Metal- and Polymer-Based Nanoparticles for Advanced Therapeutic and Diagnostic System Applications

Nicole J. Bassous and Thomas J. Webster

Abstract Solutions for distinct clinical conditions that arise due to the application of nanotechnology, pertaining to refined diagnostics and therapeutics, are steadily revolutionizing the medical field. Presently, distinct modalities have emerged which advocate the manipulation of nanomaterials to produce medical devices. While several of these constructs are actively being used in the clinic, a greater number are being audited for clinical safety and efficacy, and many more are under various stages of development. Nanomaterials that are frequently investigated and that have been approved for clinical use include capsules, dendrimers, polymeric nanoparticles, nanocages, nanoshells, biopolymer nanocarriers, fullerenes, carbon nanotubes, and various inorganic materials. Due to the vibrancy of the nanomedical field, novel solutions are continuously being developed and adapted to meet standard patient needs and to exceed the capabilities of antiquated hospital diagnostic and treatment systems. In this review, the integration of biomaterials and nanotechnology, to yield nanomaterial building blocks, is investigated, especially with pertinence to the fabrication of contemporary medical devices that can be used to treat or diagnose a broad range of bacterial infections. Although nanotechnology has been credited with advancing numerous clinical breakthroughs, substantial efforts must be directed toward extensive cytotoxicity, biodegradation, administration, distribution, and metabolic analyses, among other performance identifiers, prior to the adoption of nanoparticles and/or nanomaterials as dependable drug substitutes, carriers, implants, or sensor elements.

Keywords Nanotechnology · Biomaterials · Metal nanoparticles · Mechanisms of action · Antimicrobial · Drug delivery vehicles · Polymers · Advanced imaging systems · Surface-enhanced Raman spectroscopy (SERS)

N. J. Bassous · T. J. Webster (✉)
Department of Chemical Engineering, Northeastern University, Boston, MA, USA
e-mail: th.webster@neu.edu

B. Li et al. (eds.), *Racing for the Surface*,
https://doi.org/10.1007/978-3-030-34475-7_16

Introduction to Nanotechnology

Types of Nanomaterials

Presently, discoveries in biomaterials are enriched by breakthroughs in nanotechnology, and the medical research and clinical scene have been propelled substantially forward through the foundation of technologies based on nanomaterials [1]. Since the inception of the US National Nanotechnology Initiative in 2000, the adoption of nanotechnologies for the enhancement of consumer or manufacturing products has been thoroughly well received on the world stage. Significantly, within the past two decades, various principles of nanotechnology have permeated into diverse sectors integral to societal advancement, including computing, manufacturing, energy, electronic devices, and, pertinent to the current review, health [2]. Such solutions are dependent on the manipulation of elementary constituents on the nanoscale, where the *nano-* prefix is dimensionally indicative of 10^{-9} units of measure.

In particular, as the result of a ubiquitous understanding that optimal quantum effects and enhanced surface area-to-volume ratios are associated with dimensions on the order of 100 nm or less, the nanoscale designation in scientific literature is generally assigned to constituents that meet this standard in size, from extremity to extremity [3, 4]. A variety of shapes, sizes, chemical compositions, and surface functionalities are, nevertheless, attributable to nanomaterials [5]. Commonly researched contemporary nanomaterials are classified according to structural properties as zero dimensional (0D), one dimensional (1D), or two dimensional (2D). 0D, 1D, and 2D nanomaterials include nanoparticles; nanorods, nanotubes, and nanowires; and nanocoatings, nanofilms, and nanolayers, respectively [6]. Different nanomaterial configurations are presented in Fig. 1. Materials that possess any of

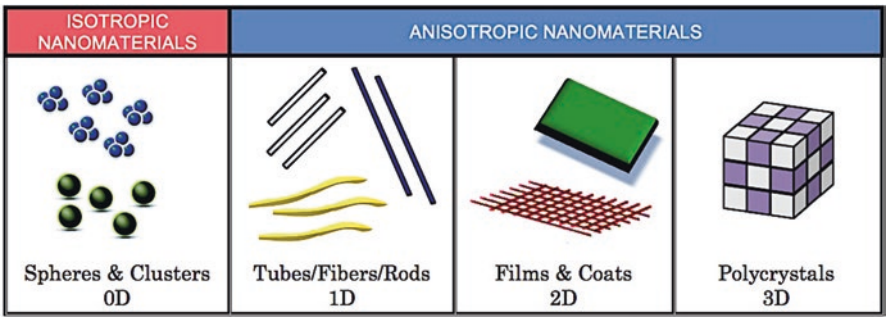


Fig. 1 0D, 1D, and 2D nanomaterials are naturally or synthetically derived [7, 8]. Common types of 0D, 1D, 2D, and 3D materials include organic nanoparticles like lipid micelles; inorganic nanorods; polymeric nanocoatings; and the carbon allotrope for diamond, respectively [9]

these size distributions generally display excellent tunability with regard to their anticipated function, whether biological, electrical, optical, thermal, or magnetic in nature [5]. Innovative strategies, such as self-assembly or electrospinning, are continuously being adapted by scientists to generate complex higher-order architectures from basic nanostructural units [6].

Applying Nanotechnology to Resist Infectious Diseases

The application of nanotechnology has become prevalent among researchers as a unique strategy for counteracting antibiotic resistance in bacteria. Prions, parasites, fungi, bacteria, and viruses are the most widely recognized classes of virulent pathogens that contribute to transmissible infectious diseases worldwide, and over 1400 microorganisms have been known to prompt disease in humans [10, 11]. Due to the prevalence of pathogenic illness among a global population, and as the result of the significant mortality rates attributable to these organismal types, infectious diseases are classified as a major health and well-being risk to humans. Actions are perpetually underway to counteract the prevalence, sustainability, and communicableness of many major pathogens. Advanced pasteurization approaches, novel vaccines, and antibacterial agents are continuously studied and generated [2]. Despite these efforts, microorganisms are steadily evolving to overcome risks to their own security, and unique solutions are being sought. In recent years, the rapid maturation of antibiotic-resistant bacteria, set on by genetic mutations and propagated by horizontal gene transfer, has weakened the efficacy of antibiotic therapies that have in the past demonstrated clinical feasibility [12]. As this evolutionary element continues to confer robustness to bacterial strains, new clinical practices that supplement or supplant antibiotics are needed to counter probable societal ill effects.

The scientific literature has been saturated with numerous studies investigating a diversity of approaches for utilizing nanomaterials to diagnose and treat infections, especially those caused by antibiotic-resistant strains of bacteria. Indeed, noble metal nanoparticles, metal oxide nanoparticles, carbon-based nanomaterials, bionanomaterials, and polymeric nanomaterials have all been demonstrated to aid in the detection or treatment of illnesses across a broad spectrum of disease states [13]. Acute or chronic bacterial infections are among the human afflictions that have been shown to be responsive to these nanomedicine therapies. This is an existential result of the ancillary properties conferred to nanoparticles and materials due to their engineered shape and size characteristics. Modifications in the synthesis parameters or conditions of nanomaterials frequently result in unique architectures that combat disease through elaborate and sometimes uncommon mechanisms. In the following sections, a variety of nanomaterials with the capacity to confer medically applied devices with capabilities ranging from sensing to diagnostics, therapeutics, and targeted therapy will be examined.

Noble Metal and Metal Oxide Nanoparticles as Antibacterial Agents

Metal Nanoparticle-Induced Pathogenic Toxicity: Mechanisms and Actions

Among the classes of noble metal and metal oxide nanoparticles, gold (Au), silver (Ag), platinum (Pt), palladium (Pd), zinc oxide (ZnO), cerium oxide (CeO_2), iron oxide (Fe_2O_3), and copper oxide (CuO) are distinguished due to the antibacterial effects either directly or indirectly associated with their application within in vitro and in vivo environments [13]. Common metal-based nanoparticle types are tabulated in Table 1, and a few of their unique applications, besides antimicrobial efficacy, are summarized [14–21]. Strategies for preparing nanoparticles include traditional hydrothermal and solvothermal syntheses, thermal decomposition, spray pyrolysis, ball milling, and chemical precipitation [14]. Emerging green methods are nutrient, plant, fungus, or polymer mediated [14].

Table 1 Common metal nanoparticle identities and their physical properties are tabulated

Nanoparticle identity	Group	Classification	Crystal structure	Select biomedical applications	References
Cerium oxide (CeO_2)	Ce 3	Lanthanoid	HCP	Alteration of mitochondrial metabolism Reshaping immune microenvironment Reduction in tumor growth	[14]
Copper oxide (CuO)	Cu 11	Transition metal	FCC	Targeted cancer therapy Wound healing	[15]
Gold (Au)	Au 11	Transition metal	FCC	Antifungal and anticancer Excellent catalytic activity Plasmonic properties	[16]
Iron oxide (Fe_3O_4, Fe_2O_3)	Fe 8	Transition metal	BCC	MRI contrast agent Magnetic hyperthermia for cancer treatment Tissue repair	[17]
Palladium (Pd)	Pd 10	Transition metal	FCC	Anticancer and anti-tumor Electrocatalytic uses	[18]
Platinum (Pt)	Pt 10	Transition metal	FCC	Catalytic activity Anti-inflammatory	[19]
Silver (Ag)	Ag 11	Transition metal	FCC	Catalytic redox properties Surface-enhanced Raman scattering Calorimetric Sensing	[20]
Zinc oxide (ZnO)	Zn 12	Transition metal	*HCP*	Use in positron emission tomography Gene delivery	[21]

Select applications are additionally outlined [14–21]
Abbreviations: *FCC* face centered cubic, *HCP* hexagonal close packed, *BCC* body centered cubic

Researchers have described extensively within the literature many strategies for experimentally inhibiting bacterial proliferation using elementally pure or hybridized metallic nanoparticles, and modifications have been investigated which facilitate these inhibition effects. The presentation of bacteriostatic and bactericidal properties by noble metal and metal oxide nanoparticles is attributable to their unique physiochemical properties, pertaining to size, morphology, and electronic responsiveness [22]. Often times, nanoparticle interactions with bacterial membranes prompt, or invoke, critical processes that significantly deplete cells of their energy sources or disrupt internal mechanistic channels. Biomolecular impairment and ATP depletion are common responses that suppress bacterial activity [23].

Membrane damage and depolarization are significant stimulants of microbial cell degradation, and these are often brought on by antagonistic interactions with metallic nanoparticles. Frequently, the cationic nature of a number of metallic nanoparticle types, or of their constituents, promotes selective electrostatic interactions with anionic bacterial membranes. Positively charged nanoparticles have demonstrated the capability to invoke physical damage to the bacterial wall and to eventually exhaust the electron transport chain [2]. In the case of magnesium oxide (MgO) and magnesium hydroxide ($Mg(OH)_2$) nanoparticles, for example, the main modes of action are adsorption onto and destruction of the cell wall [24, 25]. Here, preeminently in the case of $Mg(OH)_2$, it is believed that extracellular nanoparticle aggregation damages the bacterial cell envelope and alters the normal texture or thickness of the cell. However, aggregation is not therapeutically admissible, due to the potential adverse impact on healthy human cells, blockage of normal blood flow, and the possible reduction in bacterial cell–particle interactions [26]. Penetration or endocytosis of adsorbed nanoparticles across the bacterial wall is common among alternative particles types, leading to selective intracellular damage and cytotoxicity effects [2].

