Understanding the Biological Activities of Nanoparticles Using Murine Models

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Abstract

The advent of nanotechnological interventions in the biomedical and pharmaceutical sectors has revolutionized the current therapeutic strategies by significantly complementing the conventional approaches. Deciphering the widespread biomedical potential of engineered nanomaterials, it is highly important to develop potential model systems. Among the different model systems used to study the biological evaluations of nanomaterials, in vivo model systems gained considerable attention. Among the various in vivo model systems, exploitation of murine models including experimental rats and mice is frequently being used owing to their phylogenetic relatedness to human system, their ability to decipher the biodistribution and bioavailability profile of administered drug candidates, and their ability to determine the different physiological and biochemical responses following the therapeutic administration. Though the limitations such as ethical considerations and other technical issues are frequently being questioned on the use of the animal models in scientific research, the use of murine models remains highly essential in finding the scientific purposes as promising alternative model systems are not available in the current scenario. In this context, murine models are being exploited to decipher the extensive biomedical applications such as antimicrobial, anti-infectives, anti-biofilm, anticancer, wound healing, radioprotective, and anti-diabetic potential of engineered nanomaterials. The nano-based platforms not only provided the widespread biomedical applications but also complemented the therapeutic efficacy of antibiotics and other drug candidates as evidenced from the in vivo studies. This chapter summarizes the advent of nanotechnological platforms in the field of biomedicines thereby improving the therapeutic efficacy of antibiotics and other drug

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candidates. The use of experimental murine models in understanding the biomedical potential of the engineered nanomaterials is also described in this chapter. This chapter will provide an in-depth understanding of utilizing appropriate model systems to decipher the biological properties of various nanomaterials and the drug-encapsulated nanomaterials.

Keywords
Nanotechnology · Murine model · Antimicrobials · Anti-infectives · Anticancer · Wound healing · Radioprotection

11.1 Introduction

11.1.1 Conventional Therapeutics and Limitations

No doubt, the invention of antibiotics and antimicrobial therapeutics in the twentieth century has revolutionized the biomedical sectors by critically avoiding the potential risks associated with conventional biomedical practices including complicated invasive processes (Ashkenazi 2013). However, the irrational and indiscriminate uses of these antibiotics lead to the development of antibiotic resistance, making it difficult to treat life-threatening infections in the twenty-first century (Chen et al. 2014; Prestinaci et al. 2015). The incidence of antimicrobial resistance not only provided serious global health issues but also contributed a significant impact on global economy in the developing countries as well as developed countries (Rather et al. 2017). In this context, it is important to quest for novel strategies which could not only bypass the resistance profile but also improve the therapeutic index of the administered drugs (Frieri et al. 2017).

11.1.2 Emergence of Nanotechnology

The nanoscience and nanotechnology are the study and application of extremely small things in multidisciplinary fields including material science, chemistry, biology, physics, and engineering. The widespread involvement of nanotechnology in the field of biology has given new dimension to the nanoscience platforms in the form of nanobiotechnology which showed promising applications in agriculture, bioremediation, pharmaceutical sectors, biomedicines, food industries, and biomedical engineering (Mostafavi et al. 2019). The promising applications of nanotechnology could be attributed to the advantageous features such as their physicochemical properties including high surface area to volume ratio, tunable size, ease in surface modification, higher reactivity, slow release efficacy, high drug payload, and high therapeutic index (Hussain et al. 2016; Hamdan et al. 2017). In particular, the nano-based platforms are frequently being used as delivery vehicle for the sustained delivery of therapeutic drug moieties, antibiotics, phytochemicals,

peptides, and genes at the target sites bypassing the different cellular barriers suggesting their enhanced therapeutic index as compared to their bulk counterparts (Reddy and Couvreur 2011).

The advent of nanotechnological platforms being used as promising drug delivery systems could be promising in the development of next-generation therapeutics owing to their ability to enhance the therapeutic index, drug release efficacy, biocompatibility, bioavailability, and long-term therapeutic actions with improved stability of the loaded drug moieties (Marta et al. 2016). The advanced and unique characteristics of the synthesized nanomaterials, used as tools for widespread application in biomedical and pharmaceutical sectors, could be attributed to their typical small size. The nano-sized materials have the inherent potential to bypass the cellular and sub-cellular barriers and interact closely with the important cellular and sub-cellular components including DNA, proteins, and lipid-containing cell membrane thereby modulating the physiological process in a sophisticated and controlled way at the cellular level (Aggarwal et al. 2009). The metal-based nanomaterials as well as polymeric nanoparticles alone or functionalized with different chemical moieties or antibiotics showed promising attributes as next-generation nanotherapeutics in the fight against microbial infections and related health issues (Hemeg 2017).

