Drug Metabolism Reviews

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/idmr20

Janus nanoparticles: an efficient intelligent modern nanostructure for eradicating cancer

Farshid Gheisari, Mostafa Shafiee, Milad Abbasi, Ali Jangjou, Peyman Izadpanah, Ahmad Vaez & Ali Mohammad Amani

To cite this article: Farshid Gheisari, Mostafa Shafiee, Milad Abbasi, Ali Jangjou, Peyman Izadpanah, Ahmad Vaez & Ali Mohammad Amani (2021): Janus nanoparticles: an efficient intelligent modern nanostructure for eradicating cancer, Drug Metabolism Reviews, DOI: 10.1080/03602532.2021.1878530

To link to this article: https://doi.org/10.1080/03602532.2021.1878530

Published online: 09 Feb 2021.

DRUG METABOLISM REVIEWS
https://doi.org/10.1080/03602532.2021.1878530

Taylor & Francis
Taylor & Francis Group

REVIEW ARTICLE

Janus nanoparticles: an efficient intelligent modern nanostructure for eradicating cancer

Farshid Gheisari[a], Mostafa Shafiee[b], Milad Abbasi[b], Ali Jangjou[c], Peyman Izadpanah[d], Ahmad Vaez[e] and Ali Mohammad Amani[b]

[a]Department of Nuclear Medicine, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran; [b]Department of Medical Nanotechnology, School of Advanced Medical Sciences and Technologies, Shiraz University of Medical Sciences, Shiraz, Iran; [c]Department of Emergency Medicine, School of Medicine, Namazi Teaching Hospital, Shiraz University of Medical Sciences, Shiraz, Iran; [d]Department of Cardiology, School of Medicine, Namazi Teaching Hospital, Shiraz University of Medical Sciences, Shiraz, Iran; [e]Department of Tissue Engineering and Applied Cell Sciences, School of Advanced Medical Sciences and Technologies, Shiraz University of Medical Sciences, Shiraz, Iran

ABSTRACT

In the modern age, the struggle to generate appropriate bio-based materials and nano-scaled colloidal particulates for developed application domains, has already resulted in remarkable attempts in the advancement of regulated size and shape, anisotropy, and characteristics of nanostructures. The bottom-up development strategies of components are among the most important science areas throughout nanotechnology, in which the designed building blocks are often utilized to generate novel structures by random self-assembly. In biomedical applications, Janus nanoparticles (JNPs) are necessary. This is due to their effective stimulus-responsive properties, tunable structure, biocompatibility, containing two surfaces with various hydrophobic characteristics and distinct functional groups. Featuring two parts with differing hydrophobicity has been the most critical aspect of the Janus amphiphilic particles. Development of JNPs has been afforded, using imaging agents (e.g. gold (AU) for photoacoustic imaging processing (PAI), silver for surface-enhanced Raman scattering (SERS), and Fe_3O_4 and MnO_2 to magnetic resonance imaging (MRI)). It is also to be mentioned that a number of other properties become salient – properties such as integration imaging factors into JNPs (like quantum dots, fluorescent dyes), multiple imaging methods for screening and diagnosis application can indeed be accomplished. Janus nanostructures have been promising platforms for bioengineering as therapeutic carriers, drug delivery vehicles, and biosensor equipment; they may also be employed for the transport of bioactive hydrophilic and hydrophobic materials. The main production approaches and major advancement of JNPs in the biomedical sector and cancer therapy will be described in this paper.

ARTICLE HISTORY
Received 12 November 2020
Accepted 16 January 2021

KEYWORDS
Janus nanoparticles; biomedical; cancer; drug delivery; self-assembly

1. Introduction

All throughout history, living creatures have frequently functioned as starting points for the science and technology advancement of components across all kinds, even though the natural world affords a multitude of the most varied substances, operating systems, infrastructures, and mechanisms. Natural resources are distinguished by organizational frameworks at dimensions varying between nanometers to millimeters: these involve all types of characteristics appearing at such different structural grades. Thereby, a wide variety of patterns can indeed be identified for the implementation of shapely nanoparticles and microparticles with different purposes (Sanchez 2010). Nature as an inspirational approach and a requirement toward developed operational structures containing unique characteristics has resulted in a rapidly growing, extremely creative, and exciting field of investigation termed nanotechnology, which encompasses not just physics but furthermore biology, chemistry, and materials engineering. Nanoscience is currently facing an unbelievable explosion of data and techniques throughout the past 20 years. This demonstrates that nanoparticle sciences may be among the more crucial elements of advanced technology developed in the 21 Century. Furthermore,

CONTACT Peyman Izadpanah izadpanahpeyman52@gmail.com Department of Cardiology, School of Medicine, Namazi Teaching Hospital, Shiraz University of Medical Sciences, Shiraz, Iran; Ahmad Vaez ahmadvaez@yahoo.com Department of Tissue Engineering and Applied Cell Sciences, School of Advanced Medical Sciences and Technologies, Shiraz University of Medical Sciences, Shiraz, Iran; Ali Mohammad Amani amani_a@sums.ac.ir Department of Medical Nanotechnology, School of Advanced Medical Sciences and Technologies, Shiraz University of Medical Sciences, Shiraz, Iran

the natural world introduces tremendous instances of spontaneously broken symmetry within the shape of proteins, lipids, microtubules, tissues, and so on, for the implementation of different complicated biochemical processes (Wiemer 2017). The attempts in search for huge leaps in bringing about absolutely unbeknown developments within this field are actually matched with the generation of some of the best bio-based materials. During the last 20 years, the search for innovative intelligent substances with designed characteristics and required capabilities has motivated researchers toward the field of nanoscience (Edwards 2007). The vision is that, by decreasing very much the dimension at which the substance is controlled, unparalleled regulation upon the component features can indeed be accomplished. Considerable focus has also been given to the development of different forms of building blocks for nanoparticle production, like anisotropic nanomaterials. Experimental research had already demonstrated that anisotropic particulates might be extremely advantageous for handling molecular identification or even for self-assembling procedures, which also are among the most exciting or rather challenging perspectives of existing materials engineering (Fendler 1996).

The synthesis of Janus nanoparticles (JNPs) (Figure 1) is presently a direction that is being exhaustively investigated (Walther and Muller 2013). A Janus particle (JP) has been described as having various surface physical/chemical compositions and properties over both sides of the particle. It was originally titled just after dual-faced Roman God Janus. Janus was commonly viewed with two faces back-to-back meaning that he could glance in two different directions simultaneously. The area of JP's experimental synthesis was motivated by De Gennes, who focused many workers' attention on JP's during his Nobel Prize lecture (De Gennes 1992).

Since their introduction, JPs have proven to become a quite promising category of nanostructures for many researchers. Owing to these particular non-centrosymmetric characteristics, the production of JPs becomes very complicated. On the other hand, the absence of centrosymmetric in Janus structures has resulted in the development of novel features and also unexpected accumulation behavior within complexes. Such chemical asymmetry generates extremely extraordinary