Cellular damage caused by nanoparticles is characteristically propagated by a variety of processes, especially those involving the release of metal ions and oxidative or non-oxidative stresses [22]. Metallic nanoparticles that are suspended in an aqueous environment can release charged ions as the result of a naturally imposed electrochemical potential. It is regularly observed among researchers that a greater degree of nanoparticle dissolution yields a higher concentration of ions, which is directly correlated with mammalian cell toxicity [27–30]. Enhanced dissolution rates, and hence toxicity effects, are defined among smaller and rougher nanoparticles [29]. Ions are soluble and therefore suited for uniformly confining bacterial cells [22]. The localization potential of intact, electrostatically interactive nanoparticles about a membrane domain promotes the regional generation of ions. High, localized ion concentrations facilitate cell membrane disengagement. For instance, in the case of Ag nanoparticles, the uptake of silver particles or ions by the cell can be observed by the presence of irregular pits on the bacterial surface [31]. Alternative hypotheses, again with reference to silver, predict that Ag^+ ions transcend the cellular wall through cation-selective pathways [32]. The association of Ag nanoparticles with bacterial walls has demonstrated an interplay in which the bacterial wall deteriorates or is transcended, to enable the influx of cytotoxic Ag^+ ions into the cellular cytosol [33, 34].

Evidence supporting the claim that metal ions incontrovertibly impose toxicity on bacterial cells is profound in the literature. For instance, exposing *Escherichia coli* (*E. coli*) cells to titanium dioxide (TiO_2) or aluminum oxide (Al_2O_3) nanoparticles, under uniform conditions, contributes to the body of evidence that substantiates that Al_2O_3 is a more potent membrane disruptor than TiO_2 [26]. This correlates with the assertion that ions contribute to bacterial death, in that Al_2O_3 releases Al^{3+} ions in solution, whereas Ti^{4+} ions are not detected in the case of the TiO_2 formulation [26]. To corroborate this theory, and to eliminate the possibility of alternative contributing factors, comparisons can be drawn between the effect of nanoparticle control treatments on bacterial cells and the effect of nanoparticle suspensions that are leached of their ions. Research has shown that, upon the removal of impurities from nanoparticle systems, especially of metal ions, nanoparticle toxicity is significantly reduced [35].

Nevertheless, other factors come into play when evaluating the agents responsible for nanoparticle efficacy. For example, although CuO nanoparticles yield a higher ion count than Ag nanoparticles in solution, Ag nanoparticles are more bactericidal. In this specific case, the cause is attributed to the understanding that Cu is an essential element and, as such, can be eliminated from the intracellular environment by pathways maintained due to natural homeostasis [36, 37]. In contrast, Ag is nonessential to cellular stability and can bind irreversibly to cysteine molecules [22]. This cysteine binding can impair intracellular enzymatic mechanisms, leading to possible perturbation of the electron transport chain or energy production.

Cellular leakage is a common disruption process that is compelled by metal nanoparticles and their ions. When examined under an electron microscope, bacteria lysed by nanoparticle–cell interactions may exhibit partial or complete disengagement of the intracellular environment from the cell wall, depending on the nature of the applied nanoparticle treatment [38]. Electron-dense inessential matter or granules, presumably generated by the interactions of anionic compounds found inside the bacterial cell wall with cationic species, are often detected in regions surrounding the lysed cells [38, 39]. It is predicted that the release of ions destabilizes the bacterial wall and compels membrane dislocation. These processes are emulative of the phenomena involved in plasmolysis, in which cells are depleted of their water sources [40]. Bacterial membrane impairment, resulting in leakage, has been observed from exposing gram-positive and gram-negative bacterial cells primarily to Ag, ZnO, MgO, and TiO_2 nanoparticles [41–43]. By performing temporal growth and electron imaging experiments, researchers have concluded that, generally, nanoparticles such as Ag are more effective at cleaving the bacterial walls of gram-negative bacteria than of gram-positive bacteria. This is attributed to the thick peptidoglycan layer that protects the bacterial cytoplasmic membrane in gram-positive organisms [29, 35, 38].

Membrane damage and cellular leakage due to nanoparticle agglomeration, adsorption, and ion production are not the only mechanisms responsible for bacterial cell death, and nanoparticles are very multifaceted in their efficacy routes. Commonly, chemically responsive reactive oxygen species (ROS) are generated upon the interaction of metal nanoparticles and cell walls [41]. ROS, including

superoxides, peroxides, and free radicals, are produced naturally during basic metabolic processes in which oxygen is passed through one or several states of reduction, and have critical roles in maintaining homeostasis and cell signaling pathways. However, the generation of ROS in excess, due to external or environmental stresses, could invoke cellular and biomolecular damage [44]. In fact, this effect is pronounced with the adoption of nanoparticle regimens, since a variety of metal nanoparticle types have been proven experimentally to stimulate the production of high levels of ROS, especially free radicals. This outcome, of elevated ROS generation, is observed even among *Cupriavidus metallidurans* (*C. metallidurans*) strains upon exposure to nanoparticles, despite their known survivability in a heavy metal stress environment [26]. Moreover, nanoparticles can be subjected to auxiliary stresses to activate the production of more ROS. For example, light- and UV-activated ZnO nanoparticles that are introduced into a water-rich environment split the water molecules to produce H^+ and OH^-, which react to form H_2O_2 [45]. Similar phenomena have been widely observed with Ag nanoparticles. The chemical processes involved in ROS production, and the activation of Ag nanoparticles to impose antibacterial toxicity, are outlined in Fig. 2.

ROS that are present in excess within the vicinity of a cell, either intra- or extracellularly, will alter the cell membrane by a number of mechanisms. Typically, the peroxidation of membrane lipids inhibits bacterial growth [46]. Moreover, DNA replication and ATP generation are impeded in the presence of ROS [47]. Nevertheless, the mechanisms involved in ROS toxicity are complex, and insufficient evidence is available to distinguish the primary mode of killing. Indicative of this complexity is the research observation that although DNA damage is imposed in the presence of ROS, it is not uncommon to distinguish intact bacterial membranes among cells that are thus affected [48]. Moreover, research evidence indecisively marks the dominant antimicrobial mechanism as the cause of oxidative stresses or thiol-containing protein inactivation. In support of the oxidative or catalytic stress

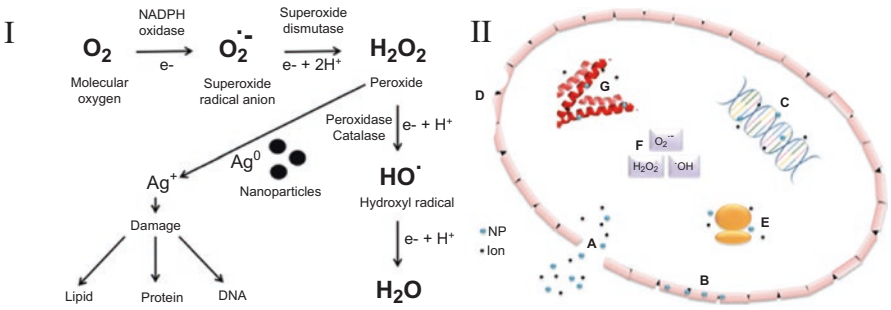


Fig. 2 In Part **I**, the reaction mechanisms involved in ROS production and Ag nanoparticles toxicity are represented. Part **II** outlines the impact of Ag nanoparticles on bacterial cells, including (A) cell wall disintegration, (B) periplasmic space separation, (C) DNA damage, (D) cell pit formation, (E) ribosomal inhibition, (F) ROS production, and (G) protein interactions [22]. Permissions for figure reuse were assumed under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/)

theory, a study was performed by Wang et al. that magnified the role of H_2O_2 in debilitating *E. coli* cells [49]. Here, it was also demonstrated that Ag^+ ions generated by Ag nanoparticles aid in intracellular ROS production, although not to the extent in which extracellular ROS stimulate the production of intracellular ROS. The protein inactivation proposition was derived earlier in the research of Xiu et al., who observed that Ag^+ ions demonstrated no significant differences in toxicity under aerobic versus anaerobic conditions [50]. From these contradictory hypotheses, it is practicable to conclude that the circumstances involved in metal nanoparticle–bacterial interactions are so complex that a diversity of interrelated events contributes to cellular toxicity. It is difficult to identify a single species, activity, or mechanism that predominantly compels bacterial cell death.

Strategies for Modifying and Encapsulating Nanoparticles for Disease Applications

A variety of strategies have been devised to augment the properties, functions, and delivery of metallic nanoparticles. These include structural and surface modifications, such as doping, capping, and halogen treating; or encapsulation routines, in which one or more nanospecies are incorporated into polymer- or biomolecule-based nano delivery vehicles. Several cases examining the optimization of metal nanoparticles for utilization in the clinic are highlighted here.

Doping, Capping, and Halogenating

Physical and chemical fabrication methods for the preparation of doped metallic nanoparticles are described extensively within the literature. Physical techniques for the conversion of metal-organic precursors are classified according to the primary process utilized in nanoparticle preparation, including spray pyrolysis [51], thermochemical/flame decomposition [52, 53], and vapor condensation [54]. Likewise, chemical routes entail the application of at least one characteristic technique such as sol–gel transition [55], thermal hydrolysis [56], or hydrothermal processing [57]. Due to the well-defined nature of conventional doping strategies, the process of incorporating different species into a crystal structure is quite feasible, despite the complications involved in synthesis. The inclusion of supplements that can complement the activity of, or positively alter, pure substances has been scrutinized extensively in nanomedicine.

Recently, Azam et al. demonstrated that the doping of ZnO nanoparticles, using cobalt (Co) and/or magnesium (Mg), yielded enhanced antibacterial efficacy, in comparison to non-doped ZnO nanoparticles [2]. Moreover, the antibacterial properties of cobalt, for instance as a stable metal coordination complex [4], and magnesium, even in its pure elemental form, have been demonstrated in the literature [58].

Quantitative and qualitative analyses were designed by Azam et al. to assess the auxiliary and synergistic properties afforded to ZnO species upon complexation [2]. Empirical trends indicated that the antibacterial characteristics of nanocrystalline ZnO were significantly enhanced by the addition of Co or Mg to the crystal lattice. This effect was slightly more pronounced in the circumstance of Co doping versus Mg doping. In vitro experiments were designed based on standard temporal growth curve and zone of inhibition procedures. The growth behaviors of four types of bacteria, including gram-negative *Escherichia coli* (*E. coli*) and *Pseudomonas aeruginosa* (*P. aeruginosa*), and gram-positive *Bacillus subtilis* (*B. subtilis*) and *Staphylococcus aureus* (*S. aureus*), in the presence of the different nanoparticle types were analyzed [2]. The data indicated that all bacterial types underwent a perceptible and significant reduction in cell viability when treated with ZnO or doped ZnO nanoparticles. In particular, a positive trend was observed, in which a higher Co or Mg concentration within the primary aggregate ZnO nanostructure produced an increase in the antimicrobial activity. The minimum inhibitory concentration (MIC) of the doped ZnO particles was lower than the MIC of the non-doped particles, and the zone of inhibition increased with nanoparticle doping. These observations align well with the characterization measurements, which indicate that an increase in the nanoparticle Co or Mg concentration corresponds with a decrease in particle size. The higher surface area-to-volume ratio attributed to smaller particle sizes promotes interactions between the nanoparticles and bacterial cells, which improves nanoparticle efficacy. Refer to Fig. 3 for relevant data representations.