11.1.3 Applications of Nanotechnology in Biomedicines

The recent concept of nanomedicines has revolutionized the current understanding of conventional therapeutics and diagnostic approaches and thus could be considered as next-generation therapeutics in healthcare settings. The undue potential and novel avenues provided by the development of nanomedicine could provide new dimensions for efficient diagnosis and treatment of diseases (Donahue et al. 2019). The unique physicochemical properties, versatility in design and synthesis, and widespread functional importance have made the nanotechnological interventions as an attractive and alternative therapeutic choice for biomedical applications (Sakhtianchi et al. 2013). The multifaceted platforms of nanomedicines enable their widespread biomedical applications ranging from biosensing, bioimaging, early molecular diagnostics, and localized drug delivery at the target sites (Fig. 11.1) (Sankar et al. 2013).

The advent of nanotechnological therapeutic approaches not only provides wide spectrum biomedical applications but also essentially complements the conventional therapeutics by critically enhancing the bioefficacy of the traditional drug moieties (Subhaswaraj et al. 2019). The nanotechnological interventions not only provided widespread antimicrobial properties but also combated the microbial drug resistance profile thereby providing an aided arsenal in the fight against chronic microbial infections and related health diseases (Baptista et al. 2018; Baranwal et al. 2018). The nanotechnological interventions provide novel avenues in increasing the therapeutic efficacy of poorly soluble drugs, in maintaining the stability of administered therapeutic drugs, and in modulating the circulation and tissue distribution of the encapsulated drugs (Bertrand et al. 2014; Subhaswaraj et al. 2018). The key aspect of any therapeutic drugs is the stability profile after administered

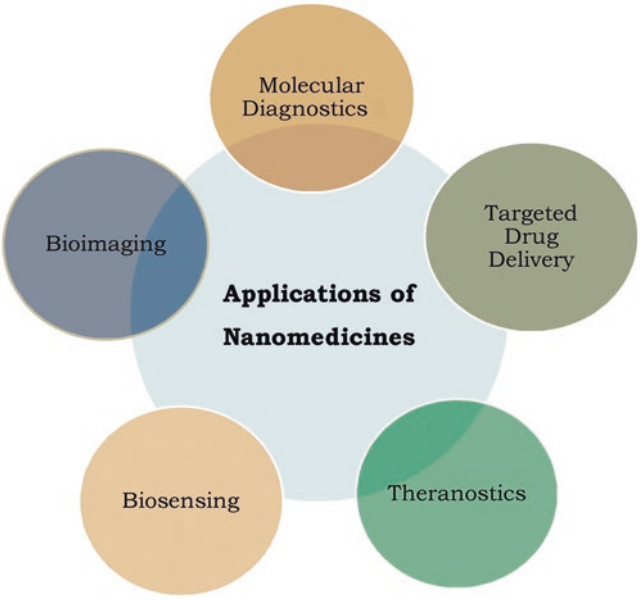

Fig. 11.1 Schematic overview of widespread biomedical applications of nanomedicines

into the biological system. The therapeutic efficacy fails when the administered drugs subjected for early degradation before being reached at the target sites. In this context, the limitations of early degradation of therapeutic drugs and their undesirable interactions could be avoided by providing novel nano-based platforms by specifically tuning the physicochemical characteristics of the encapsulated drug candidates (Zaidi et al. 2017).

11.1.4 Understanding the Mode of Action of Nanoparticles Using Model System

The exploitation of animals in scientific research and development of novel antibiotics and therapeutic drugs is an age-old process, and the involvement of animals from invertebrates to vertebrates remains an interesting buzz in the society. The use of animal models in particular the exploitation of mammalian models in developing novel therapeutics against various lethal diseases and disorders is due to the remarkable anatomical, physiological, and phylogenetic relatedness with the humans. The employment of different mammalian models owing to their greater relatedness with humans has given new dimensions to the scientific societies to discover the biological mechanisms associated with the disease progression and thus prompted to develop novel therapeutic strategies in animal models before being applied to humans (Barre-Sinoussi and Montagutelli 2015). In the development of nanomedicines, it is

important to understand the interactions of the nanomaterials with the cellular and sub-cellular components and their effect on modulating the cellular and metabolic processes. The important physiological parameters such as cellular uptake, cellular retention, biocompatibility, biodistribution profile, and exocytosis process following the uptake and toxicological aspects of the administered nanomaterials are equally important in design and development of novel nanomaterials for biomedical applications (Sakhtianchi et al. 2013).