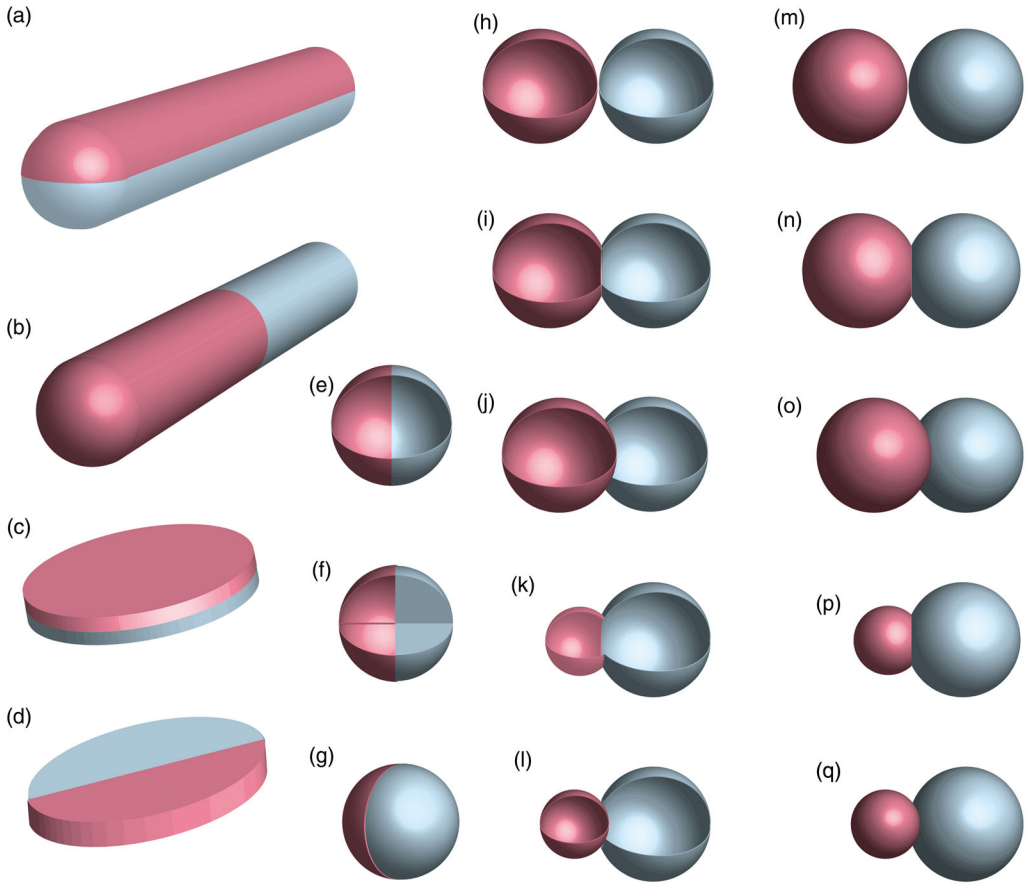

Figure 1. Diverse kinds of Janus particles (JPs): (a, b) two kinds of spherical, (c, d) disc formed, (e–q) different forms of dumbbell formed JPs including globular, asymmetrical or snowman figure, symmetrical shape, connected nodes, eccentric encapsulation, and vesicular or capsular Janus.

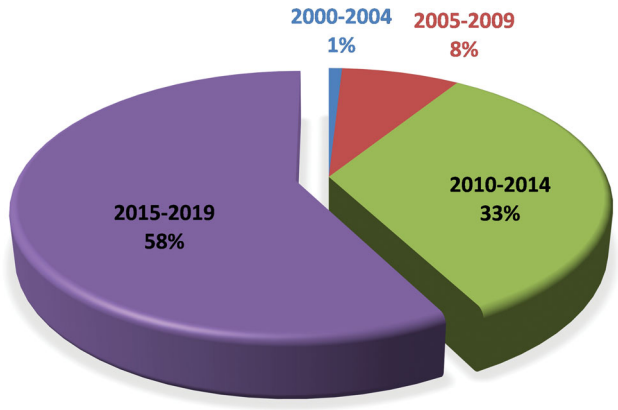

Figure 2. Published statistics of Janus particulates.

characteristics and, as an outcome, a broad variety of possible applications allow this field of study to act as a multidisciplinary domain of investigation across the various perspective. The percentage of papers regarding JPs has risen nearly exponentially over the past several years. This tendency continued through expansive main perspectives varying mostly from production to the implementation of Janus particulates (Figure 2) (Yang 2012).

At first, synthetic procedures for the production of Janus particulates have been limited by low reaction yields during preparation, therefore, curtailing future researches. Nowadays, innovative methods have resolved these constraints so that the formation of large amounts of nanoparticles has been turned out to be feasible. Several researchers documented the effective preparation of different kinds of JPs with a variety of forms, morphology, chemistry, polarizability, functionality, and characteristics utilizing various synthetic procedures. An overview of some synthetic processes, self-assembly processes, and characteristics, as well as capabilities, is described below (Roh 2007).

The major advancement of JNPs in the biomedical sector and cancer therapy will be described in this paper. At first, we are going to define several major production approaches of JNPs besides nanomedicine. After that, the capabilities of JNPs in cancer treatment, as well as therapeutics, will be further outlined. Of even greater importance is the fact that Janus nanostructures have been able to provide significant promising nanostructured systems for bioengineering as therapeutic carriers, drug delivery vehicles, and biosensor equipment (Roh 2005).

2. Synthetic procedures

A wide variety of particulates with various chemical compositions have been acquired over the last decades and their intricacy is ramping up owing to the diversity of novel methodologies. Particulates on any size range, inorganic, organic, or hybrid substances have been provided with many distinct forms, varying from globular, disc-like, cylindrical, raspberry-, hamburger- to snowman-, like forms. Hence, many various synthetic processes such as microfluidic approaches (Roh 2005, 2007), the regulated phase separation method (Gu 2004; Vilain 2007), lithography (Dendukuri 2007), template-directed self-assembly (Yin 2001; Nagle and Fitzmaurice 2003; Walther and Müller 2008), temporary masking (Bao 2002; Paunov and Cayre 2004), and controlled nucleation of the surface (Teranishi 2004; Gao 2005) have been advanced. The Monte Carlo computer simulations were also utilized to demonstrate all types of Janus particulates and one's accumulation process (Vanakaras 2006). Throughout this chapter, we will reassess the major approaches introduced through the literary works for the development of JNPs up to now. Researchers understand that the formation of JNPs is still a significant obstacle frequently demanding inventive methodologies that can already be classified into three main groups: masking, phase separation, and self-assembly, graphically displayed in Figure 3.

2.1. Janus nanoparticles through the self-assembly process

The self-assembly process of triblock and diblock copolymers seems to be the earliest preparation method of JNPs which applies mostly to the polymeric form (Yang 2012). Block copolymers can form unified nanometer-scale sites through microphase segregation. Block copolymers are triblock and diblock copolymers that may be employed to implement this technique and generate Janus micelles. Multiple compositions can indeed be achieved from distinct blocks with dissimilar molecular and chemical masses (Han and Jiang 2011). Development of a core by self-assembly procedure can be achieved through the use of AC and AB copolymer blends under which the 'A' region is generated via an insoluble hydrophobic polymer into a suitable solvent or even by the preparing of CD and AB copolymer combinations wherein the C and A polymers possess a high binding affinity altogether. BC and AB diblock co-polymers can also be combined to co-assemble both throughout Janus multi-compartment or patchy micelles and within both. The Monte Carlo visualization analysis demonstrated that AB/BC diblock co-polymer blend could even shape Janus micelles through trying to balance (Jiang and Granick 2007) hydrogen bonding among both B blocks and repulsive interaction in both