It is postulated that several factors are at play in conferring bacteriostatic function to ZnO nanoparticles. Electrostatic interactions between the ZnO particles and the bacterial wall compel a complex series of processes that invoke cellular dysfunction. Zn^{+} ions invoke bacterial cell wall or membrane damage, which is aggravated by an influx of nanoparticles and ions into the cell body. This influx stimulates cellular swelling and consequential bursting. Concomitantly, ZnO nanoparticles produce high yields of ROS, especially hydroxyl radicals and peroxides, which contribute to cell damage and death [59–62]. Further, modifications to the ZnO crystal lattice, that is, doping, can be applied to improve in the antimicrobial efficacy of the composite nanospecies. Due to this wide range of action associated with pure ZnO nanoparticles, and due to their potential for optimization through structural modification, ZnO nanoparticles hold great promise for the clinical obstruction of infections. Moreover, doping has emerged as a practicle means for enhancing the properties of metal-based nanoparticles, although additional data on the in vivo interactions of such species must be obtained prior to their being applied as medical devices.

Alternative approaches to modifying the precise configurations of metallic nanoparticles involve the incorporation of capping agents or halogens into the composite nanostructure. Nanoparticle fabrication strategies, implicating the use of a wide selection of capping agents are abundant. Generally, capping agents are associated with the enhanced stability and good dispersion of nanoparticles in suspension [22]. Due to the tendency of capped nanoparticles to remain as separate entities for extended time periods, with minimal agglomeration, nanoparticle tox-

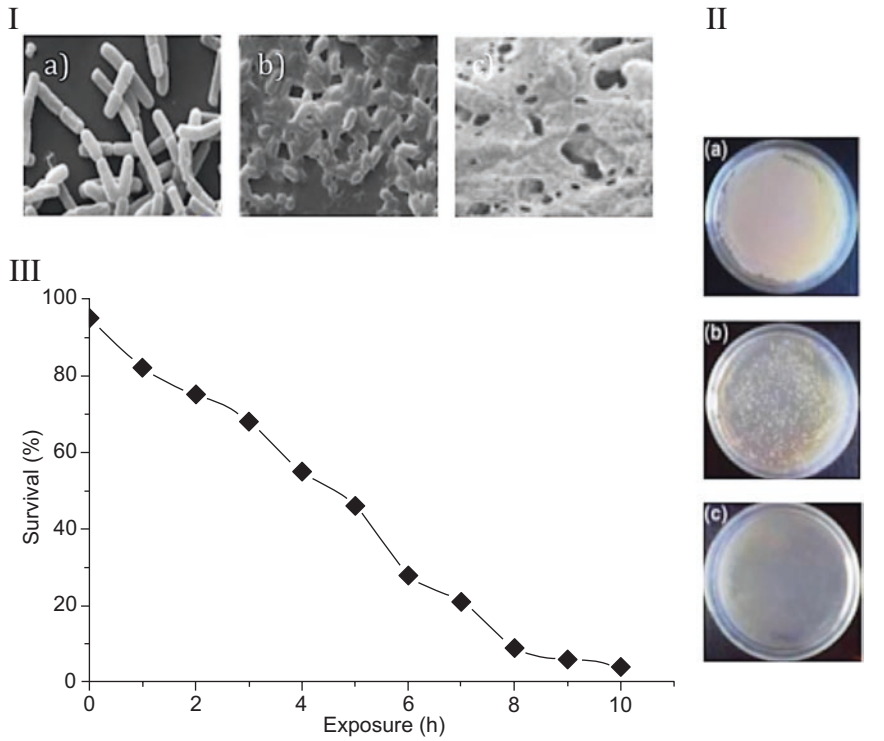


Fig. 3 A survival assay of *Bacillus subtilis* bacteria in the presence of ZnO nanoparticles was performed [2]. Parts **I** and **II** show SEM micrographs and nutrient agar plates, respectively. Different time points were tested, in which (*a*) corresponds to 2 h, (*b*) 6 h, and (*c*) 10 h incubation of bacteria and ZnO nanoparticles. A cell survival curve is represented in Part **III**

icity in comparison to the standard, uncapped form is altered. Specifically, metal nanoparticles such as Ag significantly inhibit bacterial growth when applied in combination with common capping agents like chitosan, citrate, and polyvinyl acetate. In the case of Ag nanoparticle capping, the antimicrobial activity is significantly enhanced through the incorporation of chitosan and citrate, potentially due to the increase in the generation of Ag^{+} ions that is propelled by the inclusion of a capping material [63]. 11-mercaptoundecanoic acid demonstrates improved virulence in comparison to other types of organic layers such as citrate [64]. Generally, this effect may be attributed to the poor stability of 11-mercaptoundecanoic acid in solution, which promotes the release of destructive metal ions from the core nanoparticle body; the occurrence of Cd^{2+} ions in solution indicate the general instability of 11-mercaptoundecanoic acid. Moreover, in the case of Ag nanoparticles capped by 11-mercaptoundecanoic acid, for example, adherence to the hydrophilic cell wall of *P. aeruginosa* indicates that specific interactions or affinities

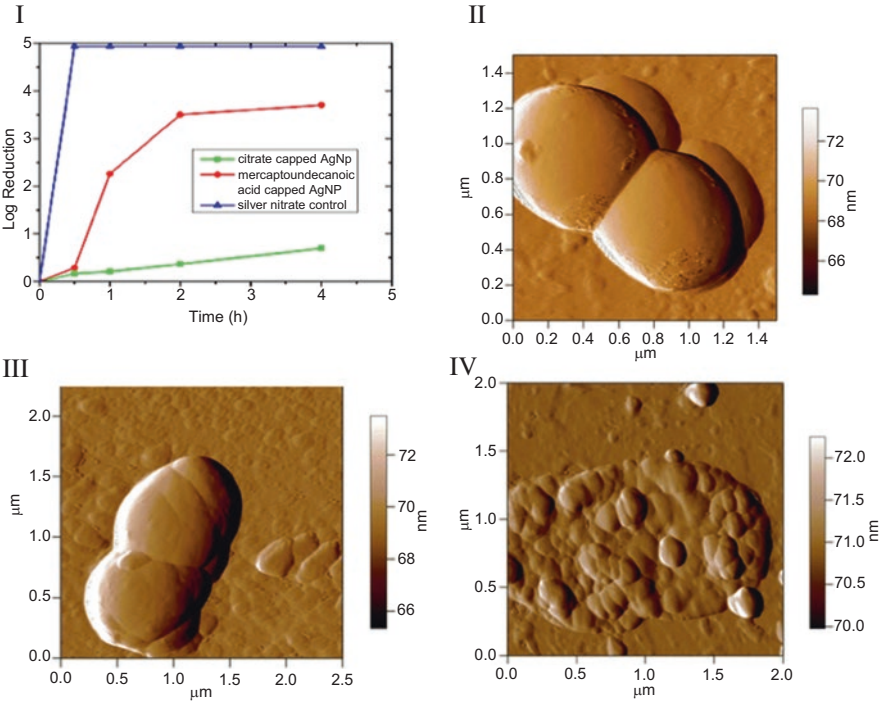


Fig. 4 A log reduction plot was produced examining the effect of citrate capped and 11-mercaptoundecanoic acid-capped Ag nanoparticles on *P. aeruginosa*, in comparison to a silver nitrate control (**I**). AFM representations of *P. aeruginosa* are shown in (**II**) before treatment, (**III**) after citrate-capped Ag treatment, and (**IV**) after 11-mercaptoundecanoic acid-capped Ag treatment [64]

may be involved in the induction of 11-mercaptoundecanoic acid toxicity [64]. The microbicidal activities of citrate- and 11-mercaptoundenanoic acid-capped Ag nanoparticles, in comparison to a silver nitrate control, are outlined in Fig. 4.

Other types of stabilizers utilize the principles of green technology. In most cases, biogenic silver has been produced through routes involving the application of natural plant materials composed of -OH, -SH, $-NH_2$, and -COOH functional groups. For instance, the *Ocimum sanctum* (Tulsi) aqueous extract and gum arabic have been applied as capping agents, and their reception has been favorable, especially due to their overall efficacy and omission of hazardous organic solvents during synthesis [65]. Surfactants such as cetyltrimethylammonium bromide (CTAB) are additionally utilized during such syntheses in order to direct morphological arrangements during particle formation [65]. Besides chemical- and green-based capping agents, halogens have been investigated as feasible functional groups for improving the antimicrobial behaviors of metal nanoparticles. The ability of halogens to confer potency to nanospecies is attributed principally to their oxidizing potential [42].

Polymeric Nanomaterials and their Usefulness as Drug or Particle Carriers

In addition to surface modifying metal nanoparticles in order to achieve enhanced efficacy or stability, nanoparticle encapsulation has been widely investigated as a means for providing adequate delivery or promoting therapeutic synergism. Variable particle types can be tuned to accommodate distinct functionalities and to address issues of biodegradability and biostability as they pertain to a particular end operation. In particular, carrier micro- and nanoparticles preferentially adopt dendrimer, micelle, liposome, polymersome, or other capsule-based morphologies. These particles typify possible cell body architectures. Particle selection is dependent on the intended final use or distribution route. Regularly, biomaterials that are facilely expelled from the body after performing their function are desired in particle assembly, and biodegradable substances are favored in the fabrication of such nanomaterials.

For example, poly(lactic-*co*-glycolic acid) (PLGA), polylactide (PLA)-based enantiomers, and poly(*ε*-caprolactone) (PCL) are biodegradable and suitable for use in solid drug delivery vehicles, polymersomes, micelles, or other particles that assemble using synthetic polymers as their main body [66]. Nanoparticles assembled using these or any of an array of biocompatible polymers commonly unload their therapeutic contents through cross-membrane diffusion, controlled polymer degradation (i.e., temperature, pH, or electrical sensitivity or stimulation), or vesicular dissociation. Localized accumulation of these particles at the diseased site(s) may involve extended exposure of affected tissue to the therapeutic load. Particles can further be designed to accommodate a diverse group of therapeutic molecules, depending on their membrane properties.

It is possible to incorporate hydrophilic and/or hydrophobic species into several synthetic cell body types. One conceivable advantage of particle configurations, that is, capsules, retaining a hydrophobic core is the potential for solubilizing hydrophobic drugs within the core and, as a result, increasing the concentration and enhancing the effectiveness of this hydrophobic drug in an aqueous environment. Generally, excipients like Kolliphor EL, which cause autoimmunity or hypersensitivity, have been used to deliver poorly water-soluble drugs [67–71]. The solubilization and delivery of hydrophobic drugs utilizing a hydrophobic particle core would help circumvent comparable undesirable reactions or side effects.

In the fabrication of nano drug carriers, terminal particle size distributions must be optimized to satisfy the physical restrictions imposed by administration and discharge routes. Cell bodies injected into or otherwise taken up by the vasculature should be designed to cap at 1–2 μm in their outer diameter in order to bypass possible agglomeration in small blood vessels and capillaries [72]. The in vivo fate of these particles is further subjected to dimensionality constraints. Literature sources suggest that particles having a diameter of 200 nm or less experience an extended stay in circulation as compared to larger particles, due to a reduced rate of clearance from the body [72]. Extended circulation times may be attributed to a

decline in the efficiency of opsonin binding. The high radius of curvature characteristic of smaller particles has been directly correlated with this phenomenon.