In understanding the interactions between the nanomaterials and the biological systems, it is also important to understand the interactions of the nanomaterials with the different primary biological barriers such as skin epithelial barrier, gastrointestinal tract (GIT), and the air-blood lung barriers. Apart from these primary biological barriers, blood-brain barrier, reproductive system barrier, and circulation barrier also interact with various nanomaterials. The important function of these biological barriers is to act as primary defense system in checking the access of nanomaterials to the cellular and sub-cellular components. In this context, it is highly important to design and develop novel nanomaterials such that it could bypass these biological barriers for efficient biological actions. In this regard, the development of quantitative structure activity relationships (QSARs) as well as exploitation of promising model systems in sequestering the nano-bio interactions could provide new dimensions to the current therapeutic approaches (Meng et al. 2018).

Among the different biological barriers, the intestinal epithelial barrier proved to be instrumental in providing a check point to the oral delivery of low-permeable drug moieties. In this context, it is important to develop promising nanocarriers for the oral delivery of low-permeable drugs bypassing the intestinal epithelial barriers. The design and development of such nanocarriers should be based on their ability to follow three sequential steps including endocytosis (clathrin-mediated endocytosis/lipid raft mediated endocytosis/macropinocytosis) at the apical side, followed by transport through the cytoplasm and finally exocytosis at the basolateral side (Fan et al. 2016). In the process of understanding the abovementioned physiological processes and the effect on metabolic pathways when treated with different nanomaterials, the use of appropriate in vivo model systems is proved to be highly influential owing to their physiological and phylogenetic relatedness with human physiology.

11.2 In Vivo Model Systems to Study Biological Activities of Nanoparticles

The in vitro models are regularly used for the assessment of biological activities of different engineered nanomaterials owing to their unique features including simplicity, reliability, and cost-effectiveness. However, in vitro results could not provide reliable characteristics such as biodistribution profile, effective clearance pathways, and systemic toxicity. In this context, in vivo models could provide new dimensions in the assessment of biological actions of the nanomaterials in the biological system (Kumar et al. 2017). Despite the continuous eyebrows being raised due to ethical considerations and other limitations associated with the use of animal

models, the use of an appropriate model is essential for understanding the pathophysiology of human diseases as well as evaluating the biological significance of drugs used in in vitro conditions. The involvement of an appropriate animal model is prerequisite to establish the in vitro findings into clinical settings followed by human consumptions by critically enduring the physiological relationships during the drug administrations, their metabolism, and the mechanisms of action (Hajishengallis et al. 2015). In the assessment of biological activities of different nanomaterials, both invertebrate as well as vertebrate models are used as in vivo model systems. Among the invertebrate model systems, *Caenorhabditis elegans* (nematode model) and *D. melanogaster* (insect model) gained considerable attention in determining the biological activities of nanoparticles including the systemic toxicity profile of administered nanomaterials. Meanwhile, zebrafish (*Danio rerio*) and mammalian models including mice and rats showed immense potential in depicting the mechanism of biological actions (Fig. 11.2).

11.2.1 Invertebrate Model

Among the different invertebrate models used, the nematode model, *C. elegans*, gained considerable attention in depicting the pathophysiology of various diseases

