello, C.B., Nascimento, M.H.M., Seabra, A.B.: Synthesis, characterization, and cytotoxicity of Fe_3O_4@Ag hybrid nanoparticles: promising applications in cancer treatment. J. Clust. Sci. **31**, 535–547 (2020)
29. Kango, S., Kalia, S., Celli, A., Njuguna, J., Habibi, Y., Kumar, R.: Surface modification of inorganic nanoparticles for development of organic–inorganic nanocomposites—a review. Prog. Polym. Sci. **38**, 1232–1261 (2013)
30. Xie, Y., Hill, C.A.S., Xiao, Z., Militz, H., Mai, C.: Silane coupling agents used for natural fiber/polymer composites: a review. Compos. Part A. Appl. Sci. Manuf. **41**, 806–819 (2010)
31. Hideshima, S., Hinou, H., Ebihara, D., Sato, R., Kuroiwa, S., Nakanishi, T., et al.: Attomolar detection of influenza A virus hemagglutinin human H1 and avian H5 using glycan-blotted field effect transistor biosensor. Anal. Chem. **85**, 5641–5644 (2013)
32. Basuki, J.S., Esser, L., Zetterlund, P.B., Whittaker, M.R., Boyer, C., Davis, T.P.: Grafting of P (OEGA) onto magnetic nanoparticles using Cu(0) mediated polymerization: comparing grafting "from" and "to" approaches in the search for the optimal material design of nanoparticle MRI contrast agents. Macromolecules **46**, 6038–6047 (2013)
33. Chatterjee, S., Karam, T.E., Rosu, C., Wang, C.-H., Youm, S.G., Li, X., et al.: Silica–conjugated polymer hybrid fluorescent nanoparticles: preparation by surface-initiated polymerization and spectroscopic studies. J. Phys. Chem. C **122**, 6963–6975 (2018)
34. Chen, H., Wang, G.D., Chuang, Y.-J., Zhen, Z., Chen, X., Biddinger, P., et al.: Nanoscintillator-mediated X-ray inducible photodynamic therapy for *in-vivo* cancer treatment. Nano. Lett. **15**, 2249–2256 (2015)
35. Tong, S., Hou, S., Zheng, Z., Zhou, J., Bao, G.: Coating optimization of superparamagnetic iron oxide nanoparticles for high T2 relaxivity. Nano. Lett. **10**, 4607–4613 (2010)
36. Raula, J., Shan, J., Nuopponen, M., Niskanen, A., Jiang, H., Kauppinen, E.I., et al.: Synthesis of gold nanoparticles grafted with a thermoresponsive polymer by surface-induced reversible-addition-fragmentation chain-transfer polymerization. Langmuir **19**, 3499–3504 (2003)
37. Pfaff, A., Schallon, A., Ruhland, T.M., Majewski, A.P., Schmalz, H., Freitag, R., et al.: Magnetic and fluorescent glycopolymer hybrid nanoparticles for intranuclear optical imaging. Biomacromol **12**, 3805–3811 (2011)
38. Yan, J., Li, S., Cartieri, F., Wang, Z., Hitchens, T.K., Leonardo, J., et al.: Iron oxide nanoparticles with grafted polymeric analogue of dimethyl sulfoxide as potential magnetic resonance imaging contrast agents. ACS Appl. Mater. Interfaces **10**, 21901–21908 (2018)
39. Kievit, F.M., Veiseh, O., Bhattarai, N., Fang, C., Gunn, J.W., Lee, D., et al.: PEI–PEG–chitosan-copolymer-coated iron oxide nanoparticles for safe gene delivery: synthesis, complexation, and transfection. Adv. Funct. Mater. **19**, 2244–2251 (2009)
40. Cole, A.J., David, A.E., Wang, J., Galbán, C.J., Hill, H.L., Yang, V.C.: Polyethylene glycol modified, cross-linked starch-coated iron oxide nanoparticles for enhanced magnetic tumor targeting. Biomaterials **32**, 2183–2193 (2011)
41. Liong, M., Shao, H., Haun, J.B., Lee, H., Weissleder, R.: Carboxymethylated polyvinyl alcohol stabilizes doped ferrofluids for biological applications. Adv. Mater. **22**, 5168–5172 (2010)
42. Zhu, N., Ji, H., Yu, P., Niu, J., Farooq, M.U., Akram, M.W., et al.: Surface modification of magnetic iron oxide nanoparticles. Nanomaterials **8**, 810 (2018)

43. Li, F., Lu, J., Kong, X., Hyeon, T., Ling, D.: Dynamic nanoparticle assemblies for biomedical applications. Adv Mater **29**, 1605897 (2017)
44. Nie, Z., Petukhova, A., Kumacheva, E.: Properties and emerging applications of self-assembled structures made from inorganic nanoparticles. Nat. Nanotechnol. **5**, 15–25 (2010)