The intrinsic dimensionality of moderately sized nanoparticles brings about diminished renal clearance [73]. As a reference, a 10 nm effective pore size cutoff and a 30–50 kDa molecular weight cutoff are typically associated with glomerular filtration [74]. Therefore, prior to biodegradation, particles <200 nm in the outer diameter will avoid filtration by the kidneys. This general coupling, of a sufficiently small particle diameter and extended circulation times, has been demonstrated to enhance therapeutic reservoir discharge within tissue that is presumptively diseased. Within this context, presumptively diseased tissue constitutes regions of abnormal lymphatic drainage, as in tumor, inflammation, or infection sites, or otherwise excessively permeable vascular structures. This drug targeting strategy passively assists in the identification of disease and the concurrent evasion of healthy tissue, and is conventionally termed the enhanced permeability and retention (EPR) effect [75, 76]. As a result of this discussion, the majority of artificial cells considered as part of the current research will be nanoparticles, with diameters in the 1–1000 nm range, and preferentially in the 50–500 nm range. Dimensions will be defined, or the *micro-* prefix attached, for vesicles having spherical or longitudinal diameters exceeding 1000 nm.

From the literature, it is apparent that several materials can successfully self-assemble, and form the fundamental framework for guided biological, chemical, or sensory delivery [66, 77–81]. Proteins including albumin, collagen, and gelatin, and polysaccharides including alginate, starch, and dextran have all been utilized as solid particle drug carriers. Alternatively, phospholipids like phosphatidylcholine have been used to form lipid bilayer-containing vesicles called liposomes. Contemporary research predispositions favor the use of synthetic polymers instead of naturally extracted polymers or materials. This is due in part to documented or anticipated improved particle stability, tunability, and chemical versatility when select synthetic polymers are employed in place of other organic or inorganic materials. These synthetic polymers include the previously cited PLGA, PLA, and PCL, in addition to poly(vinyl alcohol) (PVA), poly(vinyl pyrrolidone) (PVP), poly(hydroxyethyl methacrylate) (pHEMA), poly(butadiene) (PBD), polyphosphazene, silicones, and polyanhydrides [66, 77–81]. Common polymers used to fabricate drug delivery vehicles are outlined in Table 2.

Amphiphilic di- or tri-block copolymers are commonly used to synthesize a wide array of multifaceted nanoparticles. Block copolymers are derived via polymerization of multiple monomers within the same system. Preferentially, this results in a polymer with interconnected chains that have a local aversion or attraction toward aqueous mixtures or solutions. This dual hydrophobic and hydrophilic character enables subsequent facile production of functionalizable nanoparticles. Typically, when intended for use in clinical applications, these copolymers are constructed using biocompatible and biodegradable hydrophobic blocks made of poly(amino acids) or polyesters, for example. Ideally, the selected hydrophobic polymer block is covalently linked to a hydrophilic block that is similarly biocompatible. Although polyethylene glycol (PEG), or polyethylene oxide (PEO), is fre-

Table 2 The chemical structures, names, and abbreviations of select polymers that are used to fabricate organic nanoparticles

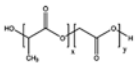
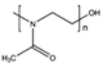
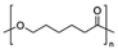
Hydrophilic Polymer Blocks			Hydrophobic Polymer Blocks		
	poly(vinyl pyrrolidone)	**PVP**		poly(hydroxyethyl methacrylate)	**pHEMA**
	polyethylene glycol/ polyethylene oxide	**PEG/PEO**		poly(lactic-co-glycolic acid)	**PLGA**
	poly(acrylic acid)	**PAA**		poly(D,L-lactide)	**PDLLA**
	poly(2-ethyl-2-oxazoline)	**PEtOx**		poly(dimethylsiloxane)	**PDMS**
	poly(2-methyl-2-oxazoline)	**PMOXA**		polycaprolactone	**PCL**

Table 3 Synthetic methods for producing polymeric vesicles

Method of preparation	Type	Size	Additives	Polydispersity
Film rehydration	Solvent free	SUV, MLV	–	High
Solid rehydration	Solvent free	SUV, MLV	–	High
Electroformation	Solvent free	GUV	–	Low
Gel-assisted hydration	Solvent free	GUV	Agarose or PVA	Low
Solvent injection	Solvent displacement	SUV	Solvent	High
Emulsion phase transfer	Solvent displacement	GUV	Solvent, surfactant	Low
Microfluidics	Solvent displacement	SUV or GUV	Solvent, surfactant, polymer, and so on	Low

Abbreviations: *SUV* small unilamellar vesicles, *MLV* multilamellar vesicles, *GUV* giant unilamellar vesicles. This table is adapted from the work of Rideau et al. [85]

quently adopted as the hydrophilic block of choice, suitable alternatives include PVP, poly(acrylic acid) (PAA), and poly(2-ethyl-2-oxazoline) (PEtOx) [82]. It is generally observed that particle circulation times are augmented by the incorporation of PEG, which has been until recently described as a "stealth" molecule—or an immune system evader [83], into nano drug delivery devices. Scientific evidence does demonstrate that water in the body forms a dense barrier around PEGylated surfaces that impedes opsonin adhesion [83]. However, recent literature by Abu Lila et al. suggests that anti-PEG antibodies are evolving in synchrony with the heightened utility of PEG in medical or other products. This anomaly is associated with the resulting so-called accelerated blood clearance (ABC) phenomenon [84], and alternatives to PEG are frequently investigated in the development of nanomaterials that will be applied or administered internally.

Several block copolymers have been studied that integrate an assortment of hydrophobic and hydrophilic blocks of variable block lengths and molecular weights. Often, amphiphilic block composition and synthesis routine influence the terminal structure of a polymeric nanoparticle. Refer to Table 3 for a summary of common methods of fabrication.

Hydrophobic block identity further governs the release of therapeutic loads. For example, poly(D,L-lactide) (PDLLA) degrades at an accelerated rate at physiological temperatures of 37 °C [86]. Similarly, poly(diethylaminoethylmethacrylate) (PDEAEM)-based assemblies will release their cargo as a result of abrupt changes in pH that are common, for example, at tumor sites [87]. A few amphiphilic block copolymers, especially mPEG-b-PCL, have the capacity to modulate species efflux across membranes that have P-glycoprotein expression [88]. This has significant implications for the transfer of therapeutic agents, for instance, across the blood–brain barrier, drug-resistant tumors, or intestinal epithelia.

Researchers have described extensively within the literature many instances of successfully encapsulating polymer-based nanoparticles for various disease or imaging applications. Synthetic polymeric bodies are rendered biofunctional through the integration of drugs, metal nanoparticles, proteins (including antibodies, peptides, and enzymes), DNA, fluorescent molecules, or other species that demonstrate the capacity to interact with local physiological events or conditions [89–93].

Spulber et al. generated ceria nanoparticle-loaded nanoreactors made from poly(*N*-vinylpyrrolidone)-block-poly(dimethylsiloxane)-block-poly(*N*-vinylpyrrolidone) (PDMS-PNVP) that possess negligible cytotoxicity, in comparison to free ceria nanoparticles, toward HeLa cells [94]. The ceria-loaded vesicles were highly stable and possessed exceptional superantioxidant activity. In a similarly translatable study, Geilich et al. developed dual Ag nanoparticle- and ampicillin-loaded mPEG-b-PDLLA polymersome vesicles, by a phase inversion strategy, that synergistically inhibited the proliferation of a multiple-drug resistant *Escherichia coli* (*E. coli*) strain that was mutated to express the *bla* gene for ampicillin resistance [95]. Here, in vitro bacterial proliferation assays confirmed that the dual delivery of metal nanoparticles and antibiotics inside a robust delivery vehicle effectively hindered bacterial proliferation. There are a few mechanistic validations for this outcome [95]. First, the bilayer membrane protected the antibiotics from hydrolysis by β-lactamase enzymes released by bacteria and promoted the sustained contact between the antibiotic and the bacterial membrane. Second, the Ag nanoparticles disrupted the bacterial cell membranes and weakened lipopolysaccharide permeability barriers. This morphological debilitation was aggravated by the reactive oxygen species (ROS) of Ag ions released from the Ag nanoparticles.

A similar study was performed in which the mPEG-b-PDLLA polymersomes were encapsulated by superparamagnetic iron oxide nanoparticles (SPIONs) and methicillin [96]. This dual therapy was targeted toward *Staphylococcus epidermidis* (*S. epidermidis*) biofilms that often occur along the surfaces of medical devices post-implantation. Following the application of an external magnetic field to an in vitro system containing *S. epidermidis* and co-functionalized polymersomes, bacterial biofilm permeation associated with cellular killing was significant, with 20 μm of penetration depth ascribed to the interaction. Figure 5 illustrates the advantages of using dual-functionalized SPION–antibiotic polymersomes that are directed by a magnetic field.

Thus, fabricated nano drug carriers may be bound to medical devices including orthopedic prosthetics to counteract the likelihood of rejection due to autoimmunity or bacterial seeding onto the implant. The principle of self-defending surfaces by

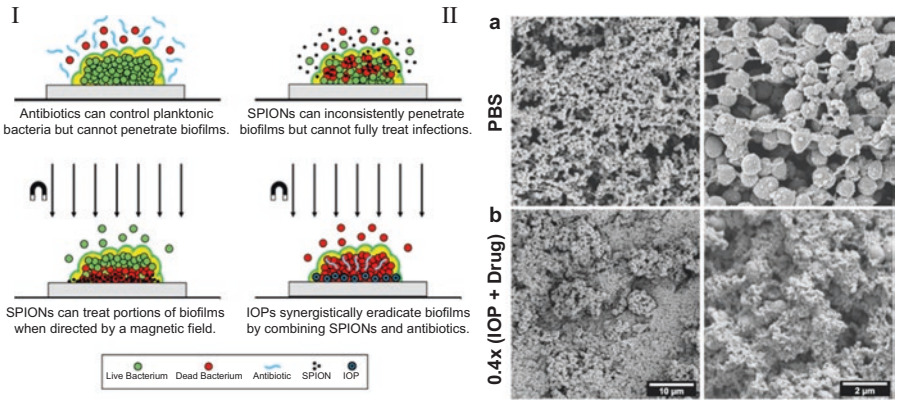


Fig. 5 Combination strategies for inhibiting bacterial biofilms are shown in Part **I** [96]. Summarily, SPIONs and antibiotics, delivered concurrently within IOPs, can penetrate and eradicate bacterial biofilms when directed by a magnetic field. Abbreviations: *IOP* iron oxide-encapsulating polymersome, *SPION* superparamagnetic iron oxide nanoparticle. TEM images in Part **II** illustrate the morphology of *S. epidermidis* biofilms and the surrounding polymer matrix (**a**) before and (**b**) after IOP treatment

the immobilization of PMOXA-b-PDMS-PMOXA polymersomes was explored by Langowska et al. [97]. Specifically, vesicles loaded with the biocatalyst penicillin acylase were anchored onto solid support surfaces by Schiff base formation and reductive amination [97]. The resulting surfaces were bioactive, stable, and antibacterial, enzymatically releasing regulated levels of antibiotics that effectively restricted *E. coli* cell growth [97]. Such models can be feasibly adapted to satisfy various clinical objectives related to implant antifouling or biosensing.