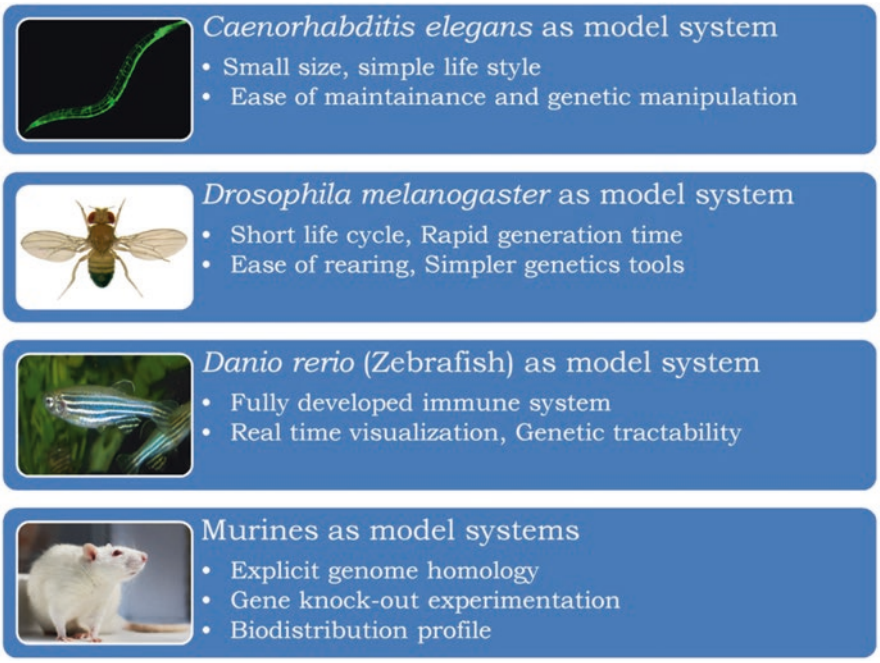

Fig. 11.2 A schematic overview of different invertebrate and vertebrate model systems exploited for understanding the biological activities of nanoparticles

and microbial infections as well as in determining the mechanism of various drug moieties and nanomaterials. The unique characteristics including small size, simple life style, cost-effectiveness, ease of maintenance, invariant developmental trajectory, conserved and well-annotated genome, and ease in genetic manipulation provide the undue importance of *C. elegans* as a convenient model (Gonzalez-Moragas et al. 2017; Hu et al. 2018). Apart from *C. elegans*, *D. melanogaster* is also considered to be influential as promising invertebrate model system in depicting the various biological functions such as tissue regeneration and developmental genetics. The characteristic attributes such as short life cycle, rapid generation time, large progeny profile, ease of rearing, cost-effectiveness, maintenance, and simpler genetics tools are considered as influential in the candidature of *D. melanogaster* as promising model organism (Markow 2015; Tolwinski 2017).

11.2.2 Vertebrate Model

The problems and limitations associated with the invertebrate model systems could be complemented with the use of vertebrate model systems which are phylogenetically closer to human beings. In this context, in the last few years, zebrafish (*D. rerio*) became the household name as promising model system in depicting the pathophysiological processes during chronic microbial infections and life-threatening diseases. The interesting attributes such as close homology with human genome, cost-effective experimentation, transparency of embryo, real-time visualization, fully developed immune system, large population size for experimentation, and genetic tractability proved to be influential in establishing zebrafish as promising model system (Fako and Furgeson 2009; Fehr et al. 2015; Chakraborty et al. 2016). Owing to the characteristic attributes of zebrafish as promising model system, zebrafish could also be used for the development of novel therapeutics and nano-based therapeutics against microbial infections as well as different life-threatening diseases (Lorenz et al. 2016). The exploitation of zebrafish could also be directed toward evaluating the toxicological aspects of engineered nanomaterials (Dai et al. 2014). Though zebrafish is considered to be an alternative model system, the use of mammalian models especially murine models remains the most extensively used model systems owing to their more relatedness with human beings with explicit genome homology. The use of murine models mice is observed to be appropriate model system in understanding the pathophysiology of disease progression and the metabolic responses of administered drugs and nanomedicines inside the biological system and in deciphering the toxicity profile of engineered nanomaterials. The unique advantage of using murine model is to understand the interactions of nanomaterials with the biological machinery, biodistribution profile of nanomaterials, and their explicit clearance from the cells as well as biological system (Yang et al. 2017).

11.3 Murine Model as Promising In Vivo Model Systems

Among the different vertebrate models used for depicting the mechanism of biological activities of therapeutic drugs or nanotechnology-based therapeutic approaches, murine models gained considerable interest. The reason behind the exploitation of murine models as promising model system is not only their evolutionary closeness to the human physiology but also due to their small size, ease of handling, inexpensiveness, and ease of gene knockout and overexpression profile (Radermacher and Haouzi 2013). One of the interesting aspects of murine model is their ability to mimic the physiological and metabolic processes in human beings thereby providing new horizons in deciphering the various pathophysiological conditions as well as development of novel therapeutic strategies (Almeida et al. 2011). Among the different murine models, because of their phylogenetic relatedness to humans, the ease of maintenance, ease of laboratory breeding, and availability of many inbred strains, house mouse, *Mus musculus*, has been exploited as promising model in understanding the human biology and related diseases. The exploitation of mouse as promising model system has genuinely provided novel avenues and powerful tools for understanding the pathophysiology of different diseases and development of new therapeutic approaches in combating the severity of disease progression (Perlman 2016).