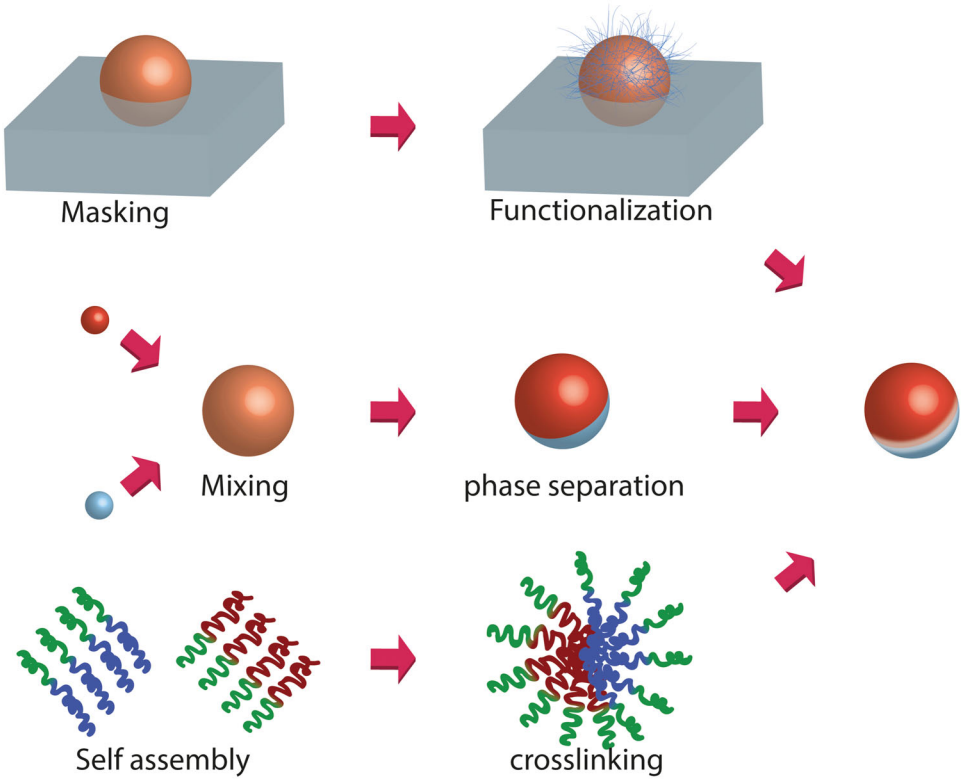

Figure 3. Schematic graph outlining the three major techniques for the production of Janus nanoparticles: self-assembly, masking, and phase separation.

A and C blocks, such that unsolvable B blocks can create the core. As a result, although A and C shape some form of a corona, they still remain soluble (Han and Jiang 2011). Traditionally, the very first strategies used for the synthesis of JNPs depended mostly on the self-assembly process of block copolymers and also upon the cooperative adsorption between incompatible ligands on the outer surface of pre-constructed core–shell or homogeneous particulates. The self-assembly process of such block copolymers is a dynamic procedure that can be widely used in various kinds of polymers. It, however, tends to take significant benefit of the increasingly larger utilization of living free-radical polymerization process, which further allows the fabrication of block copolymers using well-specified scalable architecture, morphology, and small molecular mass distribution (Braunecker and Matyjaszewski 2007; Bradley 2016). A development of Janus nanostructures based on block copolymers needs an excellent understanding of the basic physics of polymer blends, and also the impact of all factors influencing the self-assembly process, such as pH, temperature, and ion strength. The scalability properties of this approach for the preparation of Janus nanomaterials are rather constrained because the block assembly in elevated concentrations might not be an excellently controlled process (Zhang et al. 2017a). Computer simulation models can, even so, offer valuable hints of how we can resolve such restrictions. The production of JNPs by cooperative adsorption of ligands has obtained much less interest, owing to its high capacity, as indicated by certain current research or even simulation techniques. The prevalence of information throughout this field is still minimal (Yi 2016).

2.1.1. Self-assembly process of the block copolymer

The self-assembly process of block copolymers in bulk density is indeed a versatile technique that can be used for several different forms of polymers. Owing to the heterogeneity of various polymers, block copolymers in the bulk mass demonstrate microphase separation compositions. The heat and mass transfer explanation of the formation mechanism of the polymer couple can be provided through the Flory–Huggins formula (Walther and Muller 2013). Flory–Huggins solution principle provides a crystal structure framework of the fluid dynamics of polymer fluids which take into consideration the considerable differences in molecular dimensions in adjusting the ordinary concept for the entropy of blending. The existence of such nanoparticles is defined not just by the Flory–Huggins activity coefficient between such block copolymers, but also with the weight percentage of the level of polymerization. The development stage graphs of the diblock copolymers seem to be experimentally and theoretically well studied (Yang 2012). Typically, many

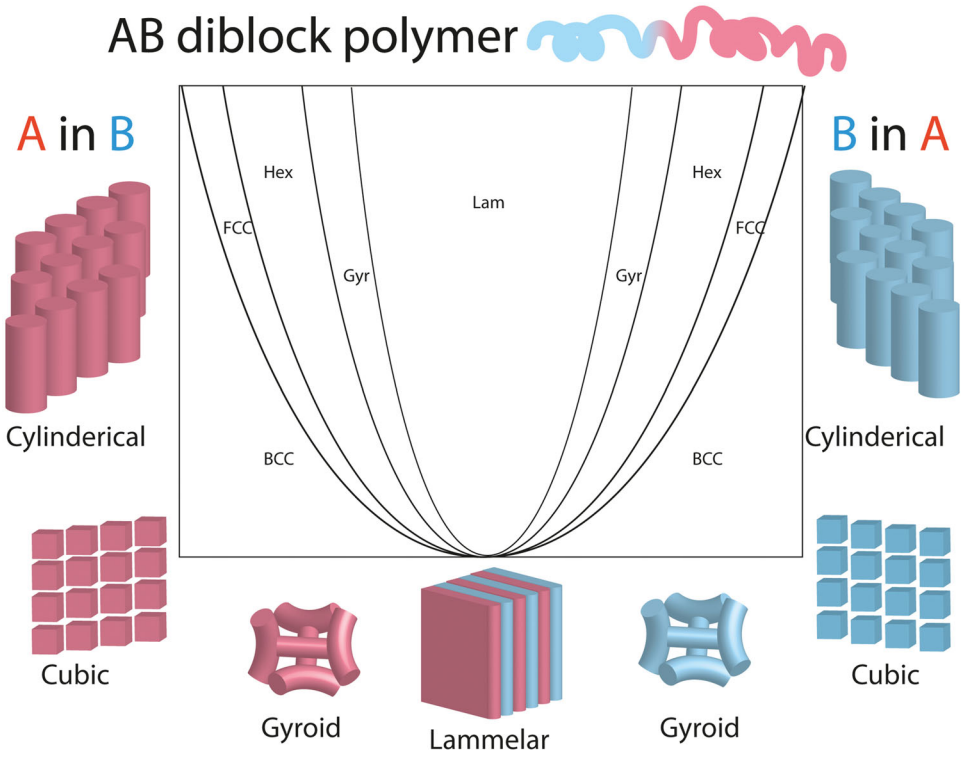

Figure 4. The phase illustration of the diblock copolymer with its morphologies.

architectural changes can be identified by an increment in mass proportion over one block between 0 and 50% in volume proportion – beginning from its blended stage, through the spherical phase, the cylindrical phase, the gyroid phase, and eventually finishing within the lamellar phase (Figure 4).

Even so, with the addition of a third component to the method, the problem gets more complex owing to the rapid increase in the number of variables or even probable methylation patterns (Kobaku 2019). As a direct cause, it is impossible to determine the consistency of such morphologies. Stadler was a leader in the development of block terpolymers and formed a ternary phase illustration for poly(styrene)-b-poly(butadiene)-b-poly(-methyl methacrylate) (SBM) tri-block terpolymers. The phase schematic in SBM triblock terpolymers and perhaps other triblock terpolymers consists of a plurality of stage-segregated configurations on a nanometer range (Han et al. 2019; Baran 2020). Attention has been given to the synthesis of Janus particulates focused on block terpolymer volume framework, primarily block terpolymer compositions with symmetrical external parts (Hückstädt 2000). Morphological experiments on phase separating of ABC terpolymers – composed of three chemically distinct components – have been experimentally and theoretically performed. Only a small difference in the mass fraction (or even a difference in the interacting variables across the various blocks) has been identified to result in a major shift throughout the microphase-separated structure. An enhancement in the internal proportion of polybutadiene (PB), even when helping to keep the terminal blocks of poly(methylmethacrylate) (PMMA) and polystyrene (PS) symmetric, contributes to five distinct morphologies (Gröschel and Müller 2015). Small percentages of PB contribute to globular domains of PB at the lamellar phase of PS and PMMA, guided by PB cylinders with a greater rise in PB. For SBM block terpolymers with three identical mass fractions, the lamella phase by different thicknesses of PMMA, PB, and PS can be obtained (Martin 2017).