45. Ling, D., Hackett, M.J., Hyeon, T.: Surface ligands in synthesis, modification, assembly and biomedical applications of nanoparticles. Nano. Today **9**, 457–477 (2014)
46. Grzelczak, M., Vermant, J., Furst, E.M., Liz-Marzán, L.M.: Directed self-assembly of nanoparticles. ACS Nano **4**, 3591–3605 (2010)
47. Ling, D., Lee, N., Hyeon, T.: Chemical synthesis and assembly of uniformly sized iron oxide nanoparticles for medical applications. Acc. Chem. Res. **48**, 1276–1285 (2015)
48. Kim, J.S., Rieter, W.J., Taylor, K.M.L., An, H., Lin, W., Lin, W.: Self-assembled hybrid nanoparticles for cancer-specific multimodal imaging. J. Am. Chem. Soc. **129**, 8962–8963 (2007)
49. Si, S., Raula, M., Paira, T.K., Mandal, T.K.: Reversible self-assembly of carboxylated peptide-functionalized gold nanoparticles driven by metal-ion coordination. Chem. Phys. Chem. **9**, 1578–1584 (2008)
50. Klajn, R., Olson, M.A., Wesson, P.J., Fang, L., Coskun, A., Trabolsi, A., et al.: Dynamic hook-and-eye nanoparticle sponges. Nat. Chem. **1**, 733–738 (2009)
51. Prasad, S., Achazi, K., Böttcher, C., Haag, R., Sharma, S.K.: Fabrication of nanostructures through self-assembly of non-ionic amphiphiles for biomedical applications. RSC Adv. **7**, 22121–22132 (2017)
52. Horcajada, P., Gref, R., Baati, T., Allan, P.K., Maurin, G., Couvreur, P., et al.: Metal–organic frameworks in biomedicine. Chem. Rev. **112**, 1232–1268 (2012)
53. He, C., Liu, D., Lin, W.: Nanomedicine applications of hybrid nanomaterials built from metal–ligand coordination bonds: nanoscale metal–organic frameworks and nanoscale coordination polymers. Chem. Rev. **115**, 11079–11108 (2015)
54. Moon, H.R., Lim, D.-W., Suh, M.P.: Fabrication of metal nanoparticles in metal–organic frameworks. Chem. Soc. Rev. **42**, 1807–1824 (2013)
55. Wang, L., Zheng, M., Xie, Z.: Nanoscale metal–organic frameworks for drug delivery: a conventional platform with new promise. J. Mater. Chem. B **6**, 707–717 (2018)
56. Wu, M., Yang, Y.: Metal–organic framework (MOF)-based drug/cargo delivery and cancer therapy. Adv. Mater. **29**, 1606134 (2017)
57. Stock, N., Biswas, S.: Synthesis of metal-organic frameworks (MOFs): routes to various MOF topologies, morphologies, and composites. Chem. Rev. **112**, 933–969 (2012)
58. Chen, B., Yang, Z., Zhu, Y., Xia, Y.: Zeolitic imidazolate framework materials: recent progress in synthesis and applications. J. Mater. Chem. A **2**, 16811–16831 (2014)
59. Xuan, W., Zhu, C., Liu, Y., Cui, Y.: Mesoporous metal–organic framework materials. Chem. Soc. Rev. **41**, 1677–1695 (2012)
60. Fang, J., Nakamura, H., Maeda, H.: The EPR effect: unique features of tumor blood vessels for drug delivery, factors involved, and limitations and augmentation of the effect. Adv. Drug Deliv. Rev. **63**, 136–151 (2011)
61. Greish, K.: Enhanced Permeability and Retention (EPR) Effect for Anticancer Nanomedicine Drug Targeting, pp. 25–37. Springer, Cancer Nanotechnol. (2010)
62. Nichols, J.W., Bae, Y.H.E.P.R.: Evidence and fallacy. J. Control Release **190**, 451–464 (2014)
63. Koh, K., Wong-Foy, A.G., Matzger, A.J.: A crystalline mesoporous coordination copolymer with high microporosity. Angew. Chemie. Int. Ed. **47**, 677–680 (2008)
64. Han, L., Qi, H., Zhang, D., Ye, G., Zhou, W., Hou, C., et al.: A facile and green synthesis of MIL-100 (Fe) with high-yield and its catalytic performance. New. J. Chem. **41**, 13504–13509 (2017)
65. Miller, M.A., Wang, C.-Y., Merrill, G.N.: Experimental and theoretical investigation into hydrogen storage via spillover in IRMOF-8. J. Phys. Chem. C **113**, 3222–3231 (2009)
66. Ishiwata, T., Furukawa, Y., Sugikawa, K., Kokado, K., Sada, K.: Transformation of metal–organic framework to polymer gel by cross-linking the organic ligands preorganized in metal–organic framework. J. Am. Chem. Soc. **135**, 5427–5432 (2013)