11.3.1 Advantages and Implication of Murine Models

Though ethical considerations and other technical limitations are associated with the use of animal experimentation especially the use of mammalian models, the role of murine models remains quintessential in understanding the fundamental concept of disease progression and to discover novel therapeutic strategies in the treatment of various life-threatening diseases and infections (Vandamme 2014). The small animal models, including the murine models, have the unique advantage of phylogenetic relatedness to the human genome, ease of breeding and maintenance, availability of many inbred strains for experimentation, and affordable experimental setup. These unique characteristics provided new horizons to the use of small animal models in understanding different biological functions (Moran et al. 2016). In the development of cancer therapeutics, the exploitation of murine models has provided novel avenues in understanding the process of oncogenesis, molecular genetics in cancer cells, and metastasis and also significantly contributed in the development of novel therapeutic approaches (Kohnken et al. 2017). The extensive exploitation of different murine models remains the center of attention in the scientific community to understand the pathophysiological changes during microbial infections and diseased conditions and physiological alterations after the therapeutic administration. Mice are observed to be much more interesting as favorable models owing to the availability of various inbred, outbred, and transgenic strains as per the requirement of scientific purposes. In addition, mice are relatively easy to maintain and have a high fecundity in scientific findings as compared to rats (Stortz et al. 2017).

11.3.2 Diversity of Murine Models for Experimental Investigations

The murine models, in particular the mice model, are regularly employed in understanding the insight into the pathophysiological mechanisms during diseased conditions, to determine the efficacy of drug candidates when interacted with the biological system and to evaluate the responses on administration of therapeutic drug moieties (Justice and Dhillon 2016). The exploitation of murine models in biomedical research and preclinical drug evaluation has created a paradigm shift providing new dimensions to the current drug discovery programs (Zuberi and Lutz 2016). It is highly important to choose an appropriate model to study the highly complex interactions between the administered drugs with the biological systems thereby predicting the complexity and relatedness of the therapeutic options before being considered for human applications (Swearengen 2018).

11.4 Assessment of Biological Activities of Nanoparticles Using Murine Models

11.4.1 Antimicrobial Activity

Murine skin infection model in rats is established as a promising platform to evaluate the ability of different therapeutic drug moieties, antibiotics, or drug-conjugated nanomaterials in attenuating the bacterial burden from the infection site. In this context, biogenically synthesized silver nanoparticles (AgNPs) using *Acacia rigidula* plant as reducing and capping agent were experimentally investigated for their efficacy in minimizing the multidrug-resistant *P. aeruginosa* burden from the infection site (Escarega-Gonzalez et al. 2018). From historical perspectives, the advent of nanomaterials not only promotes intensive biomedical applications but also advocates their synergistic biomedical potential when administered in combination with therapeutic drug moieties, antibiotics, or native phytochemicals. In this context, allicin, bioactive phytochemical of garlic (*Allium sativum* L.), was used in combination with AgNPs to fight against chronic skin infection caused by methicillin-resistant *S. aureus* (MRSA). The combined therapeutic potential of allicin and AgNPs significantly decreased the MRSA burden in the skin infection site of mice model as compared to allicin and AgNPs administered individually (Sharifi-Rad et al. 2014). Apart from silver nanoparticles (AgNPs), zinc oxide nanoparticles (ZnO NPs) also showed widespread biomedical applications including antimicrobial activity, drug delivery, cancer therapy as well as diagnostic probes (Mishra et al. 2017). The biopolymer-capped ZnO NPs showed tremendous antibacterial activity against both Gram-negative and Gram-positive bacterial pathogens by altering the membrane integrity, reducing the surface hydrophobicity properties and generation of reactive oxygen species (ROS) (Fig. 11.3) (Pati et al. 2014).

11.4.2 Anti-Infective Potential

The world is currently facing a serious global issue in the form of microbial drug resistance to the conventional antibiotics (Aderibigbe 2017). In the process of development of novel therapeutic strategies to tackle the problems associated with microbial drug resistance, the advent of non-drug antimicrobials in the form of metallic nanoparticles, polymeric nanoparticles, and carbon-based nanomaterials provided promising avenues (Rai et al. 2015; Tran et al. 2019). Nanoparticles have the inherent property to be functionalized with specific chemical moieties thereby modulating the pharmacokinetic profile. These pharmacokinetic modulations have provided the target recognition and increase the efficacy of the encapsulated anti-infective drug candidates (Colino et al. 2018). The drug resistance profile of pathogenic microorganisms are basically regulated by the formation of recalcitrant biofilm as well as the activation of efflux pumps, which have the inherent property of drug extrusion thereby decreasing the drug therapeutic efficacy. In recent times, metallic nanoparticles are considered as an arsenal against these efflux pumps thereby bypassing the drug resistance profile of the encapsulated drug moieties (Gupta et al. 2017).