Analytical results estimating the Janus-type structure of polymer-based micelles in the context of star co-polymers, refer back approximately to 1998. The first laboratory findings were presented throughout a seminal paper by the Müller Team in 2001, wherein the crosslinked Janus polymer-based nanoparticles by the self-assembly process of terpolymers were developed (Zhang et al. 2017a; Chattopadhyay and Simmchen 2019; Kierulf 2019; Su 2019). Their groundbreaking study has benefited from a broad range of different morphologies with a significant level of spatial regulation which can be randomly achieved by the self-assembly process of terpolymers throughout film formation. This is virtually based on molecular masses and chemical structure(s) of the various blocks. The initial instance, composed of lamellae-sphere phases, is generated via PS-b-PB-b-PMMA terpolymers with fairly low molecular volume distribution functions (achieved from

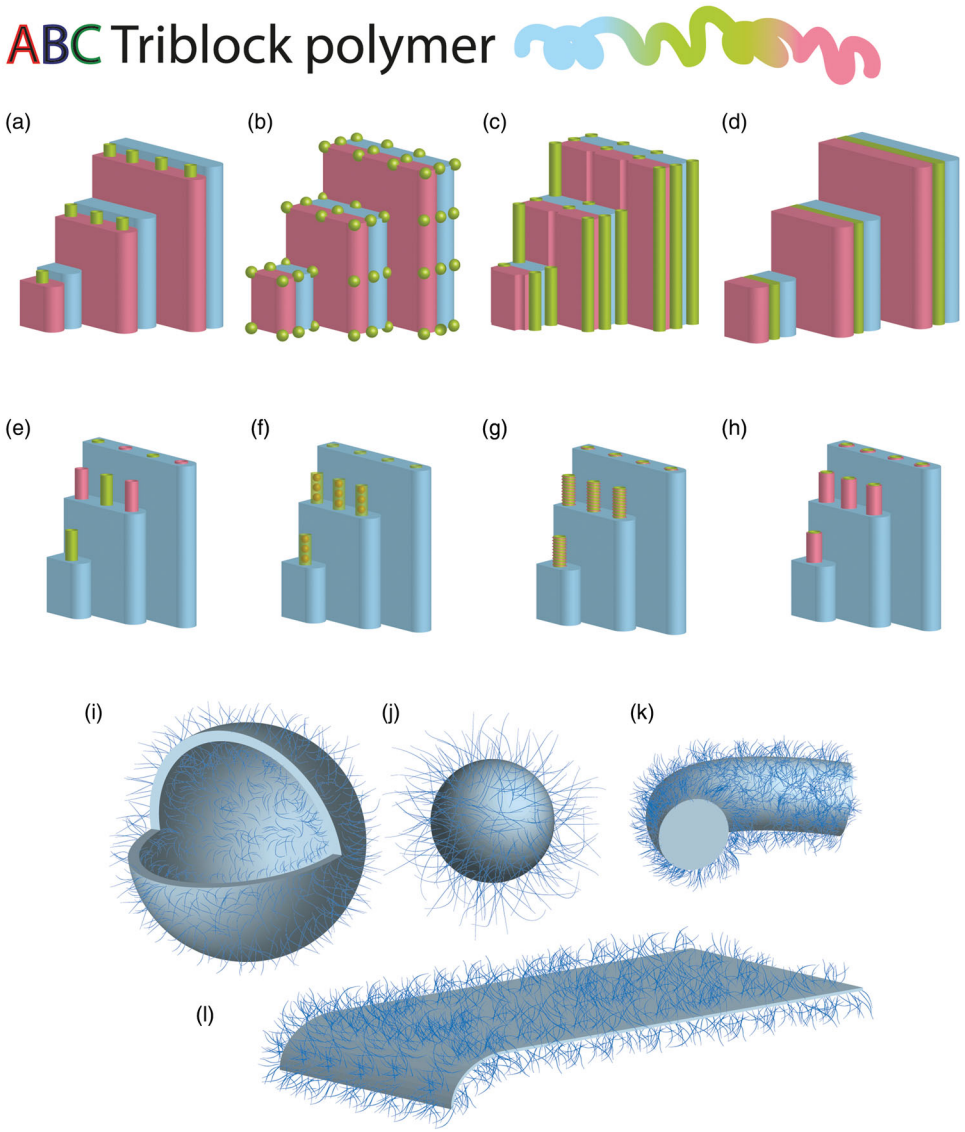

Figure 5. Illustration of the formation of Janus nanoparticles through terpolymers. The procedure beginning from the film molding of the terpolymer, accompanied by a crosslinking of the transitional block and, eventually, dissolution and even sonication. Based on the composition and molecular mass of the terpolymer, film casting creates a matrix with different morphologies, eventually leading to Janus nanoparticles having various forms after dissolution: cylindrical, spherical, and disk-like.

anionic polymerization), whereas PMMA and PS create alternating lamellae. All this is despite the fact that PB produced tiny spheres is placed between the set of lamellae. By altering the molecular mass of the blocks, various structures of the three phases can be gained, including the lamellae cylinders and, very lately, the lamellae morphologies (Poggi and Gohy 2017; Song 2018; Kirillova 2019; Kobaku 2019). An illustration of the particular implementation approach is displayed in Figure 5.

2.2. Janus nanomaterials through masking technique

The preservation is one aspect of the nanoparticle surface layer whereby the covered layer becomes unavailable for chemicals and polymerization, modifications, functionalization, or some other chemical processes. These are performed upon the unsupervised part throughout the nanostructure, deemed as the masking process (Song 2018). While trigger particulates are partly caught by the template, patchy particles can indeed be acquired. However, if half of such targeting particles shield, JPs can be attained. In many instances, asymmetrical functionalization of the particulates and nanomaterials is performed by either preserving a section of the particle surface through capturing the particulates upon a solid substrate or even at the boundary of two states. This means that only the visible area of each particle is accessible for chemical functionalization (Poggi and Gohy 2017). There have been two

approaches to the masking procedure. One of these is a solid substrate masking process through evaporative single-crystal polymer templating, electrostatic adsorption, and deposition pattern. Another is the suspension of nanomaterials at the interface between two liquid phases, including the Pickering emulsion process. Moreover, the Pickering emulsion frequently provides a technique for phase separation. The masking method by binding the particulate matter to a solid surface through a masking process can be commonly implemented to sizeable particles which are less acceptable to utilize far smaller nanostructure. This is in contrast to the fact that Pickering emulsion is effective in the development of tiny JNPs. A significant variety of techniques for the preparation of JNPs utilizes several variations of the masking procedure. It implies that the asymmetrical modifications of nanostructures are accomplished by introducing only one portion (or, in particular, a part) of one's surface to an area under which an interaction becomes performed (Song 2018). Nonetheless, the remaining portion of the layer is shielded. Usually, the masking procedure has been performed through caging nanomaterials at the phase boundary of liquid or through depositing and solubilized particles on a solid layer. Masking is possibly the most adaptable among all of the methodologies used to develop JNPs because it is appropriate to practically any kind of substance. It can also provide the potentiality of modifying the surface areas of nanomaterials by a broad range of functional groups (Kirillova 2019). Since this surface modification of particulates accumulated on clear solid material gives the fullest variety of surface modification possibilities, there are also major problems with scalability. Otherwise, by the application of distributed phases of particulates and tiny particles to have a (greater) surface area, nanostructures and nanocrystals can indeed be captured. It appears to be a suitable option for producing greater amounts of JNPs but restricts the number of surface modifications that can be implemented. By means of advances throughout our knowledge of Pickering emulsions production, regulated by nanoparticles, greater amounts of JNPs are anticipated to become accessible (Yang and Loos 2017a).