Disease Detection Through the Application of Imaging Methods and Nanoparticles

Nanoparticles for treating bacterial infections and for delivering antimicrobial agents have been reviewed. A novel possibility that has been explored in the scientific literature is the application of these nanoparticles as integral components of combination therapies, and in conjunction with microscopy and imaging methods, to diagnose or sense infections before they intractably progress. Augmented disease diagnostics is crucial for the management of infectious agents, as the early detection of pathogens could aid hospital workers to subdue interperson transmission and to more effectively treat affected individuals. Conventional diagnostic approaches can be time-consuming, inefficient, and inaccurate; and they typically involve some form of microscopy, cell culture, enzyme-linked immunoassay (ELISA), lateral flow immunoassay (LFA), or polymerase chain reaction (PCR), applied either independently or in combination. Novel approaches facilitate the use of nanomaterials,

such as quantum dots, gold nanoparticles, and magnetic nanoparticles for diagnostic purposes. Moreover, various detection modalities have emerged recently, involving for example fluorescence-, electrochemical-, or thermometry-based biosensing techniques in combination with various nanoparticle formulations. A few of the nanoparticle types reported in this chapter will be reintroduced as potential diagnostic aids, and detection modes will be briefly examined.

Nanoparticles with unique physiochemical properties, including magnetic iron (III) oxide (Fe_3O_4) and gold (Au), serve as good contrast agents for imaging applications [98, 99]. Nanoparticles decorated with ligands enable the enhanced, non-invasive imaging of diseased regions and provide a platform for the targeted delivery of large therapeutic and diagnostic loads. These nanocarriers effectively function as molecular imaging probes, maintaining some capacity for quantifying the pervasiveness of an infection and the efficacy of targeted treatments. Ideally, the operability of discrete imaging modalities is reinforced by the incorporation of compatible probes.

Ultrafine Fe_3O_4 nanoparticles, otherwise classified as SPIONs, have been shown to enhance the resolution of images obtained using magnetic resonance imaging (MRI) and to aid in adaptability studies of targeted cells or molecules [98, 99]. SPIONs can be further modified to track tissue abnormalities and to detect the onset of inflammation or disease, to serve as gene therapy or magnetic hyperthermia devices for the treatment of medical conditions, and to aid with the sequencing of biomolecules that require magnetic separation. In fact, with their high magnetization potential and unique properties, SPIONs greatly enhance the resolution of MR images without the emergence of acute side effects in vivo. In relation to infection monitoring, Lefevre et al. demonstrated the usefulness of ultrasmall SPIONs in the MRI monitoring of macrophage levels in vivo [100, 101]. Septic arthritis was induced by the inoculation of methicillin-susceptible *S. aureus* into the joints of adult female New Zealand White rabbits. It was determined noninvasively that, in comparison to control organisms that underwent antibiotic treatment, macrophage infiltration was more highly detectable within the synovium of rabbits that were not administered an antibiotic [100]. Indeed, SPION formulations (e.g., Feridex I.V. and Combidex) have been previously approved by the Food and Drug Administration (FDA) for applications in MRI contrast imaging, although currently many of these formulations have been discontinued clinically until further validations of their safe administration [102]. Alternatively, empirical evidence corroborates the usefulness of colloidal Au nanoparticles (AuNPs) in optical imaging, surface-enhanced Raman imaging (SERS), and in dark-field imaging. Qian et al. developed PEGylated Au nanoparticles modified by Raman reporter molecules and conjugated with anti-epidermal growth factor receptor (EGFR) antibodies [103]. These tumor-targeting probes applied under SERS are capable of identifying human cancer cells with high specificity and, in animal models, of localizing along tumor xenografts containing EGFRs. Au nanoparticles coated with Raman reporter molecules have been utilized in the detection of Rift Valley and West Nile fever viruses, by the specific identification of capsid and surface envelope antigens. Numerous research studies further validate the application of SERS-based methods for the detection of bacterial biomarkers,

such as those indicating pathogenic assault in common urinary tract or periprosthetic joint infections, for example [104, 105].

These principles can be extended to the detection of bacterial infections. Stimuli-responsive micelles, made out of polypyrrole, have been self-assembled and coated onto the surfaces of implantable devices that are designed to sense the proliferation of bacteria [106]. Antibacterial or anticancer drugs and nanoparticles incorporated into the cores of such micelles may be exploited as in vivo imaging probes. For better diffusion and transport properties, the polypyrrole micelles have been embedded into temperature-sensitive hydrogels. The properties described here are applicable to other drug delivery systems.

Recall that Ag nanoparticles indent bacterial membranes and facilitate the controlled influx of antibiotics into bacterial cells when used as part of Ag–antibiotic combination therapies. Similarly, formulated polymersomes can be utilized dually in disease treatment and prognosis. Ag nanoparticles are viable agents for molecular labeling using SERS [98]. This is a direct result of the optical properties, including surface plasmon resonance (SPR) and extensive light scattering effects, associated with Ag nanoparticles. Alternate imaging modalities that are enhanced by the incorporation of metallic nanoparticles include computed tomography (CT), X-ray, ultrasound (US), and positron emission tomography (PET).

Due to the versatility and potential for novel applicability in the clinic attributed to Raman spectroscopy, this technique, in addition to inherent shortcomings and enrichment strategies, will be discussed in greater detail. Raman spectroscopy is an optical and analytical tool for evaluating the chemical constitution of the cellular matrices, and fluids that occupy biological moieties [107, 108]. In particular, a spectrum is generated when incident light strikes vibrating molecules in the region of interest (i.e., the sample), which prompts inelastic light scattering. The user maintains the ability to retrieve diverse spectra obtained from the analysis of similar samples and to develop a cumulative multivariate model that supports precise diagnostics of independent specimens. An important feature of Raman spectroscopy is its capacity to generate precise molecular data with minimal sample preparation or perturbation (i.e., staining, labeling, etc.). Due to characteristic light backscattering, light transmission through a specimen is not required, and Raman spectroscopy can be applied effectively for direct in vivo imaging or in the analysis of dense or otherwise bulky tissue samples.

The applicability of Raman spectroscopy as an imaging modality is both qualitatively and lucratively feasible, and it is anticipated that Raman spectroscopy will achieve autonomy as a diagnostic tool when critical deficiencies have been redressed. Classically, Raman spectroscopy is associated with poor signals and protracted acquisition periods, which could be circumvented by spatial under-sampling and poor signal-to-noise fractions [107, 108]. Strategies have been devised to counteract these base infrastructural defects and to enable a clinically pertinent imaging technology. For instance, Raman signals have been augmented using nonlinear optics and metallic nanoparticles. Further, integration of photonic devices including miniature lasers and optical fibers improve intrinsic performance and acquisition times. SERS generally refers to the use of metallic nanoparticles for improving poor

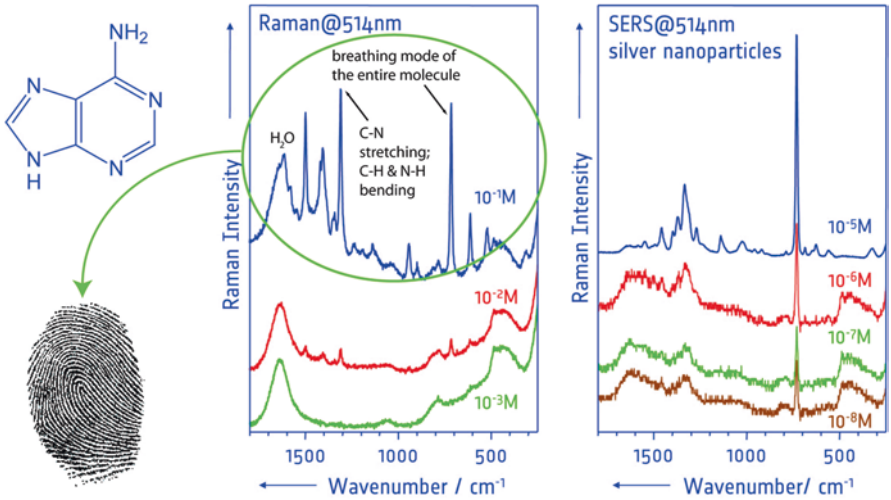


Fig. 6 From the Raman bands for adenine under non-SERS and SERS conditions, the detection limit is improved by the application of SERS and Ag nanoparticles [109]

Raman signals. Metallic nanoparticles that reside along the sample region excite surface plasmons that interact resonantly with incident light and generate an enhanced electric field in the area being investigated. Raman bands for the molecules under inspection are effectually amplified about 10^5–10^6 fold. Figure 6 shows the Raman bands of the biomolecule adenine, where an improvement in the Raman spectroscopy detection limit is observed upon the addition of Ag nanoparticles. Chemisorption of sample molecules and metallic nanoparticles complements this effect. Chemisorption may additionally be useful in the attachment of Raman reporter molecules to metallic nanoparticles prior to imaging, which propagates extrinsic SERS processing. Thus, decorated nanoparticles may further be PEGylated and appended by homing devices.

Raman microscopy has been implemented in vivo and in vitro by researchers investigating the molecular anomalies associated with brain, breast, lung, skin, esophageal, prostate, and colorectal cancers; subtle protein chemistry changes caused by bone diseases like osteoarthritis; blood serum or biofluid constitutions that aid in the diagnosis of asthma or other diseases, including malaria, and enable the quantification of disease severity; blood glucose changes in diabetics; fibrinogen and heparin levels in blood samples obtained from patients undergoing surgery or medical procedures that require enhanced or reduced blood coagulation; and concentration fluctuations of C-reactive protein (CRP) in the blood plasma that are indicative of a developing or subsiding inflammatory response [107, 108]. This final consideration, regarding blood plasma CRP levels, can be synchronized with research that investigates the efficacy of antimicrobial polymersomes or other drug delivery vehicles, for example. CRP concentration in the blood plasma is generally correlated with the intensity of a bacterial infection, and a strong intensity grade

obtained by Raman spectroscopy suggests the presence of an infection. In addition, precise biomarkers have been identified using Raman spectroscopy that discriminate, with an 80% success rate, between physiological sepsis and systemic inflammatory response syndrome (SIRS) [107, 108]. In the orthopedics research scene specifically, SERS has been adapted for the rapid and precise diagnosis of prosthetic joint infections and osteoarthritis [110, 111]. Fargašová et al. demonstrated the efficacy of this detection route in their SERS-based analysis of knee joint fluid infected by *Staphylococcus aureus* and *Streptococcus pyogenes* [110].

Future Perspectives in Nanoparticle Research

The biomedical applications of nanoparticles have spanned the delivery of therapeutics, genes, and contrast agents for the treatment of various disease conditions, and imaging and tissue engineering practices have been enhanced through the incorporation of nanostructured materials [112–115]. Moreover, characteristics have been defined which correlate the efficacy of varying nanospecies with their morphologies [116, 117]. Reported in the literature are several in vitro and animal studies recommending the use of nanoparticles in the clinic to treat pathogenic infections and various cancers, among other conditions, and nanoparticle treatments are already being actively administered to patients [118, 119]. For instance, albumin- and liposomal carriers loaded with anticancer drugs have been introduced to the market since 1995, starting with Doxil®, and are available for intravenous or intramuscular applications [120].