The advent of nanomaterials in attenuating the health consequences of infectious diseases caused by pathogenic microorganisms gained considerable attention owing to their physicochemical characteristics. Antimicrobial peptides are known for their

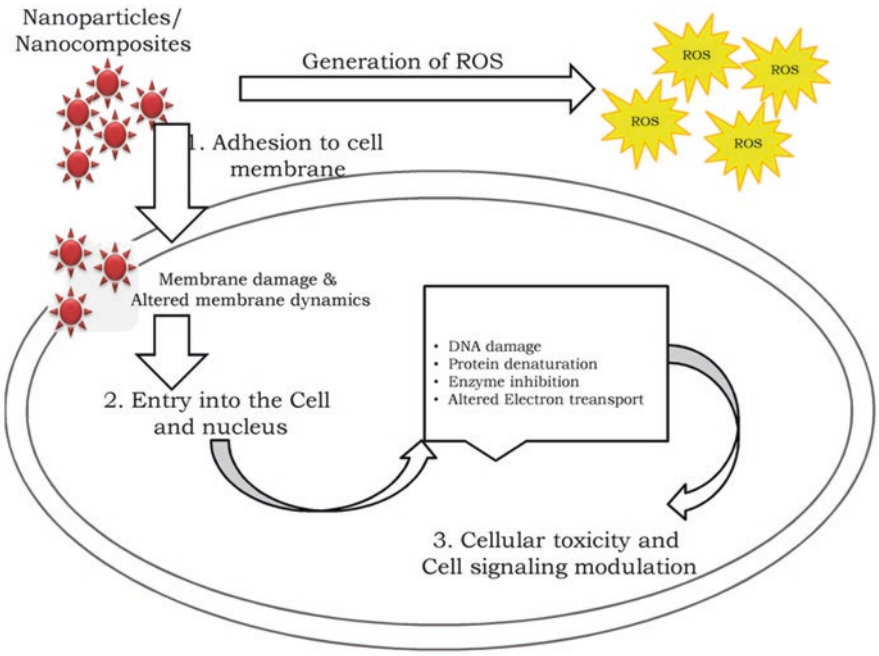

Fig. 11.3 Schematic representation of mechanism of action of antimicrobial potential of nanoparticles/nanocomposites

ability to combat multidrug-resistant microbial infections. However, when these amphiphilic antimicrobial peptides self-assembled to novel core-shell nanoparticles, they exhibited enhanced antimicrobial properties against *S. aureus* infection in mice owing to their increased therapeutic index, high drug payload, slow and sustained release profile, and their ability to cross the blood-brain barrier (Liu et al. 2009). Microbial infections are a common phenomenon found after the implantation of fixation devices for traumatic orthopedic injuries. These microbial infections in post-traumatic injuries remain a serious public concern owing to their resistance profile against wide class of antibiotics. In this context, exploitation of selenium nanoparticle (SeNPs) coatings as a potential anti-infective approach for orthopedic medical devices could be a promising alternative strategy to counteract the severity of microbial infections. SeNPs coatings significantly attenuated the methicillin-resistant *S. aureus* and *S. epidermidis* infections including orthopedic implant infections as evidenced from in vivo studies suggesting their widespread applications in counteracting the implant devices-related microbial infections (Tran et al. 2019).

11.4.3 Anti-Biofilm Activity

The emergence of multidrug resistance (MDR), extensively drug resistance (XDR), and pandrug resistance (PDR) phenomenon in pathogenic microorganisms especially ESKAPE group of pathogens (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* species) could be attributed to their inherent ability to form highly recalcitrant biofilm matrix (Magiorakos et al. 2012; Santajit and Indrawattana 2016). Biofilms are nothing but highly complex, self-made consortium of heterogenous microbial communities made up of extracellular substances including polysaccharides, proteins, lipid moieties, and nucleic acids. The biofilm-mediated sessile life style of pathogenic microorganisms is considered as an arsenal against hostile environments including host immune system, nutrient limiting conditions, and administration of therapeutic drugs (Wu et al. 2014; Ramasamy and Lee 2016; Mira et al. 2017; Dos Santos Ramos et al. 2018). One of the interesting aspects of biofilm matrix is its ability to enhance the complexity of the therapeutic strategies against human chronic wound infections which become a serious public health issue (Kim 2016). In the fight against microbial infections and associated drug resistance problems, targeting the biofilm dynamics could be instrumental in the current drug discovery programs.