2.3. Janus nanoparticles within the polymeric components for useable hybrid materials

The incorporation of nanomaterials into polymeric components is not the only available method toward the advanced design of plastic materials with improved electrical, mechanical, optical, and magnetic characteristics. Such an approach is among the greatest appealing strategies to reach an excellently defined organized structure with various adaptive-size meshes through regulating the spatial distribution of nanostructures within the polymers (Yang and Loos 2017b; Fan 2019; Kirillova 2019). The term 'polymeric nanocomposite' has been studied during the early twentieth century. It attracted widespread attention until around the 1990s (Fan 2019; Li 2019). Over the last 20 years, substantial efforts have been undertaken to generate nano-composites for functional use with designed, required, and optimized characteristics in order to better acknowledge the correlation of structural features throughout the polymer-NP composites (Le 2019; Percebom and Costa 2019; Su 2019). Management across the position and spatial arrangement of nanoparticles within the polymeric materials is, however, crucial for the generation of highly organized nanoparticle-based operating systems, such as plasma waveguides, optical lenses, photonic crystals, nanoelectronic circuits, batteries, memory storage devices, and photovoltaics (Elbert 2017; Dehghani 2018; Nie 2018). Both theoretical and experimental findings show that the distribution and position of NPs within polymers, polymer combinations, and block copolymers are controlled by a delicate balance between enthalpic and entropic shares, depending on the characteristics between both polymeric materials (inflexibility and chemical) and particulates (shape and size, specificity) (Sarkar and Alexandridis 2015; Yang 2018; Kalaj 2020). Despite the fact that a wide variety of basic approaches have been suggested, merely focused on the mechanism of macromolecular–particle interactions, it is specifically the regulating of the placement of NPs throughout the polymer matrix that poses a significant barrier to the manufacturing of polymer-NP usable components (Sarkar and Alexandridis 2015).

2.4. Phase separation process

Phase separation seems to be the third basic technique besides the production process of JNPs. This approach focuses on the separation of two or even more incompatible elements throughout the blend for the preparation of polymeric, inorganic, or polymeric hybrid JNPs. Phase separation processes rely on an emulsified approach comprising of solvent evaporation and seed emulsion polymerization throughout emulsion droplets; or even by means of an operating system procedure comprising an electrohydrodynamic jet (Jeong 2013). The same process can also be conducted most probably via a fluid nanoprecipitation system. Janus hybrid or

polymeric nanoparticles can be produced by this process using a phase separation technique. Phase isolation with two incompatible polymers and lipids is the base of the process of phase separation utilizing single oil-in-water, o/w, and the dual w/o/w emulsions. The resulting particulate structure is determined by the interfacial tension among the two concerned polymers, by the interfacial tension across each polymer, and by the aqueous phase comprising the surfactant. A broad range of morphologies can be accomplished by modifying the surface tension or by altering the concentration and form of the surfactant within the aqueous medium (Shah 2009; Jeong 2013; Tran 2014).

3. Features of Janus nanoparticles

In biomedical applications, JNPs with effective stimulus-responsive properties, tunable structure, and biocompatibility, are composed of two surfaces containing various hydrophobic characteristics and distinct functionality. Featuring two parts with differing hydrophobicity has been the most critical aspect of the Janus amphiphilic particles. They can also be utilized as surfactants for emulsifying oil in water (Jiang and Granick 2007). Considering the interaction adsorption – through rising the amphiphilicity of such particulates – as one of the first features of JPs, they may function properly than the common particle surfactants throughout the oil/water system. It is also to be noted that amphiphilic Janus nanostructures can be exploited to transport two kinds of medications with varying solubility and bioavailability levels (Jiang and Granick 2007; Walther et al. 2008).

The anisotropic integration of dyes (e.g. fluorescent pigments or metals like quantum dots, CdSe, and Au inside these particulates) results in the formation of optical JPs to bio-imaging application processes. The magnetic polarity of JPs can provide the potential to regulate the spatial location of the particulates through changing the orientation of the exerted exterior magnetic field. The stated feature has attracted extensive interest in drug delivery applications (Walther et al. 2008). The combined effect of magnetic and optical attributes inside Janus nanostructures is also beneficial to the clinical field. Particulates containing two separate parts, one part comprising magnetic nanomaterials and another one including optical agents such as fluorescent quantum dots, have optical and magnetic characteristics concurrently. Instead of utilizing compatibility agents owing to amphiphilicity, particulate nature (Pickering emulsion), JPs can be exploited as extremely effective stabilizing agents for polymer-based systems and combining of immiscible polymeric materials: they significantly reduce interfacial emulsion, melting, and suspension energies. Walther et al. noted employing JPs as a stabilizing agent for poly(methyl methacrylate) and PS blends (Walther et al. 2008; Bahrami 2014). Catalysts' behavior may be another feature of Janus nanostructures. Inorganic JNPs comprising of metallic nanomaterials and oxide particles (e.g. dumbbell-like $AuFe_3O_4$ nanoparticles) demonstrate elevated catalyst efficiency. Such efficiency may be attributed to the beneficial influence which appears at the boundary of metal and oxide components, providing binding sites for catalyst activation as well as oxygen sorption (Bahrami 2014).

4. Biomedical applications of Janus nanoparticles

In the biomedical sector, JNPs however have drawn already-increasing scientific attention, as their anisotropic configurations can fulfill quite adaptable and fairly distinct diagnostic and therapeutic processes relative to traditional hybrid nanostructures (e.g. metallic nanomaterials, core–shell nanoparticles) (Bahrami 2014). Relative to core–shell nanostructures, JNPs greatly minimize interaction between various imaging agents. Otherwise, a blend of JNPs and therapeutic factors may produce a range of therapeutic strategies, like radiation therapy, chemotherapy, magnetoelastic therapy, phototherapy, immunotherapy, gene therapy, etc. JNPs also provide various individual drug encapsulation regions, allowing the spatial and temporal autonomous release of various medications (Poggi and Gohy 2017). Besides, JNPs may function as nanomotors to carry medicines. Alternatively, they would externally eradicate tumor cells, owing to acceleration through physicochemical interactions against exterior fields. As a result, JNPs have immense promise to become upcoming-generation nanomedicines to cancer diagnostic, therapy, and theranostics (Luo 2018).

4.1. Janus nanostructures in the diagnosis and treatment of cancer

JNPs made up of various imaging agents (e.g. gold (AU), Fe_3O_4, MnO_2, etc.) have been frequently employed as contrast factors for cancer detection, including magnetic particle imaging, magnetic resonance imaging (MRI), FLI, CT, photoacoustic imaging processing (PAI), and surface-enhanced Raman scattering (SERS) (Liu 2016; Park 2018; Feng 2019). Multimodality imaging introduces further detailed and precise knowledge

regarding tumor locations and drug transmission as compared with any separate image processing method (Schick 2014; Reguera 2017). For instance, Reguera et al. planned Janus magnetic nanostars utilizing seed and nucleation growth methods, in which Fe_3O_4–Au nanodumbells were initially produced as seedlings for a planar development of asymmetrical AU nanostars. The gained nanostars could carry out MRI/CT/PAI/SERS quadrimodal imaging (Reguera 2017).

Multi-purpose polymer–inorganic Janus nanostructures that have concurrent imaging and therapeutic capabilities are extremely desirable in biomedical implementations. Spherical polydopamine/mesoporous calcium phosphate hollow JNPs were produced using an innovative and simple technique (Wang 2015). The generated JNPs were also specifically grafted and modified via indocyanine green and methoxy-poly(ethylene glycol) thiol inside this on polydopamine regions. This could be carried out to obtain optimal photoacoustic imaging efficiency and durability, whereas the other JNPs segments – containing porous cavities – acted as storage sites and routes for the antitumor medications like doxorubicin (Zhang et al. 2017b). The resulting JNPs exhibit proper drug encapsulation efficiency, great biocompatibility, strong photothermal activity, powerful near-infrared (NIR) absorption coefficient, and double-responsive NIR/pH features, enabling such JNPs to be employed for PA imaging traced to phototherapy and chemotherapy against cancer cells (Shin 2015; Zhang et al. 2017b).