67. Chen, X., Tong, R., Shi, Z., Yang, B., Liu, H., Ding, S., et al.: MOF nanoparticles with encapsulated autophagy inhibitor in controlled drug delivery system for antitumor. ACS Appl. Mater. Interfaces **10**, 2328–2337 (2018)
68. He, C., Lu, K., Liu, D., Lin, W.: Nanoscale metal–organic frameworks for the co-delivery of cisplatin and pooled siRNAs to enhance therapeutic efficacy in drug-resistant ovarian cancer cells. J. Am. Chem. Soc. **136**, 5181–5184 (2014)
69. Arun Kumar, S., Balasubramaniam, B., Bhunia, S., Jaiswal, M.K., Verma, K., Khademhosseini, A., et al.: Two-dimensional metal organic frameworks for biomedical applications. Wiley Interdiscip. Rev. Nanomed. Nanobiotechnol. e1674 (2020)
70. Chae, D.W., Kim, B.C.: Characterization on polystyrene/zinc oxide nanocomposites prepared from solution mixing. Polym. Adv. Technol. **16**, 846–850 (2005)
71. Li, S., Meng Lin, M., Toprak, M.S., Kim, D.K., Muhammed, M.: Nanocomposites of polymer and inorganic nanoparticles for optical and magnetic applications. Nano. Rev. **1**, 5214 (2010)
72. Yuan, W., Wang, F., Chen, Z., Gao, C., Liu, P., Ding, Y., et al.: Efficient grafting of polypropylene onto silica nanoparticles and the properties of PP/PP-g-SiO_2 nanocomposites. Polymer (Guildf) **151**, 242–249 (2018)
73. Chen, W.-C., Lin, R.-C., Tseng, S.-M., Kuo, S.-W.: Minimizing the strong screening effect of polyhedral oligomeric silsesquioxane nanoparticles in hydrogen-bonded random copolymers. Polymers (Basel) **10**, 303 (2018)
74. Zhang, L., Su, H., Cai, J., Cheng, D., Ma, Y., Zhang, J., et al.: A multifunctional platform for tumor angiogenesis-targeted chemo-thermal therapy using polydopamine-coated gold nanorods. ACS Nano **10**, 10404–10417 (2016)
75. Hu, W.-H., Huang, K.-W., Chiou, C.-W., Kuo, S.-W.: Complementary multiple hydrogen bonding interactions induce the self-assembly of supramolecular structures from heteronucleobase-functionalized benzoxazine and polyhedral oligomeric silsesquioxane nanoparticles. Macromolecules **45**, 9020–9028 (2012)
76. Wu, Y.-C., Kuo, S.-W.: Self-assembly supramolecular structure through complementary multiple hydrogen bonding of heteronucleobase-multifunctionalized polyhedral oligomeric silsesquioxane (POSS) complexes. J. Mater. Chem. **22**, 2982–2991 (2012)
77. Cheng, Y., Zeiger, D.N., Howarter, J.A., Zhang, X., Lin, N.J., Antonucci, J.M., et al.: *In-situ* formation of silver nanoparticles in photocrosslinking polymers. J. Biomed. Mater. Res. Part B. Appl. Biomater. **97**, 124–131 (2011)
78. Shen, X.-J., Yang, S., Shen, J.-X., Ma, J.-L., Wu, Y.-Q., Zeng, X.-L., et al.: Improved mechanical and antibacterial properties of silver-graphene oxide hybrid/polylactid acid composites by *in-situ* polymerization. Ind. Crops Prod. **130**, 571–579 (2019)
79. Mohammad Shafiee, M.R., Sattari, A., Kargar, M., Ghashang, M.: MnO_2/Cr_2O_3/PANI nanocomposites prepared by *in-situ* oxidation polymerization method: optical and electrical behaviors. J. Appl. Polym. Sci. **136**, 47219 (2019)
80. Liu, C., Zhang, L., Liu, H., Cheng, K.: Delivery strategies of the CRISPR-Cas9 gene-editing system for therapeutic applications. J. Control Release **266**, 17–26 (2017)
81. Ramesan, M.T., Anjitha, T., Parvathi, K., Anilkumar, T., Mathew, G.: Nano zinc ferrite filler incorporated polyindole/poly (vinyl alcohol) blend: Preparation, characterization, and investigation of electrical properties. Adv. Polym. Technol. **37**, 3639–3649 (2018)
82. Thakor, A.S., Gambhir, S.S.: Nanooncology: The future of cancer diagnosis and therapy. CA Cancer J. Clin. (2013). https://doi.org/10.3322/caac.21199
83. Padmanabhan, P., Kumar, A., Kumar, S., Chaudhary, R.K., Gulyás, B.: Nanoparticles in practice for molecular-imaging applications: an overview. Acta Biomater. (2016). https://doi.org/10.1016/j.actbio.2016.06.003