The advent of nanotechnology has provided a unique and multifaceted platform for the scientific community in developing novel therapeutic strategies to fight against microbial biofilms associated drug resistance and related health issues. The recent development in nanotechnology-based approaches could play pivotal role in controlling the highly persistent and biofilm mediated chronic wound infections. As per recent trends, metal and metal oxide nanoparticles especially AgNPs have gained considerable attention in the treatment of wound biofilm infections. The synthesized AgNPs exhibited prolific anti-biofilm potential by significantly modulating the bacterial membrane permeability, destabilizing the biofilm matrix in the

infection site by intermolecular forces and triggering the generation of reactive oxygen species (ROS) resulting in biofilm disruption followed by eradication of microbial infections (Kim 2016). Among the metal oxide nanoparticles, ZnO NPs received substantial attention owing to their widespread antimicrobial activities. Sudheesh Kumar et al. (2013) advocated the combination of ZnO NPs along with β-chitin hydrogel bandages for the treatment of skin wound infection in Sprague Dawley rat model. The composite bandage significantly improved the wound healing rate with enhanced blood clotting ability and platelet activation in the infection site by inhibiting the growth of pathogenic bacteria. The topical administration of starch-capped ZnO NPs significantly disrupted the biofilm formation in *S. aureus* and also controlled the biofilm-mediated skin infections by minimizing the bacterial load and inflammation process in the infection site in BALB/c mice model (Pati et al. 2014).

11.4.4 Anticancer Activity

Cancer is one of the most decorated and deadliest public health issues across the globe owing to its ability to cause high mortality and morbidity in both developed as well as developing countries. Cancer, a collection of related diseases, becomes the second leading cause of death in the USA, the most developed country in the world (Siegel et al. 2016). In recent years, the development of nanotechnology-based cancer therapeutic strategies characteristically complements the conventional cancer treatment by critically providing localized and targeted therapies without any side effects. In particular, gold nanoparticle-mediated hyperthermia shows promising anticancer properties in animal studies suggesting their widespread avenues in cancer therapeutics in the near future (Kennedy et al. 2011). The introduction of nanotechnology in the cancer treatment also provided complementary therapeutic efficacy against multidrug resistant cancer (Friberg and Nystrom 2016). Owing to the unique characteristics of AgNPs, they are extensively used for widespread biomedical applications. In this context, *Melia azedarach*-mediated synthesis of AgNPs was developed to evaluate the cytotoxic potential of the engineered nanomaterials against Dalton's ascites lymphoma (DAL) mice model. The biogenic AgNPs significantly increased the life span of DAL mice model by induction of apoptotic mechanism in a dose-dependent manner suggesting their efficacy in the treatment of cancer in near future (Sukirtha et al. 2012). Gold nanoparticles (AuNPs) are exploited as promising radiosensitizers which provided the functional sites for their interaction with the radiation therapy thereby optimizing the fate of radiation therapy against cancer cells (Cui et al. 2017; Her et al. 2017; Borran et al. 2018).

Among the different nanomaterials exploited for therapeutic purposes and systemic drug delivery, polymeric nanoparticles in particular chitosan-based nanocomposites grabbed considerable attention due to their unique physicochemical properties such as high drug payload, controlled delivery profile, long-term effect, and localized delivery (Pattnaik et al. 2018). A novel nanoformulation containing chitosan nanoparticles encapsulating epigallocatechin-3-gallate (Chit-nanoEGCG) was designed for the treatment of prostate cancer. On treatment with

Chit-nanoEGCG, a significant modulation in the tumorigenic factors as well as tumor-suppressing factors such as poly(ADP-ribose) polymerase cleavage, Bax protein (Bcl-2 associated X protein), antiapoptotic Bcl-2, and caspases was observed in mice model (Khan et al. 2014). In addition to chitosan-based nanomaterials, novel FDA-approved poly(lactic-co-glycolic acid) (PLGA)-based nanocomposites are being frequently used as promising anticancer therapeutics. In this regard, PLGA-curcumin nanocomposites were designed and evaluated for their anticancer effect on prostate cancer xenograft mice model. The PLGA-curcumin nanocomposites have provided significant anticancer effect by inducing apoptotic process by activating the cellular morphological changes and membrane damage. The novel nanocomposites also exhibited promising anti-tumor effect as evidenced from lower tumor volume in xenograft mice model without any side effects (Yallapu et al. 2010). In the process of improving the bioavailability and anticancer effect of bioactive curcumin, α-tocopherol polyethylene glycol 1000 succinate (TPGS)-functionalized mesoporous nanocarriers with bamboo charcoal nanoparticles (TPGS-BCNPs) was designed and developed. The novel nanocomposites critically improved the bioavailability of curcumin in cancer cells and could improve its cancer therapeutic potential (Xie et al. 2017).