A simple, scalable, and reproducible approach was investigated for the development of uniformly Au@poly(acrylic acid) JNPs. Designed JNPs were being exploited as frameworks to preferably develop the mesoporous silica ($mSiO_2$) casing and also the distinct Au sections functionalized with methoxy-poly(ethylene glycol)-thiol (PEG) and lactobionic acid (LA) to enhance durability for tumor special identification (Shin 2015). The achieved octopus-form JNPs have double-responsive releasing features for low pH and NIR triggers. Additionally, this DOX-loaded JNP, in 808 nm of NIR irradiation, significantly demonstrates higher *in vivo* and *in vitro* toxic effects relative to photothermal or chemotherapy treatment alone, suggesting that it may be used as a multi-purpose nanoplatforms for effectively guided and chemo/photothermal cancer treatment (Zhang et al. 2016).

The development of multipurpose therapeutic nanosystems with elevated tumor cell treatment response is the objective of nanomedicine. Fe_3O_4–Pd Janus nanostructures with double-mode MRI/PA imaging capabilities for collective chemodynamic and hyperthermia therapy were also developed. Strong magnetic-photothermal characteristics of Fe_3O_4 nanomaterials and the plasmonic photothermal impacts of Pd nanosheets, in the format of integrated Fe_3O_4–Pd JNPs, can accomplish a unique and powerful temperature rise (Zhang et al. 2016; Ma 2019). They have been shown to achieve increased heat improvement and ROS production under the rotating magnetic field and also laser irradiation. Such JNPs enable total tumor suppression without significant negative impacts upon the rotating magnetic field as well as laser irradiation directed by an MRI/PA double-mode image processing with high spatial and temporal resolution. It is also noticeable that the mentioned JNPs can offer precision double-mode hyperthermia and increased ROS mediated therapy in breast cancer (Figure 6) (Ma 2019).

Photoacoustic scanning, employing external contrast factors, has emerged mostly as a hybrid method that allows depth visualization of the optical features of elevated spatiotemporal resolution of body tissue. The capacity of such imaging modality can indeed be significantly improved through the use of contrast media which absorbs NIR visible light (Sarkar and Alexandridis 2015). Thence, optical characteristics can be controlled through sensitivity to the surrounding environment. The controllable assembly of such particulates throughout culture media has led to a significant enhancement of photoacoustic transmissions throughout the NIR range. Imaging techniques using such contrasting agents have also been applied in mammalian cells, such as breast tumor cells and macrophages (Park 2018).

Effective amphiphilic JNP, comprised of two separate parts of hydrophobic and hydrophilic biopolymers, has been provided using a strong and easy synthesis process. The surface effective hydrophilic part of this Janus structure is modified with an epithelial cell adhesion molecule aptamer to carry doxorubicin for drug therapy of colorectal adenocarcinoma metastases. It was calculated that the use of an internalization technique to promote cell absorption may enhance the anticancer activity of the Janus nanocarrier and enhance the therapeutic agents by their site delivery capability (Khezrian 2020).

$MnFe_2O_4$–$NaYF_4$ JNPs have been generated using a two-step thermolysis method. Such synthesized nanomaterials demonstrate high durability throughout aqueous media. This leads to fairly lower cytotoxicity following poly(acrylic amide) functionalization. Elevated cellular accumulation ability was exhibited for folic acid conjugate $MnFe_2O_4$–$NaYF_4$ in human esophageal carcinoma cell lines owing to upconversion luminescence features. They also highly absorb light mostly in the NIR spectrum and quickly convert it into heating energy. Mice cell proliferation may also be suppressed through the photo-thermal activity of $MnFe_2O_4$–$NaYF_4$ (Wu 2017).

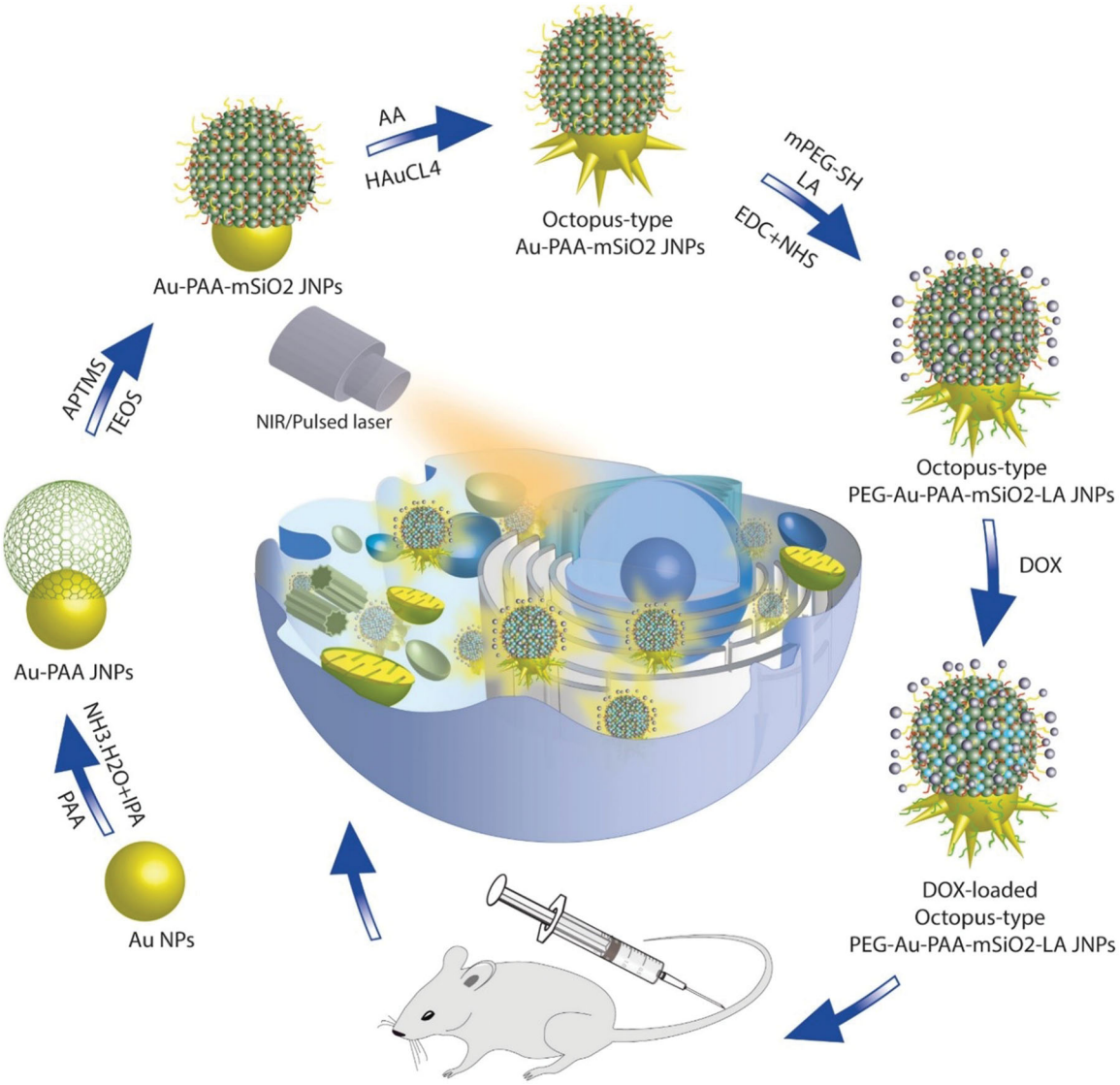

Figure 6. Producing of multi-purpose octopus-form JNPs for guided chemo/photothermal cancer treatment.