84. Pang, L., Zhang, C., Qin, J., Han, L., Li, R., Hong, C., et al.: A novel strategy to achieve effective drug delivery: exploit cells as carrier combined with nanoparticles. Drug Deliv. (2017). https://doi.org/10.1080/10717544.2016.1230903
85. Bulbake, U., Doppalapudi, S., Kommineni, N., Khan, W.: Liposomal formulations in clinical use: an updated review. Pharmaceutics (2017). https://doi.org/10.3390/pharmaceutics9020012

86. Baeza, A., Colilla, M., Vallet-Regí, M.: Advances in mesoporous silica nanoparticles for targeted stimuli-responsive drug delivery. Expert Opin. Drug Deliv. (2015). https://doi.org/10.1517/17425247.2014.953051
87. Doughty, A.C.V., Hoover, A.R., Layton, E., Murray, C.K., Howard, E.W., Chen, W.R.: Nanomaterial applications in photothermal therapy for cancer. Materials (Basel) (2019). https://doi.org/10.3390/ma12050779
88. Levchenko, I., Bazaka, K., Keidar, M., Xu, S., Fang, J.: Hierarchical multicomponent inorganic metamaterials: intrinsically driven self-assembly at the nanoscale. Adv. Mater. (2018). https://doi.org/10.1002/adma.201702226
89. Silva, C.O., Pinho, J.O., Lopes, J.M., Almeida, A.J., Gaspar, M.M., Reis, C.: Current trends in cancer nanotheranostics: metallic, polymeric, and lipid-based systems. Pharmaceutics (2019). https://doi.org/10.3390/pharmaceutics11010022
90. Murugan, C., Sharma, V., Murugan, R.K., Malaimegu, G., Sundaramurthy, A.: Two-dimensional cancer theranostic nanomaterials: synthesis, surface functionalization and applications in photothermal therapy. J. Control Release (2019). https://doi.org/10.1016/j.jconrel.2019.02.015
91. Tan, Y.Y., Yap, P.K., Xin Lim, G.L., Mehta, M., Chan, Y., Ng, S.W., et al.: Perspectives and advancements in the design of nanomaterials for targeted cancer theranostics. Chem. Biol. Interact. (2020). https://doi.org/10.1016/j.cbi.2020.109221
92. Bejarano, J., Navarro-Marquez, M., Morales-Zavala, F., Morales, J.O., Garcia-Carvajal, I., Araya-Fuentes, E., et al.: Nanoparticles for diagnosis and therapy of atherosclerosis and myocardial infarction: evolution toward prospective theranostic approaches. Theranostics (2018). https://doi.org/10.7150/thno.26284
93. Ali, E.S., Sharker, S.M., Islam, M.T., Khan, I.N., Shaw, S., Rahman, M.A., et al.: Targeting cancer cells with nanotherapeutics and nanodiagnostics: current status and future perspectives. Semin. Cancer Biol. (2020). https://doi.org/10.1016/j.semcancer.2020.01.011
94. Li, Z., Ye, E., David, L.R., Loh, X.J.: Recent advances of using hybrid nanocarriers in remotely controlled therapeutic delivery. Small (2016). https://doi.org/10.1002/smll.201601129
95. Das, S.S., Bharadwaj, P., Bilal, M., Barani, M., Rahdar, A., Taboada, P., et al.: Stimuli-responsive polymeric nanocarriers for drug delivery, imaging, and theragnosis. Polymers (Basel) (2020). https://doi.org/10.3390/polym12061397
96. Kim, H.S., Lee, D.Y.: Photothermal therapy with gold nanoparticles as an anticancer medication. J. Pharm. Investig. (2017). https://doi.org/10.1007/s40005-016-0292-6
97. Poon, W., Zhang, Y.N., Ouyang, B., Kingston, B.R., Wu, J.L.Y., Wilhelm, S., et al.: Elimination pathways of nanoparticles. ACS Nano (2019). https://doi.org/10.1021/acsnano.9b01383
98. Wu, J.L., Wang, C.Q., Zhuo, R.X., Cheng, S.X.: Multi-drug delivery system based on alginate/calcium carbonate hybrid nanoparticles for combination chemotherapy. Colloids Surfaces B Biointerfaces (2014). https://doi.org/10.1016/j.colsurfb.2014.09.047
99. Nakamura, Y., Mochida, A., Choyke, P.L., Kobayashi, H.: Nanodrug delivery: is the enhanced permeability and retention effect sufficient for curing cancer? Bioconjug. Chem. (2016). https://doi.org/10.1021/acs.bioconjchem.6b00437
100. Zhang, Z., Tongchusak, S., Mizukami, Y., Kang, Y.J., Ioji, T., Touma, M., et al.: Induction of anti-tumor cytotoxic T cell responses through PLGA-nanoparticle mediated antigen delivery. Biomaterials (2011). https://doi.org/10.1016/j.biomaterials.2011.01.067