However, a noticeable margin of difference exists between the extent of nanoparticle research performed, and the volume of clinically authorized nanoproducts that are approved for human use. This could be attributed to several factors, including the nature of the mechanisms involved in nanoparticles syntheses, the considerable toxicity effects that nanoparticles have been determined to impose on healthy mammalian cells in vitro or in vivo, and the uncertainty with respect to the long-term consequences of nanoparticle treatments [121]. Conventionally, for example, strategies involved in the production of nanoparticles regularly incorporate the use of harsh chemicals, and the energy expenditure associated with synthesis is often quite high. Interestingly, green synthesis is currently being adapted to aid in overcoming these issues [122]. Biogenic methods that utilize bacteria, plant extracts, fungi, or yeasts are prominent in the nanoparticle fabrication scene. Further research is additionally anticipated to better define the morphological elements of varying nanoparticle types in guiding cellular toxicity. This latter aim is of particular interest since nanoparticles tend to impose cytotoxicity to healthy mammalian cells, in addition to disease-causing target cells. Ideally, an optimal nanoparticle architecture could be engineered that would diminish healthy cell toxicity while promoting the perturbation and destruction of disease-producing cells. Indeed, an ingrained challenge must be overcome in the early stages of nanoparticle research before nanotechnology can evolve into a common applicatory mode for disease diagnostics and treatment.

Guidelines are available which prescribe the efficacy and safety standards that therapeutic or diagnostic agents must comply with in order to obtain approval for clinical use [123]. General and directed toxicity studies are often time-intensive, involving variable dose injections over 28 days in at least two different large animal species. Histological and other evaluations must be conducted to assess the general effect of the agents on mammalian tissues and to define the concentration limits that produce nephrotoxicity, neurotoxicity, reprotoxicity, genotoxicity, immunotoxicity, and carcinogenicity in an organism. For nanoparticles that are too large for clearance by the excretory system, biodegradation studies must be performed to define the temporal behaviors of non-endogenous particles or particle fragments and to identify their potential side effects prior to discharge. Contingent on the particle excretion or degradation rate, these studies could be short term or long term, and in the latter case, developmental study costs could rise sharply. Administration, distribution, and metabolic analyses must be performed to supplement the excretion data. These validations would all supersede comprehensive physiochemical characterizations that would ensure the uniformity and standard marketability of nanoparticle products.

The relative newness of the nanotechnology field and the ongoing drive toward nanoparticle modifications that would eliminate their toxicity effects on healthy mammalian cells, combined with the need for immediate procedural and time-demanding evaluations, directly implies that nanoproducts will one day play a significant role in medicine, although time and testing are vital before major changes are introduced to the clinic. This is especially true when considering the current context in which diagnostics and treatments are administered. Since a multitude of medicinal agents are readily available to patients, novel solutions must be proven to match or supersede current therapeutics in terms of efficacy or safety, or a combination thereof. Risk–benefit analyses must be performed extensively for any new medical product that would potentially enter the market, and intellectual property rights must be resolved, although the complexity of this often accrues with the complexity of the product. From an economic perspective, nanotechnology in medicine would be recommended upon the development of cost-effective and efficient processes that enable the production of nanodevices in high yields. Regarding these issues and established practices, nanotechnology is currently within a developmental stage, and continuing research is anticipated to prompt the widespread adoption of nanomedicine. Within the next few years, drug delivery or enhancement tools, diagnostic systems, sensor technologies, and self-healing materials, among other aspects of medical pertinence, may benefit, in terms of efficacy, safety, and reduced clinical expenditure, by the adaptation of nanotechnology to existing therapeutics.

Conclusions

Advances in nanotechnology will inevitably yield mature devices that greatly outperform primitive treatment and diagnostic tools currently utilized in the clinic. Specifically, natural and synthetic materials, modified through variable nanoassembly

approaches, are anticipated to supplant current medical devices or medications used the in the treatment of pathogenic infections, especially those related to bacteria. In this review, noble metal and metal oxide nanoparticle types are examined, and their mechanisms of action in disrupting the colonization of in vitro or in vivo systems by bacteria are elaborated. Strategies that address the improvement of metal nanoparticle functional and structural features, especially by the consolidation of distinct materials by doping, capping, or functionalization techniques, are outlined. Nanoparticle encapsulation within nanocarriers, such as nanospheres, nanocapsules, and micelles, was explored as a viable method for the targeted delivery of therapeutic loads. This is especially relevant for the elimination of antibiotic-resistant bacteria and bacterial biofilms, which require innovative and potent treatment strategies that are reciprocally non-cytotoxic toward healthy human cells. The desired end result is an index of safe and versatile nanoparticle treatments that functionally exceed current regimens or that warrant clinical solutions to otherwise untreatable complications or conditions acquired through exposure to bacteria and other pathogens.

References

1. Sethuraman S, Krishnan UM, Subramanian A (2016) Biomaterials and nanotechnology for tissue engineering. CRC Press, Boca Raton. ISBN: 9781498743747
2. Azam A, Arshad M, Dwivedi S, Ashraf MT (2017) Antibacterial applications of nanomaterials. Adv Struct Mater 83:143–158
3. Bardosova M, Wagner T (2015) Nanomaterials and nanoarchitectures: a complex review of current hot topics and their applications. In: Nanomaterials and Nanoarchitectures: a complex review of current hot topics and their applications. Springer, Dordrecht, Netherlands, pp 1–343. ISBN: 9789401799218
4. Williams D (2008) The relationship between biomaterials and nanotechnology. Biomaterials 29:1737–1738. https://doi.org/10.1016/j.biomaterials.2008.01.003
5. Kim J, Mohamed MAA, Zagorovsky K, Chan WCW (2017) State of diagnosing infectious pathogens using colloidal nanomaterials. Biomaterials 146:97–114
6. Caldorera-Moore M, Peppas NA (2009) Micro- and nanotechnologies for intelligent and responsive biomaterial-based medical systems. Adv Drug Deliv Rev 61:1391–1401
7. Saito Y, Luo X, Zhao C, Pan W, Chen C, Gong J, Matsumoto H, Yao J, Wu H (2015) Filling the gaps between graphene oxide: a general strategy toward nanolayered oxides. Adv Funct Mater 25:5683–5690. https://doi.org/10.1002/adfm.201501358
8. Richards DA, Maruani A, Chudasama V (2017) Antibody fragments as nanoparticle targeting ligands: a step in the right direction. Chem Sci 8:63–77. https://doi.org/10.1039/C6SC02403C
9. Sajanlal PR, Sreeprasad TS, Samal AK, Pradeep T (2011) Anisotropic nanomaterials: structure, growth, assembly, and functions. Nano Rev 2:5883. https://doi.org/10.3402/nano.v2i0.5883
10. Barreto ML, Teixeira MG, Carmo EH (2006) Infectious diseases epidemiology. J Epidemiol Community Health 60:192–195
11. Woolhouse MEJ, Gowtage-Sequeria S (2005) Host range and emerging and reemerging pathogens. Emerg Infect Dis 11:1842–1847. https://doi.org/10.3201/eid1112.050997
12. Andersson DI (2003) Persistence of antibiotic resistant bacteria. Curr Opin Microbiol 6:452–456

13. Maduraiveeran G, Sasidharan M, Ganesan V (2018) Electrochemical sensor and biosensor platforms based on advanced nanomaterials for biological and biomedical applications. Biosens Bioelectron 103:113–129
14. Dhall A, Self W (2018) Cerium oxide nanoparticles: a brief review of their synthesis methods and biomedical applications. Antioxidants 7:97. https://doi.org/10.3390/antiox7080097
15. Grigore ME, Biscu ER, Holban AM, Gestal MC, Grumezescu AM (2016) Methods of synthesis, properties and biomedical applications of CuO nanoparticles. Pharmaceuticals 9(4):75. https://doi.org/10.3390/ph9040075
16. Elahi N, Kamali M, Baghersad MH (2018) Recent biomedical applications of gold nanoparticles: a review. Talanta 184:537–556
17. Ali A, Zafar H, Zia M, ul Haq I, Phull AR, Ali JS, Hussain A (2016) Synthesis, characterization, applications, and challenges of iron oxide nanoparticles. Nanotechnol Sci Appl 9:49–67
18. Leso V, Iavicoli I (2018) Palladium nanoparticles: toxicological effects and potential implications for occupational risk assessment. Int J Mol Sci 19(2)
19. Pedone D, Moglianetti M, De Luca E, Bardi G, Pompa PP (2017) Platinum nanoparticles in nanobiomedicine. Chem Soc Rev 46:4951–4975
20. Caro C, Castillo P, Klippstein R, Pozo D, Zaderenko AP (2010) Silver nanoparticles: sensing and imaging applications. Silver Nanoparticles, pp 201–225. ISBN: 978-953-307-028-5
21. Zhang Y, Nayak T, Hong H, Cai W (2013) Biomedical applications of zinc oxide nanomaterials. Curr Mol Med 13:1633–1645. https://doi.org/10.2174/15665240136661311111130058
22. Slavin YN, Asnis J, Häfeli UO, Bach H (2017) Metal nanoparticles: understanding the mechanisms behind antibacterial activity. J Nanobiotechnol 15:65
23. Karakoti AS, Hench LL, Seal S (2006) The potential toxicity of nanomaterials—the role of surfaces. JOM 58:77–82
24. Leung YH, Ng AMC, Xu X, Shen Z, Gethings LA, Wong MT, Chan CMN, Guo MY, Ng YH, Djurišič AB, Lee PKH, Chan WK, Yu LH, Phillips DL, Ma APY, Leung FCC (2014) Mechanisms of antibacterial activity of MgO: non-ROS mediated toxicity of MgO nanoparticles towards Escherichia coli. Small 10:1171–1183. https://doi.org/10.1002/smll.201302434
25. Pan X, Wang Y, Chen Z, Pan D, Cheng Y, Liu Z, Lin Z, Guan X (2013) Investigation of antibacterial activity and related mechanism of a series of nano-Mg(OH)2. ACS Appl Mater Interfaces 5:1137–1142. https://doi.org/10.1021/am302910q
26. Simon-Deckers A, Loo S, Mayne-L'Hermite M, Herlin-Boime N, Menguy N, Reynaud C, Gouget B, Carriere M (2009) Size-, composition- and shape-dependent toxicological impact of metal oxide nanoparticles and carbon nanotubes toward bacteria. Environ Sci Technol 43:8423–8429. https://doi.org/10.1021/es9016975
27. Ivask A, Elbadawy A, Kaweeteerawat C, Boren D, Fischer H, Ji Z, Chang CH, Liu R, Tolaymat T, Telesca D, Zink JI, Cohen Y, Holden PA, Godwin HA (2014) Toxicity mechanisms in Escherichia coli vary for silver nanoparticles and differ from ionic silver. ACS Nano 8:374–386. https://doi.org/10.1021/nn4044047
28. Morones JR, Elechiguerra JL, Camacho A, Holt K, Kouri JB, Ramírez JT, Yacaman MJ (2005) The bactericidal effect of silver nanoparticles. Nanotechnology 16:2346–2353. https://doi.org/10.1088/0957-4484/16/10/059
29. Kim JS, Kuk E, Yu KN, Kim JH, Park SJ, Lee HJ, Kim SH, Park YK, Park YH, Hwang CY, Kim YK, Lee YS, Jeong DH, Cho MH (2007) Antimicrobial effects of silver nanoparticles. Nanomed Nanotechnol Biol Med 3:95–101. https://doi.org/10.1016/j.nano.2006.12.001
30. Soltani Nezhad S, Rabbani Khorasgani M, Emtiazi G, Yaghoobi MM, Shakeri S (2014) Isolation of copper oxide (CuO) nanoparticles resistant Pseudomonas strains from soil and investigation on possible mechanism for resistance. World J Microbiol Biotechnol 30:809–817. https://doi.org/10.1007/s11274-013-1481-3
31. Pal S, Tak YK, Song JM (2015) Does the antibacterial activity of silver nanoparticles depend on the shape of the nanoparticle? A study of the Gram-negative bacterium Escherichia coli. J Biol Chem 290:1712–1720. https://doi.org/10.1128/AEM.02218-06.
32. McQuillan JS, Shaw AM (2014) Differential gene regulation in the Ag nanoparticle and Ag(+)-induced silver stress response in Escherichia coli: a full transcriptomic profile. Nanotoxicology 5390:1–8. https://doi.org/10.3109/17435390.2013.870243.