5. Conclusions

Today, the majority of JNPs are produced by the Pickering interfacial emulsion processing, seed growth and surface nucleation, surface functionalization, co-assembly processes, and phase isolation. Janus nanoparticles have always been applied to a wide range of application scenarios, from particle surfactants to drug delivery systems besides the biomedical regime for effective treatment. JNPs have remarkable characteristics like nanoscale dimensions, cytocompatibility, effective stimulus-responsive characteristics, and often optical or magnetic capabilities that can be exploited in biomedical purposes such as drug delivery, clinical diagnostics, and medicinal marking. As a targeted drug delivery system, they might be used for co-loading medications with various bioavailability and autonomous release kinetics. JNPs possess some unique superior characteristics upon core–shell nanomaterials for tumor therapeutic and diagnostic applications, including an autonomously controlled-release design, minimal signal disruptions between imaging components, and effective medication transportation.

Disclosure statement

No potential conflict of interest was reported by the author(s).

References

Bahrami R, Löbling TI, Gröschel AH, Schmalz H, Müller AHE, Altstädt V. 2014. The impact of Janus nanoparticles on the compatibilization of immiscible polymer blends under technologically relevant conditions. ACS Nano. 8(10): 10048–10056.

Bao Z, Chen L, Weldon M, Chandross E, Cherniavskaya O, Dai Y, Tok JB-H. 2002. Toward controllable self-assembly of microstructures: selective functionalization and fabrication of patterned spheres. Chem Mater. 14(1):24–26.

Baran Ł, Borówko M, Rżysko W. 2020. Self-assembly of amphiphilic Janus particles confined between two solid surfaces. J Phys Chem C. 124(32):17556–17565.

Bradley LC, Stebe KJ, Lee D. 2016. Clickable Janus particles. J Am Chem Soc. 138(36):11437–11440.

Braunecker WA, Matyjaszewski K. 2007. Controlled/living radical polymerization: features, developments, and perspectives. Prog Polym Sci. 32(1):93–146.

Chattopadhyay P, Simmchen J. 2019. Interactions of different Janus particles with passive tracers.

De Gennes PG. 1992. Soft matter. Rev Mod Phys. 64(3): 645–648.

Dehghani E, Salami-Kalajahi M, Roghani-Mamaqani H. 2018. Simultaneous two drugs release form Janus particles prepared via polymerization-induced phase separation approach. Colloids Surf B Biointerfaces. 170:85–91.

Dendukuri D, Gu SS, Pregibon DC, Hatton TA, Doyle PS. 2007. Stop-flow lithography in a microfluidic device. Lab Chip. 7(7):818–828.

Edwards EW, Wang D, Möhwald H. 2007. Hierarchical organization of colloidal particles: from colloidal crystallization to supraparticle chemistry. Macromol Chem Phys. 208(5): 439–445.

Elbert KC, Jishkariani D, Wu Y, Lee JD, Donnio B, Murray CB. 2017. Design, self-assembly, and switchable wettability in hydrophobic, hydrophilic, and Janus dendritic ligand–gold nanoparticle hybrid materials. Chem Mater. 29(20): 8737–8746.

Fan X, Yang J, Loh XJ, Li Z. 2019. Polymeric Janus nanoparticles: recent advances in synthetic strategies, materials properties, and applications. Macromol Rapid Commun. 40(5):1800203.

Fendler JH. 1996. Self-assembled nanostructured materials. Chem Mater. 8(8):1616–1624.

Feng Z-Q, Yan K, Li J, Xu X, Yuan T, Wang T, Zheng J. 2019. Magnetic Janus particles as a multifunctional drug delivery system for paclitaxel in efficient cancer treatment. Mater Sci Eng C Mater Biol Appl. 104:110001.

Gao X, Yu L, MacCuspie R, Matsui H. 2005. Controlled growth of Se nanoparticles on Ag nanoparticles in different ratios. Adv Mater. 17(4):426–429.

Gröschel AH, Müller AH. 2015. Self-assembly concepts for multicompartment nanostructures. Nanoscale. 7(28): 11841–11876.

Gu H, Zheng R, Zhang X, Xu B. 2004. Facile one-pot synthesis of bifunctional heterodimers of nanoparticles: a conjugate of quantum dot and magnetic nanoparticles. J Am Chem Soc. 126(18):5664–5665.

Han D, Shao Y, Tao Y-D, Han G, Zhou D-L, Yang S, Zhang W-B, Fu Q. 2019. Symmetry-guided, divergent assembly of regio-isomeric molecular Janus particles. Chem Commun (Camb). 55(45):6425–6428.

Han Y, Jiang W. 2011. Self-assembly of the AB/BC diblock copolymer mixture based on hydrogen bonding in a selective solvent: a Monte Carlo study. J Phys Chem B. 115(10):2167–2172.

Hückstädt H, Göpfert A, Abetz V. 2000. Influence of the block sequence on the morphological behavior of ABC triblock copolymers. Polymer. 41(26):9089–9094.

Jeong J, Um E, Park J-K, Kim MW. 2013. One-step preparation of magnetic Janus particles using controlled phase separation of polymer blends and nanoparticles. RSC Adv. 3(29): 11801–11806.

Jiang S, Granick S. 2007. Janus balance of amphiphilic colloidal particles. Maryland: American Institute of Physics.

Kalaj M, Bentz KC, Ayala S Jr, Palomba JM, Barcus KS, Katayama Y, Cohen SM. 2020. MOF-polymer hybrid materials: from simple composites to tailored architectures. Chem Rev. 120(16):8267–8302.

Khezrian S, Khoee S, Caceres M. 2020. Synthesis of combinatorial Janus nanoparticles based on EpCAM-PEG/PCL for targeted therapy of human colorectal adenocarcinoma. J Biomed Mater Res. 108(11):2291–2304.

Kierulf A, Azizi M, Eskandarloo H, Whaley J, Liu W, Perez-Herrera M, You Z, Abbaspourrad A. 2019. Starch-based Janus particles: proof-of-concept heterogeneous design via a spin-coating spray approach. Food Hydrocolloids. 91: 301–310.

Kirillova A, Marschelke C, Synytska A. 2019. Hybrid Janus particles: challenges and opportunities for the design of active functional interfaces and surfaces. ACS Appl Mater Interfaces. 11(10):9643–9671.

Kobaku SP, Snyder CS, Karunakaran RG, Kwon G, Wong P, Tuteja A, Mehta G. 2019. Wettability engendered templated self-assembly (WETS) for the fabrication of biocompatible, polymer–polyelectrolyte Janus particles. ACS Macro Lett. 8(11):1491–1497.

Le TC, Zhai J, Chiu W-H, Tran PA, Tran N. 2019. Janus particles: recent advances in the biomedical applications. Int J Nanomedicine. 14:6749–6777.

Li J, Wang J, Yao Q, Yu K, Yan Y, Zhang J. 2019. Cooperative assembly of Janus particles and amphiphilic oligomers: the role of Janus balance. Nanoscale. 11(15):7221–7228.

Liu Y, Yang X, Huang Z, Huang P, Zhang Y, Deng L, Wang Z, Zhou Z, Liu Y, Kalish H, et al. 2016. Magneto-plasmonic Janus vesicles for magnetic field-enhanced photoacoustic and magnetic resonance imaging of tumors. Angew Chem Int Ed Engl. 55(49):15297–15300.

Luo M, Feng Y, Wang T, Guan J. 2018. Micro-/nanorobots at work in active drug delivery. Adv Funct Mater. 28(25): 1706100.

Ma X, Wang Y, Liu X-L, Ma H, Li G, Li Y, Gao F, Peng M, Fan HM, Liang X-J. 2019. Fe_3O_4–Pd Janus nanoparticles with amplified dual-mode hyperthermia and enhanced ROS generation for breast cancer treatment. Nanoscale Horiz. 4(6):1450–1459.