101. Ge, J., Lei, J., Zare, R.N.: Bovine serum albumin—poly(methyl methacrylate) nanoparticles: an example of frustrated phase separation. Nano Lett. (2011). https://doi.org/10.1021/nl201303q
102. Kang, S., Ahn, S., Lee, J., Kim, J.Y., Choi, M., Gujrati, V., et al.: Effects of gold nanoparticle-based vaccine size on lymph node delivery and cytotoxic T-lymphocyte responses. J. Control Release (2017). https://doi.org/10.1016/j.jconrel.2017.04.024
103. Zhang, L., Wu, S., Qin, Y., Fan, F., Zhang, Z., Huang, C., et al.: Targeted codelivery of an antigen and dual agonists by hybrid nanoparticles for enhanced cancer immunotherapy. Nano. Lett. (2019). https://doi.org/10.1021/acs.nanolett.9b00030

104. Huh, Y.M., Lee, E.S., Lee, J.H., Jun, Y.W., Kim, P.H., Yun, C.O., et al.: Hybrid nanoparticles for magnetic resonance imaging of target-specific viral gene delivery. Adv. Mater. (2007). https://doi.org/10.1002/adma.200701952
105. You, Y.H., Lin, Y.F., Nirosha, B., Chang, H.T., Huang, Y.F.: Polydopamine-coated gold nanostar for combined antitumor and antiangiogenic therapy in multidrug-resistant breast cancer. Nanotheranostics (2019). https://doi.org/10.7150/ntno.36842
106. Wu, F., Liu, Y., Wu, Y., Song, D., Qian, J., Zhu, B.: Chlorin e6 and polydopamine modified gold nanoflowers for combined photothermal and photodynamic therapy. J. Mater. Chem. B (2020). https://doi.org/10.1039/c9tb02646k
107. Schweiger, C., Pietzonka, C., Heverhagen, J., Kissel, T.: Novel magnetic iron oxide nanoparticles coated with poly(ethylene imine)-g-poly(ethylene glycol) for potential biomedical application: synthesis, stability, cytotoxicity and MR imaging. Int. J. Pharm. (2011). https://doi.org/10.1016/j.ijpharm.2010.12.046
108. Park, W., Cho, S., Han, J., Shin, H., Na, K., Lee, B., et al.: Advanced smart-photosensitizers for more effective cancer treatment. Biomater. Sci. (2018). https://doi.org/10.1039/c7bm00872d
109. Wang, M., Chen, Z., Zheng, W., Zhu, H., Lu, S., Ma, E., et al.: Lanthanide-doped upconversion nanoparticles electrostatically coupled with photosensitizers for near-infrared-triggered photodynamic therapy. Nanoscale (2014). https://doi.org/10.1039/c4nr01826e
110. Morgan, N.Y., Kramer-Marek, G., Smith, P.D., Camphausen, K., Capala, J.: Nanoscintillator conjugates as photodynamic therapy-based radiosensitizers: Calculation of required physical parameters. Radiat. Res. (2009). https://doi.org/10.1667/RR1470.1
111. Kamkaew, A., Chen, F., Zhan, Y., Majewski, R.L., Cai, W.: Scintillating nanoparticles as energy mediators for enhanced photodynamic therapy. ACS Nano (2016). https://doi.org/10.1021/acsnano.6b01401
112. Bos, A.J.J.: Thermoluminescence as a research tool to investigate luminescence mechanisms. Materials (Basel) (2017). https://doi.org/10.3390/ma10121357
113. Jing, X., Yang, F., Shao, C., Wei, K., Xie, M., Shen, H., et al.: Role of hypoxia in cancer therapy by regulating the tumor microenvironment. Mol. Cancer (2019). https://doi.org/10.1186/s12943-019-1089-9
114. Senthebane, D.A., Rowe, A., Thomford, N.E., Shipanga, H., Munro, D., Al Mazeedi, M.A.M., et al.: The role of tumor microenvironment in chemoresistance: to survive, keep your enemies closer. Int. J. Mol. Sci. (2017). https://doi.org/10.3390/ijms18071586
115. Yang, G., Tian, J., Chen, C., Jiang, D., Xue, Y., Wang, C., et al.: An oxygen self-sufficient NIR-responsive nanosystem for enhanced PDT and chemotherapy against hypoxic tumors. Chem. Sci. (2019). https://doi.org/10.1039/c9sc00985j
116. Lin, T., Zhao, X., Zhao, S., Yu, H., Cao, W., Chen, W., et al.: O_2-generating MnO_2 nanoparticles for enhanced photodynamic therapy of bladder cancer by ameliorating hypoxia. Theranostics (2018). https://doi.org/10.7150/thno.22465
117. Jha, S., Sharma, P.K., Malviya, R.: Hyperthermia: role and risk factor for cancer treatment. Achiev. Life Sci. (2016). https://doi.org/10.1016/j.als.2016.11.004