33. McQuillan JS, Infante HG, Stokes E, Shaw AM (2012) Silver nanoparticle enhanced silver ion stress response in Escherichia coli K12. Nanotoxicology 6:857–866
34. Lok C-N, Ho C-M, Chen R, He Q-Y, Yu W-Y, Sun H, Tam PK-H, Chiu J-F, Che C-M (2007) Silver nanoparticles: partial oxidation and antibacterial activities. J Biol Inorg Chem 12:527–534. https://doi.org/10.1007/s00775-007-0208-z
35. El Badawy AM, Silva RG, Morris B, Scheckel KG, Suidan MT, Tolaymat TM (2011) Surface charge-dependent toxicity of silver nanoparticles. Environ Sci Technol 45:283–287. https://doi.org/10.1021/es1034188
36. Linder MC, Hazegh-Azam M (1996) Copper biochemistry and molecular biology. Am J Clin Nutr 63:797S–811S
37. Berthon G (2009) Critical evaluation of the stability constants of metal complexes of amino acids with polar side chains. Pure Appl Chem 67:1117–1240
38. Jung WK, Koo HC, Kim KW, Shin S, Kim SH, Park YH (2008) Antibacterial activity and mechanism of action of the silver ion in Staphylococcus aureus and Escherichia coli. Appl Environ Microbiol 74:2171–2178. https://doi.org/10.1128/AEM.02001-07
39. Feng QL, Wu J, Chen GQ, Cui FZ, Kim TN, Kim JO (2000) A mechanistic study of the antibacterial effect of silver ions on Escherichia coli and Staphylococcus aureus. J Biomed Mater Res 52:662–668. https://doi.org/10.1002/1097-4636(20001215)52:4<662::AID-JBM10>3.0.CO;2-3
40. Tamayo LA, Zapata PA, Vejar ND, Azócar MI, Gulppi MA, Zhou X, Thompson GE, Rabagliati FM, Páez MA (2014) Release of silver and copper nanoparticles from polyethylene nanocomposites and their penetration into Listeria monocytogenes. Mater Sci Eng C 40:24–31. https://doi.org/10.1016/j.msec.2014.03.037
41. Ramalingam B, Parandhaman T, Das SK (2016) Antibacterial effects of biosynthesized silver nanoparticles on surface ultrastructure and nanomechanical properties of Gram-negative Bacteria viz. Escherichia coli and Pseudomonas aeruginosa. ACS Appl Mater Interfaces 8:4963–4976. https://doi.org/10.1021/acsami.6b00161
42. Stoimenov PK, Klinger RL, Marchin GL, Klabunde KJ (2002) Metal oxide nanoparticles as bactericidal agents. Langmuir 18:6679–6686. https://doi.org/10.1021/la0202374
43. Sohm B, Immel F, Bauda P, Pagnout C (2015) Insight into the primary mode of action of TiO2 nanoparticles on Escherichia coli in the dark. Proteomics 15:98–113. https://doi.org/10.1002/pmic.201400101
44. Manke A, Wang L, Rojanasakul Y (2013) Mechanisms of nanoparticle-induced oxidative stress and toxicity. Biomed Res Int 2013(1):942916
45. Padmavathy N, Vijayaraghavan R (2008) Enhanced bioactivity of ZnO nanoparticles—an antimicrobial study. Sci Technol Adv Mater 9:035004. https://doi.org/10.1088/1468-6996/9/3/035004
46. Madl AK, Plummer LE, Carosino C, Pinkerton KE (2014) Nanoparticles, lung injury, and the role of oxidant stress. Annu Rev Physiol 76:447–465. https://doi.org/10.1146/annurev-physiol-030212-183735
47. Mukha IP, Eremenko AM, Smirnova NP, Mikhienkova AI, Korchak GI, Gorchev VF, Chunikhin AY (2013) Antimicrobial activity of stable silver nanoparticles of a certain size. Appl Biochem Microbiol 49:199–206. https://doi.org/10.1134/S0003683813020117
48. Choi O, Hu Z (2008) Size dependent and reactive oxygen species related nanosilver toxicity to nitrifying bacteria. Environ Sci Technol 42:4583–4588. https://doi.org/10.1021/es703238h
49. Wang L, He H, Yu Y, Sun L, Liu S, Zhang C, He L (2014) Morphology-dependent bactericidal activities of Ag/CeO2 catalysts against Escherichia coli. J Inorg Biochem 135:45–53. https://doi.org/10.1016/j.jinorgbio.2014.02.016
50. Xiu Z-M, Ma J, Alvarez PJJ (2011) Differential effect of common ligands and molecular oxygen on antimicrobial activity of silver nanoparticles versus silver ions. Environ Sci Technol 45:9003–9008. https://doi.org/10.1021/es201918f
51. Kodas TT (1989) Generation of complex metal oxides by aerosol processes: superconducting ceramic particles and films. Adv Mater 1:180–192
52. Ulrich GD, Rieh JW (1982) Aggregation and growth of submicron oxide particles in flames. J Colloid Interface Sci 87:257–265. https://doi.org/10.1016/0021-9797(82)90387-3

53. Skandan G, Chen YJ, Glumac N, Kear BH (1999) Synthesis of oxide nanoparticles in low pressure flames. Nanostruct Mater 11:149–158. https://doi.org/10.1016/S0965-9773(99)00028-8
54. Granqvist CG, Buhrman RA (1976) Log-normal size distributions of ultrafine metal particles. Solid State Commun 18:123–126. https://doi.org/10.1016/0038-1098(76)91415-0
55. Vorkapic D, Matsoukas T (1998) Effect of temperature and alcohols in the preparation of titania nanoparticles from alkoxides. J Am Ceram Soc 81:2815–2820. https://doi.org/10.1111/j.1151-2916.1998.tb02701.x.
56. Park HK, Kim DK, Kim CH (1997) Effect of solvent on titania particle formation and morphology in thermal hydrolysis of TiCl4. J Am Ceram Soc 80:743–749. https://doi.org/10.1111/j.1151-2916.1997.tb02891.x
57. Smiya S (2003) Hydrothermal processing in ceramics. In: Handbook of advanced ceramics: materials, applications, processing and properties, vol 1–2, pp 471–513. ISBN: 9780080532943
58. Chang EL, Simmers C, Knight DA (2010) Cobalt complexes as antiviral and antibacterial agents. Pharmaceuticals 3:1711–1728
59. Sawai J, Kawada E, Kanou F, Igarashi H, Hashimoto A, Kokugan T, Shimizu M (1996) Detection of active oxygen generated from ceramic powders having antibacterial activity. J Chem Eng Jpn 29:627–633. https://doi.org/10.1252/jcej.29.627
60. Sawai J, Kojima H, Igarashi H, Hashimoto A, Shoji S, Takehara A, Sawaki T, Kokugan T, Shimizu M (1997) Escherichia coli damage by ceramic powder slurries. J Chem Eng Jpn 30:1034–1039. https://doi.org/10.1252/jcej.30.1034
61. Sawai J, Shoji S, Igarashi H, Hashimoto A, Kokugan T, Shimizu M, Kojima H (1998) Hydrogen peroxide as an antibacterial factor in zinc oxide powder slurry. J Ferment Bioeng 86:521–522. https://doi.org/10.1016/S0922-338X(98)80165-7
62. Applerot G, Lipovsky A, Dror R, Perkas N, Nitzan Y, Lubart R, Gedanken A (2009) Enhanced antibacterial activity of nanocrystalline ZnO due to increased ROS-mediated cell injury. Adv Funct Mater 19:842–852. https://doi.org/10.1002/adfm.200801081
63. Cavassin ED, de Figueiredo LFP, Otoch JP, Seckler MM, de Oliveira RA, Franco FF, Marangoni VS, Zucolotto V, Levin ASS, Costa SF (2015) Comparison of methods to detect the in vitro activity of silver nanoparticles (AgNP) against multidrug resistant bacteria. J Nanobiotechnol 13:64. https://doi.org/10.1186/s12951-015-0120-6
64. Dorobantu LS, Fallone C, Noble AJ, Veinot J, Ma G, Goss GG, Burrell RE (2015) Toxicity of silver nanoparticles against bacteria, yeast, and algae. J Nanopart Res 17:172. https://doi.org/10.1007/s11051-015-2984-7
65. Aazam ES, Zaheer Z (2016) Growth of Ag-nanoparticles in an aqueous solution and their antimicrobial activities against Gram positive, Gram negative bacterial strains and Candida fungus. Bioprocess Biosyst Eng 39:575–584. https://doi.org/10.1007/s00449-016-1539-3
66. Quintanar-Guerrero D, Allémann E, Fessi H, Doelker E (1998) Preparation techniques and mechanisms of formation of biodegradable nanoparticles from preformed polymers. Drug Dev Ind Pharm 24:1113–1128. https://doi.org/10.3109/03639049809108571
67. Simon-Gracia L, Hunt H, Scodeller PD, Gaitzsch J, Braun GB, Willmore a-M a, Ruoslahti E, Battaglia G, Teesalu T (2016) Paclitaxel-loaded polymersomes for enhanced intraperitoneal chemotherapy. Mol Cancer Ther 15:670–680. https://doi.org/10.1158/1535-7163.MCT-15-0713-T
68. Shuai X, Merdan T, Schaper AK, Xi F, Kissel T (2004) Core-cross-linked polymeric micelles as paclitaxel carriers. Bioconjug Chem 15:441–448. https://doi.org/10.1021/bc034113u
69. Xie J, Wang CH (2005) Self-assembled biodegradable nanoparticles developed by direct dialysis for the delivery of paclitaxel. Pharm Res 22:2079–2090. https://doi.org/10.1007/s11095-005-7782-y
70. Kim SY, Lee YM (2001) Taxol-loaded block copolymer nanospheres composed of methoxy poly(ethylene glycol) and poly(ε-caprolactone) as novel anticancer drug carriers. Biomaterials 22:1697–1704. https://doi.org/10.1016/S0142-9612(00)00292-1
71. Zhang X, Jackson JK, Burt HM (1996) Development of amphiphilic diblock copolymers as micellar carriers of taxol. Int J Pharm 132:195–206. https://doi.org/10.1016/0378-5173(95)04386-1