Martin L, Irusta L, Gonzalez A, Tercjak A, Kortaberria G. 2017. Nanostructured polymer blends based on polystyrene-b-polybutadiene-b-poly (methyl methacrylate) triblock copolymers modified with polystyrene and/or poly (methyl methacrylate) homopolymers. Polym Int. 66(7):1031–1036.

Nagle L, Fitzmaurice D. 2003. Templated nanowire assembly on the surface of a patterned nanosphere. Adv Mater. 15(11):933–935.

Nie H, Liang X, He A. 2018. Enthalpy-enhanced Janus nanosheets for trapping nonequilibrium morphology of immiscible polymer blends. Macromolecules. 51(7):2615–2620.

Park JH, Dumani DS, Arsiwala A, Emelianov S, Kane RS. 2018. Tunable aggregation of gold-silica Janus nanoparticles to enable contrast-enhanced multiwavelength photoacoustic imaging in vivo. Nanoscale. 10(32):15365–15370.

Paunov VN, Cayre OJ. 2004. Supraparticles and "Janus" particles fabricated by replication of particle monolayers at liquid surfaces using a gel trapping technique. Adv Mater. 16(910):788–791.

Percebom AM, Costa LHM. 2019. Formation and assembly of amphiphilic Janus nanoparticles promoted by polymer interactions. Adv Colloid Interface Sci. 269:256–269.

Poggi E, Gohy J-F. 2017. Janus particles: from synthesis to application. Colloid Polym Sci. 295(11):2083–2108.

Reguera J, de Aberasturi DJ, Henriksen-Lacey M, Langer J, Espinosa A, Szczupak B, Wilhelm C, Liz-Marzán LM. 2017. Janus plasmonic-magnetic gold-iron oxide nanoparticles as contrast agents for multimodal imaging. Nanoscale. 9(27):9467–9480.

Roh K-H, Martin DC, Lahann J. 2005. Biphasic Janus particles with nanoscale anisotropy. Nat Mater. 4(10):759–763.

Roh KH, Yoshida M, Lahann J. 2007. Compartmentalized, multiphasic nanocolloids with potential applications in drug delivery and biomedical imaging. Materialwissenschaft Werkstofftech. 38(12):1008–1011.

Sanchez C, Rozes L, Ribot F, Laberty-Robert C, Grosso D, Sassoye C, Boissiere C, Nicole L. 2010. "Chimie douce": a land of opportunities for the designed construction of functional inorganic and hybrid organic-inorganic nanomaterials. CR Chim. 13(1–2):3–39.

Sarkar B, Alexandridis P. 2015. Block copolymer–nanoparticle composites: structure, functional properties, and processing. Prog Polym Sci. 40:33–62.

Schick I, Lorenz S, Gehrig D, Schilmann A-M, Bauer H, Panthöfer M, Fischer K, Strand D, Laquai F, Tremel W. 2014. Multifunctional two-photon active silica-coated Au@MnO Janus particles for selective dual functionalization and imaging. J Am Chem Soc. 136(6):2473–2483.

Shah RK, Kim JW, Weitz DA. 2009. Janus supraparticles by induced phase separation of nanoparticles in droplets. Adv Mater. 21(19):1949–1953.

Shin T-H, Choi Y, Kim S, Cheon J. 2015. Recent advances in magnetic nanoparticle-based multi-modal imaging. Chem Soc Rev. 44(14):4501–4516.

Song Y, Zhou J, Fan JB, Zhai W, Meng J, Wang S. 2018. Hydrophilic/oleophilic magnetic Janus particles for the rapid and efficient oil–water separation. Adv Funct Mater. 28(32):1802493.

Su H, Price C-AH, Jing L, Tian Q, Liu J, Qian K. 2019. Janus particles: design, preparation, and biomedical applications. Mater Today Bio. 4:100033.

Teranishi T, Inoue Y, Nakaya M, Oumi Y, Sano T. 2004. Nanoacorns: anisotropically phase-segregated CoPd sulfide nanoparticles. J Am Chem Soc. 126(32):9914–9915.

Tran L-T-C, Lesieur S, Faivre V. 2014. Janus nanoparticles: materials, preparation and recent advances in drug delivery. Expert Opin Drug Deliv. 11(7):1061–1074.

Vanakaras AG. 2006. Self-organization and pattern formation of Janus particles in two dimensions by computer simulations. Langmuir. 22(1):88–93.

Vilain C, Goettmann F, Moores A, Le Floch P, Sanchez C. 2007. Study of metal nanoparticles stabilised by mixed ligand and shell: a striking blue shift of the surface-plasmon band evidencing the formation of Janus nanoparticles. J Mater Chem. 17(33):3509–3514.

Walther A, Hoffmann M, Müller AH. 2008. Emulsion polymerization using Janus particles as stabilizers. Angew Chem. 120(4):723–726.

Walther A, Müller AH. 2008. Janus particles. Soft Matter. 4(4): 663–668.

Walther A, Muller AH. 2013. Janus particles: synthesis, self-assembly, physical properties, and applications. Chem Rev. 113(7):5194–5261.

Wang Y-S, Shao D, Zhang L, Zhang X-L, Li J, Feng J, Xia H, Huo Q-S, Dong W-F, Sun H-B. 2015. Gold nanorods-silica Janus nanoparticles for theranostics. Appl Phys Lett. 106(17):173705.

Wiemer K, Dörmbach K, Slabu I, Agrawal G, Schrader F, Caumanns T, Bourone SDM, Mayer J, Steitz J, Simon U, et al. 2017. Hydrophobic superparamagnetic FePt nanoparticles in hydrophilic poly(N-vinylcaprolactam) microgels: a new multifunctional hybrid system. J Mater Chem B. 5(6):1284–1292.

Wu Q, Lin Y, Wo F, Yuan Y, Ouyang Q, Song J, Qu J, Yong KT. 2017. Novel magnetic-luminescent Janus nanoparticles for cell labeling and tumor photothermal therapy. Small. 13(39):1701129.

Yang Q, Loos K. 2017a. Design and fabrication of Janus nanoparticles for interfacial distribution in block copolymers. Macromol Chem Phys. 218(4):1600451.

Yang Q, Loos K. 2017b. Janus nanoparticles inside polymeric materials: interfacial arrangement toward functional hybrid materials. Polym Chem. 8(4):641–654.

Yang Q, Miao X, Loos K. 2018. Fabrication of nano-sized hybrid Janus particles from strawberry-like hierarchical composites. Macromol Chem Phys. 219(19):1800267.

Yang Z, Muller AH, Xu C, Doyle PS, DeSimone JM, Lahann J, Sciortino F, Glotzer S, Hong L, Aarts DA. 2012. Janus particle synthesis, self-assembly and applications. London: Royal Society of Chemistry.

Yi Y, Sanchez L, Gao Y, Yu Y. 2016. Janus particles for biological imaging and sensing. Analyst. 141(12):3526–3539.

Yin Y, Lu Y, Xia Y. 2001. A self-assembly approach to the formation of asymmetric dimers from monodispersed spherical colloids. J Am Chem Soc. 123(4):771–772.

Zhang J, Grzybowski BA, Granick S. 2017a. Janus particle synthesis, assembly, and application. Langmuir. 33(28): 6964–6977.

Zhang L, Chen Y, Li Z, Li L, Saint-Cricq P, Li C, Lin J, Wang C, Su Z, Zink JI. 2016. Tailored synthesis of octopus-type Janus nanoparticles for synergistic actively-targeted and chemo-photothermal therapy. Angew Chem Int Ed Engl. 55(6):2118–2121.

Zhang M, Zhang L, Chen Y, Li L, Su Z, Wang C. 2017b. Precise synthesis of unique polydopamine/mesoporous calcium phosphate hollow Janus nanoparticles for imaging-guided chemo-photothermal synergistic therapy. Chem Sci. 8(12):8067–8077.