118. Wang, H., Li, X., Tse, B.W.C., Yang, H., Thorling, C.A., Liu, Y., et al.: Indocyanine green-incorporating nanoparticles for cancer theranostics. Theranostics (2018). https://doi.org/10.7150/thno.22872
119. Mout, R., Ray, M., Yesilbag Tonga, G., Lee, Y.W., Tay, T., Sasaki, K., et al.: Direct cytosolic delivery of CRISPR/Cas9-ribonucleoprotein for efficient gene editing. ACS Nano (2017). https://doi.org/10.1021/acsnano.6b07600
120. Zhao, Y., Liu, W., Tian, Y., Yang, Z., Wang, X., Zhang, Y., et al.: Anti-EGFR peptide-conjugated triangular gold nanoplates for computed tomography/photoacoustic imaging-guided photothermal therapy of non-small cell lung cancer. ACS Appl. Mater. Interfaces (2018). https://doi.org/10.1021/acsami.7b19013
121. Chang, C.W., Van Spreeuwel, A., Zhang, C., Varghese, S.: PEG/clay nanocomposite hydrogel: a mechanically robust tissue engineering scaffold. Soft Matter (2010). https://doi.org/10.1039/c0sm00067a

122. Zhao, L., Tang, M., Weir, M.D., Detamore, M.S., Xu, H.H.K.: Osteogenic media and rhBMP-2-induced differentiation of umbilical cord mesenchymal stem cells encapsulated in alginate microbeads and integrated in an injectable calcium phosphate-chitosan fibrous scaffold. Tissue Eng. Part A (2011). https://doi.org/10.1089/ten.tea.2010.0521
123. Paul, A., Hasan, A., Kindi, H.A., Gaharwar, A.K., Rao, V.T.S., Nikkhah, M., et al.: Injectable graphene oxide/hydrogel-based angiogenic gene delivery system for vasculogenesis and cardiac repair. ACS Nano (2014). https://doi.org/10.1021/nn5020787
124. Noh, M., Kim, S.H., Kim, J., Lee, J.R., Jeong, G.J., Yoon, J.K., et al.: Graphene oxide reinforced hydrogels for osteogenic differentiation of human adipose-derived stem cells. RSC Adv. (2017). https://doi.org/10.1039/c7ra02410j
125. Liu, X., Miller, A.L., Park, S., Waletzki, B.E., Terzic, A., Yaszemski, M.J., et al.: Covalent crosslinking of graphene oxide and carbon nanotube into hydrogels enhances nerve cell responses. J. Mater. Chem. B (2016). https://doi.org/10.1039/c6tb01722c
126. Navaei, A., Saini, H., Christenson, W., Sullivan, R.T., Ros, R., Nikkhah, M.: Gold nanorod-incorporated gelatin-based conductive hydrogels for engineering cardiac tissue constructs. Acta Biomater. (2016). https://doi.org/10.1016/j.actbio.2016.05.027
127. Lih, E., Park, W., Park, K.W., Chun, S.Y., Kim, H., Joung, Y.K., et al.: A bioinspired scaffold with anti-inflammatory magnesium hydroxide and decellularized extracellular matrix for renal tissue regeneration. ACS Cent. Sci. (2019). https://doi.org/10.1021/acscentsci.8b00812
128. Duarah, R., Singh, Y.P., Gupta, P., Mandal, B.B., Karak, N.: High performance bio-based hyperbranched polyurethane/carbon dot-silver nanocomposite: a rapid self-expandable stent. Biofabrication (2016). https://doi.org/10.1088/1758-5090/8/4/045013
129. Jeong, D.W., Park, W., Bedair, T.M., Kang, E.Y., Kim, I.H., Park, D.S., et al.: Augmented re-endothelialization and anti-inflammation of coronary drug-eluting stent by abluminal coating with magnesium hydroxide. Biomater. Sci. (2019). https://doi.org/10.1039/c8bm01696h
130. Bassous, N., Cooke, J.P., Webster, T.J.: Enhancing stent effectiveness with nanofeatures. Methodist. Debakey Cardiovasc. J. (2016). https://doi.org/10.14797/mdcj-12-3-163
131. Akturk, O., Kismet, K., Yasti, A.C., Kuru, S., Duymus, M.E., Kaya, F., et al.: Collagen/gold nanoparticle nanocomposites: a potential skin wound healing biomaterial. J. Biomater. Appl. (2016). https://doi.org/10.1177/0885328216644536
132. Tan, A., Farhatnia, Y., Goh, D., Natasha, G., de Mel, A., Lim, J., et al.: Surface modification of a polyhedral oligomeric silsesquioxane poly(carbonate-urea) urethane (POSS-PCU) nanocomposite polymer as a stent coating for enhanced capture of endothelial progenitor cells. Biointerphases (2013). https://doi.org/10.1186/1559-4106-8-23