72. Ishida O, Maruyama K, Sasaki K, Iwatsuru M (1999) Size-dependent extravasation and interstitial localization of polyethyleneglycol liposomes in solid tumor-bearing mice. Int J Pharm 190:49–56. https://doi.org/10.1016/S0378-5173(99)00256-2
73. Jones MC, Leroux JC (1999) Polymeric micelles—a new generation of colloidal drug carriers. Eur J Pharm Biopharm 48:101–111
74. Gagliardini E, Conti S, Benigni A, Remuzzi G, Remuzzi A (2010) Imaging of the porous ultrastructure of the glomerular epithelial filtration slit. J Am Soc Nephrol 21:2081–2089. https://doi.org/10.1681/ASN.2010020199
75. Yokoyama M, Kwon GS, Okano T, Sakurai Y, Kataoka K (1994) Development of micelle-forming polymeric drug with superior anticancer activity. In: Polymeric drugs and drug administration, vol 545, pp 126–134. ISBN: 0097-6156r0-8412-2744-6
76. Hao Y-L, Deng Y-J, Chen Y, Wang K-Z, Hao A-J, Zhang Y (2005) In-vitro cytotoxicity, in-vivo biodistribution and anti-tumour effect of PEGylated liposomal topotecan. J Pharm Pharmacol 57:1279–1287. https://doi.org/10.1211/jpp.57.10.0006
77. Fujioka K (1998) Protein release from collagen matrices. Adv Drug Deliv Rev 31:247–266. https://doi.org/10.1016/S0169-409X(97)00119-1
78. Tabata Y, Ikada Y (1998) Protein release from gelatin matrices. Adv Drug Deliv Rev 31:287–301. https://doi.org/10.1016/S0169-409X(97)00125-7.
79. Dumitriu S, Chornet E (1998) Inclusion and release of proteins from polysaccharide-based polyion complexes. Adv Drug Deliv Rev 31:223–246. https://doi.org/10.1016/S0169-409X(97)00120-8.
80. Lambert G, Fattal E, Couvreur P (2001) Nanoparticulate systems for the delivery of antisense oligonucleotides. Adv Drug Deliv Rev 47:99–112
81. Soppimath KS, Aminabhavi TM, Kulkarni AR, Rudzinski WE (2001) Biodegradable polymeric nanoparticles as drug delivery devices. J Control Release 70:1–20
82. Brinkhuis RPRP, Rutjes FPJT, van Hest JCM (2011) Polymeric vesicles in biomedical applications. Polym Chem 2:1449. https://doi.org/10.1039/c1py00061f
83. Gref R, Minamitake Y, Peracchia MT, Trubetskoy V, Torchilin V, Langer R (1994) Biodegradable long-circulating polymeric nanospheres. Science 263:1600–1603. https://doi.org/10.1126/science.8128245
84. Ishida T, Kiwada H (2008) Accelerated blood clearance (ABC) phenomenon upon repeated injection of PEGylated liposomes. Int J Pharm 354:56–62
85. Rideau E, Dimova R, Schwille P, Wurm FR, Landfester K (2018) Liposomes and polymersomes: a comparative review towards cell mimicking. Chem Soc Rev 47:8572–8610. https://doi.org/10.1039/c8cs00162f
86. Jia L, Zheng JJ, Jiang SM, Huang KH (2010) Preparation, physicochemical characterization and cytotoxicity in vitro of gemcitabine-loaded PEG-PDLLA nanovesicles. World J Gastroenterol 16:1008–1013. https://doi.org/10.3748/wjg.v16.i8.1008
87. Liu J, Huang Y, Kumar A, Tan A, Jin S, Mozhi A, Liang XJ (2014) PH-sensitive nano-systems for drug delivery in cancer therapy. Biotechnol Adv 32:693–710
88. Zastre JA, Jackson JK, Wong W, Burt HM (2008) P-glycoprotein efflux inhibition by amphiphilic diblock copolymers: relationship between copolymer concentration and substrate hydrophobicity. Mol Pharm 5:643–653
89. Bruni S, Chang TM (1989) Hepatocytes immobilised by microencapsulation in artificial cells: effects on hyperbilirubinemia in Gunn rats. Biomater Artif Cells Artif Organs 17:403–411. https://doi.org/10.3109/10731198909118855
90. Chang TMS (1972) Artificial cells. Charles C. Thomas, Springfield
91. Lopes de Menezes DE, Pilarski LM, Allen TM (1998) In vitro and in vivo targeting of immunoliposomal doxorubicin to human B-cell lymphoma. Cancer Res 58:3320–3330
92. Trubetskoy VS (1999) Polymeric micelles as carriers of diagnostic agents. Adv Drug Deliv Rev 37:81–88
93. Delgado A, Soriano I, Sánchez E, Oliva M, Évora C (2000) Radiolabelled biodegradable microspheres for lung imaging. Eur J Pharm Biopharm 50:227–236. https://doi.org/10.1016/S0939-6411(00)00109-0.

94. Spulber M, Baumann P, Liu J, Palivan CG (2015) Ceria loaded nanoreactors: a nontoxic superantioxidant system with high stability and efficacy. Nanoscale 7:1411–1423. https://doi.org/10.1039/C4NR02748E
95. Geilich BM, Singleton GL, Van De Ven AL, Sridhar S, Webster TJ (2014) Silver nanoparticle-embedded polymersome nanocarriers for the treatment of antibiotic-resistant infections. In: Proceedings of the IEEE annual northeast bioengineering conference, NEBEC, vol 2014-Decem
96. Geilich BM, Gelfat I, Sridhar S, van de Ven AL, Webster TJ (2017) Superparamagnetic iron oxide-encapsulating polymersome nanocarriers for biofilm eradication. Biomaterials 119:78–85. https://doi.org/10.1016/j.biomaterials.2016.12.011
97. Langowska K, Palivan CG, Meier W (2013) Polymer nanoreactors shown to produce and release antibiotics locally. Chem Commun 49:128–130. https://doi.org/10.1039/c2cc36345c
98. Mody VV, Siwale R, Singh A, Mody HR (2010) Introduction to metallic nanoparticles. J Pharm Bioallied Sci 2:282–289. https://doi.org/10.4103/0975-7406.72127
99. Blasiak B, Van Veggel FCJM, Tomanek B (2013) Applications of nanoparticles for MRI cancer diagnosis and therapy. J Nanomater 2013:148578
100. Lefevre S, Ruimy D, Jehl F, Neuville A, Robert P, Sordet C, Ehlinger M, Dietemann J-L, Bierry G (2011) Septic arthritis: monitoring with USPIO-enhanced macrophage MR imaging. Radiology 258:722–728. https://doi.org/10.1148/radiol.10101272
101. Neuwelt A, Sidhu N, Hu CAA, Mlady G, Eberhardt SC, Sillerud LO (2015) Iron-based superparamagnetic nanoparticle contrast agents for MRI of infection and inflammation. Am J Roentgenol 204:W302–W313. https://doi.org/10.2214/AJR.14.12733
102. Wang YXJ (2015) Current status of superparamagnetic iron oxide contrast agents for liver magnetic resonance imaging. World J Gastroenterol 21:13400–13402. https://doi.org/10.3748/wjg.v21.i47.13400
103. Qian W, Murakami M, Ichikawa Y, Che Y (2011) Highly efficient and controllable PEGylation of gold nanoparticles prepared by femtosecond laser ablation in water. J Phys Chem C 115:23293–23298. https://doi.org/10.1021/jp2079567
104. Hamm L, Gee A, Indrasekara ASDS (2019) Recent advancement in the surface-enhanced Raman spectroscopy-based biosensors for infectious disease diagnosis. Appl Sci 9:1448. https://doi.org/10.3390/app9071448
105. Alvand A, Rezapoor M, Parvizi J (2017) The role of biomarkers for the diagnosis of implant-related infections in orthopaedics and trauma. Adv Exp Med Biol 971:69–79
106. Ge J, Neofytou E, Cahill TJ, Beygui RE, Zare RN (2012) Drug release from electric-field-responsive nanoparticles. ACS Nano 6:227–233. https://doi.org/10.1021/nn203430m
107. Kong K, Kendall C, Stone N, Notingher I (2015) Raman spectroscopy for medical diagnostics—from in-vitro biofluid assays to in-vivo cancer detection. Adv Drug Deliv Rev 89:121–134
108. Stewart S, Priore RJ, Nelson MP, Treado PJ (2012) Raman Imaging. Annu Rev Anal Chem 5:337–360. https://doi.org/10.1146/annurev-anchem-062011-143152
109. Ackermann K, Bohme R, Cialla D, Dorfer T, Marz A, Moller R, Popp J, Strelau K. Surface enhanced Raman spectroscopy. http://www.photonics4life.eu/index.php/layout/set/print/Consortium/P4L-DB/All-items/Surface-enhanced-Raman-Spectroscopy
110. Fargašová A, Balzerová A, Prucek R, Sedláková MH, Bogdanová K, Gallo J, Kolář M, Ranc V, Zbořil R (2017) Detection of prosthetic joint infection based on magnetically assisted surface enhanced Raman spectroscopy. Anal Chem 89:6598–6607. https://doi.org/10.1021/acs.analchem.7b00759
111. Pavlou E, Zhang X, Wang J, Kourkoumelis N (2018) Raman spectroscopy for the assessment of osteoarthritis. Ann Joint 3:83–83. https://doi.org/10.21037/aoj.2018.09.10
112. Parveen S, Misra R, Sahoo SK (2012) Nanoparticles: a boon to drug delivery, therapeutics, diagnostics and imaging. Nanomedicine 8(2):147–166
113. Jin S, Leach JC, Ye K (2009) Nanoparticle-mediated gene delivery. Methods Mol Biol. https://doi.org/10.1007/978-1-59745-483-4_34

114. Cormode DP, Naha PC, Fayad ZA (2014) Nanoparticle contrast agents for computed tomography: a focus on micelles. Contrast Media Mol Imaging 9(1):37–52. https://doi.org/10.1002/cmmi.1551
115. Goldberg M, Langer R, Jia X (2007) Nanostructured materials for applications in drug delivery and tissue engineering. J Biomater Sci Polym Ed 18(3):241–268
116. Elkady MF, Shokry Hassan H, Hafez EE, Fouad A (2015) Construction of zinc oxide into different morphological structures to be utilized as antimicrobial agent against multidrug resistant bacteria. Bioinorg Chem Appl 2015:536854. https://doi.org/10.1155/2015/536854
117. Khodashenas B, Ghorbani HR (2015) Synthesis of silver nanoparticles with different shapes. Arab J Chem. https://doi.org/10.1016/j.arabjc.2014.12.014
118. Shaalan MI, El-Mahdy MM, Theiner S, El-Matbouli M, Saleh M (2017) In vitro assessment of the antimicrobial activity of silver and zinc oxide nanoparticles against fish pathogens. Acta Vet Scand 59:49. https://doi.org/10.1186/s13028-017-0317-9
119. Goldman E, Zinger A, Da Silva D, Yaari Z, Kajal A, Vardi-Oknin D, Goldfeder M, Schroeder JE, Shainsky-Roitman J, Hershkovitz D, Schroeder A (2017) Nanoparticles target early-stage breast cancer metastasis in vivo. Nanotechnology 28(43):43LT01. https://doi.org/10.1088/1361-6528/aa8a3d
120. Barenholz Y (2012) Doxil®—the first FDA-approved nano-drug: lessons learned. J Control Release 160(2):117–134
121. Ventola CL (2012) The nanomedicine revolution. P T 37(9):512–517, 525
122. Parveen K, Banse V, Ledwani L (2016) Green synthesis of nanoparticles: their advantages and disadvantages. AIP Conf Proc 1724:020048
123. Skotland T, Iversen T, Sandvig K (2014) Development of nanoparticles for clinical use. Nanomedicine (Lond) 9:1295–1299