133. Steinmetz, N.F., Hong, V., Spoerke, E.D., Lu, P., Breitenkamp, K., Finn, M.G., et al.: Buckyballs meet viral nanoparticles: candidates for biomedicine. J. Am. Chem. Soc. (2009). https://doi.org/10.1021/ja902293w
134. Lee, P.W., Hsu, S.H., Tsai, J.S., Chen, F.R., Huang, P.J., Ke, C.J., et al.: Multifunctional core-shell polymeric nanoparticles for transdermal DNA delivery and epidermal Langerhans cells tracking. Biomaterials (2010). https://doi.org/10.1016/j.biomaterials.2009.11.100
135. Ha, Y.J., Lee, S.M., Mun, C.H., Kim, H.J., Bae, Y., Lim, J.H., et al.: Methotrexate-loaded multifunctional nanoparticles with near-infrared irradiation for the treatment of rheumatoid arthritis. Arthritis Res. Ther. (2020). https://doi.org/10.1186/s13075-020-02230-y
136. Askari, A., Tajvar, S., Nikkhah, M., Mohammadi, S., Hosseinkhani, S.: Synthesis, characterization and *in-vitro* toxicity evaluation of doxorubicin-loaded magnetoliposomes on MCF-7 breast cancer cell line. J. Drug Deliv. Sci. Technol. (2020). https://doi.org/10.1016/j.jddst.2019.101447
137. Xu, C., Wang, B., Sun, S.: Dumbbell-like Au-Fe_3O_4 nanoparticles for target-specific platin delivery. J. Am. Chem. Soc. (2009). https://doi.org/10.1021/ja900790v
138. Gu, H., Zheng, R., Zhang, X.X., Xu, B.: Facile one-pot synthesis of bifunctional heterodimers of nanoparticles: a conjugate of quantum dot and magnetic nanoparticles. J. Am. Chem. Soc. (2004). https://doi.org/10.1021/ja0496423
139. Jiang, J., Gu, H., Shao, H., Devlin, E., Papaefthymiou, G.C., Ying, J.Y.: Bifunctional Fe_3O_4-Ag heterodimer nanoparticles for two-photon fluorescence imaging and magnetic manipulation. Adv. Mater. (2008). https://doi.org/10.1002/adma.200800498

140. Wang, G., Gao, W., Zhang, X., Mei, X.: Au nanocage functionalized with ultra-small Fe_3O_4 nanoparticles for targeting T1–T2 dual MRI and CT imaging of tumor. Sci. Rep. (2016). https://doi.org/10.1038/srep28258
141. Li, C., Chen, T., Ocsoy, I., Zhu, G., Yasun, E., You, M., et al.: Gold-coated Fe_3O_4 nanoroses with five unique functions for cancer cell targeting, imaging, and therapy. Adv. Funct. Mater. (2014). https://doi.org/10.1002/adfm.201301659
142. Ganipineni, L.P., Ucakar, B., Joudiou, N., Bianco, J., Danhier, P., Zhao, M., et al.: Magnetic targeting of paclitaxel-loaded poly(lactic-co-glycolic acid)-based nanoparticles for the treatment of glioblastoma. Int. J. Nanomed. (2018). https://doi.org/10.2147/IJN.S165184
143. Zhang, R.X., Ahmed, T., Li, L.Y., Li, J., Abbasi, A.Z., Wu, X.Y.: Design of nanocarriers for nanoscale drug delivery to enhance cancer treatment using hybrid polymer and lipid building blocks. Nanoscale (2017). https://doi.org/10.1039/c6nr08486a
144. Sailor, M.J., Park, J.H.: Hybrid nanoparticles for detection and treatment of cancer. Adv. Mater. (2012). https://doi.org/10.1002/adma.201200653
145. Ba, H., Rodríguez-Fernández, J., Stefani, F.D., Feldmann, J.: Immobilization of gold nanoparticles on living cell membranes upon controlled lipid binding. Nano. Lett. (2010). https://doi.org/10.1021/nl101454a
146. Paasonen, L., Sipilä, T., Subrizi, A., Laurinmäki, P., Butcher, S.J., Rappolt, M., et al.: Gold-embedded photosensitive liposomes for drug delivery: triggering mechanism and intracellular release. J. Control Release (2010). https://doi.org/10.1016/j.jconrel.2010.07.095
147. Wu, G., Mikhailovsky, A., Khant, H.A., Fu, C., Chiu, W., Zasadzinski, J.A.: Remotely triggered liposome release by near-infrared light absorption via hollow gold nanoshells. J. Am. Chem. Soc. (2008). https://doi.org/10.1021/ja802656d
148. Liu, T.Y., Huang, T.C.: A novel drug vehicle capable of ultrasound-triggered release with MRI functions. Acta Biomater. (2011). https://doi.org/10.1016/j.actbio.2011.06.038
149. Chen, Y., Bose, A., Bothun, G.D.: Controlled release from bilayer-decorated magnetoliposomes via electromagnetic heating. ACS Nano (2010). https://doi.org/10.1021/nn100274v
150. Mikhaylov, G., Mikac, U., Magaeva, A.A., Itin, V.I., Naiden, E.P., Psakhye, I., et al.: Ferri-liposomes as an MRI-visible drug-delivery system for targeting tumours and their microenvironment. Nat. Nanotechnol. (2011). https://doi.org/10.1038/nnano.2011.112
151. Al-Jamal, W.T., Al-Jamal, K.T., Tian, B., Lacerda, L., Bomans, P.H., Frederik, P.M., et al.: Lipid - Quantum dot bilayer vesicles enhance tumor cell uptake and retention *in-vitro* and *in-vivo*. ACS Nano (2008). https://doi.org/10.1021/nn700176a
152. Weng, K.C., Noble, C.O., Papahadjopoulos-Sternberg, B., Chen, F.F., Drummond, D.C., Kirpotin, D.B., et al.: Targeted tumor cell internalization and imaging of multifunctional quantum dot-conjugated immunoliposomes *in-vitro* and *in-vivo*. Nano. Lett. (2008). https://doi.org/10.1021/nl801488u
153. Li, H., Wang, J., Huang, G., Wang, P., Zheng, R., Zhang, C., et al.: Multifunctionalized microbubbles for cancer diagnosis and therapy. Anticancer Agents Med. Chem. (2013). https://doi.org/10.2174/18715206113130300004
154. Accardo, A., Tesauro, D., Morelli, G.: Peptide-based targeting strategies for simultaneous imaging and therapy with nanovectors. Polym. J. (2013). https://doi.org/10.1038/pj.2012.215
155. Namiki, Y., Namiki, T., Yoshida, H., Ishii, Y., Tsubota, A., Koido, S., et al.: A novel magnetic crystal-lipid nanostructure for magnetically guided *in-vivo* gene delivery. Nat. Nanotechnol. (2009). https://doi.org/10.1038/nnano.2009.202
156. Wang, W., Cheng, D., Gong, F., Miao, X., Shuai, X.: Design of multifunctional micelle for tumor-targeted intracellular drug release and fluorescent imaging. Adv. Mater. (2012). https://doi.org/10.1002/adma.201104066
157. Park, J.H., Von Maltzahn, G., Ruoslahti, E., Bhatia, S.N., Sailor, M.J.: Micellar hybrid nanoparticles for simultaneous magnetofluorescent imaging and drug delivery. Angew. Chemie. Int. Ed. (2008). https://doi.org/10.1002/anie.200801810
158. Xu, H., Cheng, L., Wang, C., Ma, X., Li, Y., Liu, Z.: Polymer encapsulated upconversion nanoparticle/iron oxide nanocomposites for multimodal imaging and magnetic targeted drug delivery. Biomaterials (2011). https://doi.org/10.1016/j.biomaterials.2011.08.053

159. Vieweger, M., Goicochea, N., Koh, E.S., Dragnea, B.: Photothermal imaging and measurement of protein shell stoichiometry of single HIV-1 Gag virus-like nanoparticles. ACS Nano (2011). https://doi.org/10.1021/nn202184x
160. Lee, S.M., Kim, H.J., Ha, Y.J., Park, Y.N., Lee, S.K., Park, Y.B., et al.: Targeted chemo-photothermal treatments of rheumatoid arthritis using gold half-shell multifunctional nanoparticles. ACS Nano (2013). https://doi.org/10.1021/nn301215q
161. Cho, H.S., Dong, Z., Pauletti, G.M., Zhang, J., Xu, H., Gu, H., et al.: Fluorescent, superparamagnetic nanospheres for drug storage, targeting, and imaging: A multifunctional nanocarrier system for cancer diagnosis and treatment. ACS Nano (2010). https://doi.org/10.1021/nn101000e
162. Wang, C., Chen, J., Talavage, T., Irudayaraj, J.: Gold Nanorod/Fe3O4 nanoparticle "nano-pearl- necklaces" for simultaneous targeting, dual-mode imaging, and photothermal ablation of cancer cells. Angew. Chemie. Int. Ed. (2009). https://doi.org/10.1002/anie.200805282
163. Bhirde, A.A., Patel, V., Gavard, J., Zhang, G., Sousa, A.A., Masedunskas, A., et al.: Targeted killing of cancer cells *in-vivo* and *in-vitro* with EGF-directed carbon nanotube-based drug delivery. ACS Nano (2009). https://doi.org/10.1021/nn800551s
164. Bertrand, N., Wu, J., Xu, X., Kamaly, N., Farokhzad, O.C.: Cancer nanotechnology: the impact of passive and active targeting in the era of modern cancer biology. Adv. Drug Deliv. Rev. (2014). https://doi.org/10.1016/j.addr.2013.11.009