11.4.5 Wound Healing Activity

Wound infections remain one of the important healthcare issues posing a serious clinical challenge owing to their ability to cause systemic infection, sepsis, and multiple organ dysfunction. This results in enhanced mortality and morbidity among the immunocompromised individuals as well as healthy individuals, if neglected (Leaper et al. 2015). The therapeutic approaches available for the treatment of chronic wound infections become more complex and complicated when the infection sites provide suitable platforms for the establishment of co-aggregating biofilm forming microbial communities (Omar et al. 2017). The recent developmental approaches in nanotechnology-based diagnostics and treatment offer novel avenues to combat the complexity of the normal wound healing process by controlling the cell type specificity as well as the pathophysiology of chronic wound infections (Fig. 11.4) (Hamdan et al. 2017). The design and development of novel nanocomposites are achieved by encapsulating therapeutically active phytochemicals or drug-like candidates in combination with various nanoplatforms for enhancing the bioefficacy of the conjugated moieties. In this context, highly bioactive phytochemical, curcumin was encapsulated into typical nanoplatforms for the efficient delivery of curcumin at the target sites. The curcumin-encapsulated nanoparticles significantly inhibited the growth of MRSA and enhanced the wound healing process in murine wound model system (Krausz et al. 2015).

In recent years, selenium nanoparticles (SeNPs) have received considerable attention in various fields owing to their unique physicochemical properties, bioavailability, good absorption capacity, high surface area, and low toxicity. In 2015, the isolated actinobacterial strain, *Streptomyces minutiscleroticus* M10A62, was

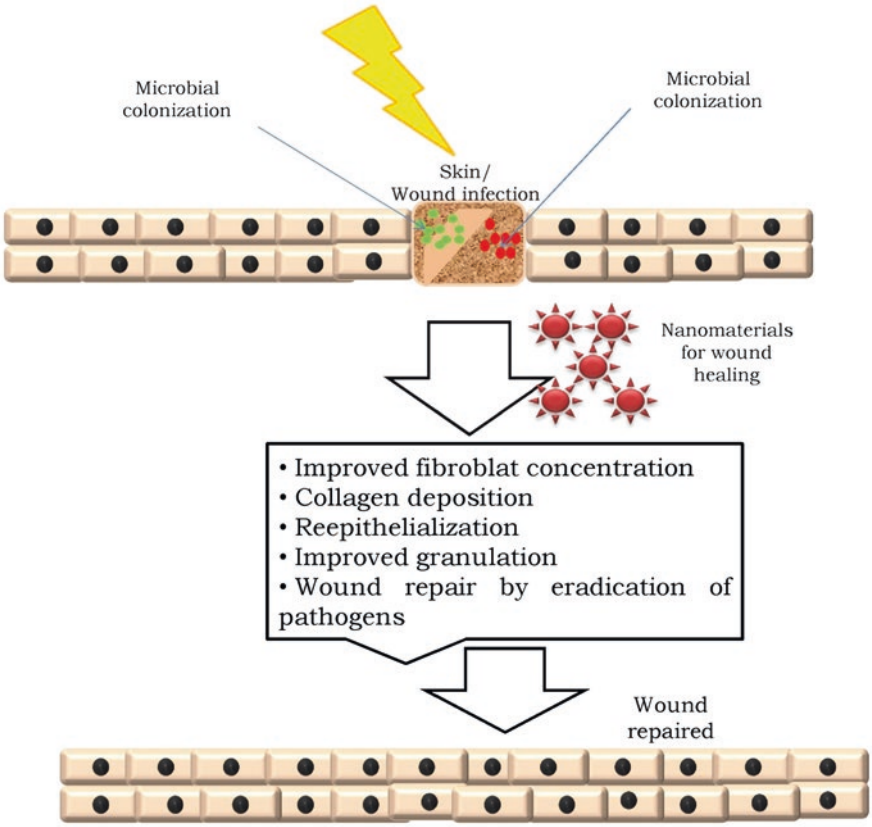

Fig. 11.4 A schematic overview of the mechanism of wound healing activity of engineered nanomaterials and specially designed nanocomposites

employed for the synthesis of SeNPs, which exhibited significant wound healing potential in the excision wound of Wistar rats as compared to the standard wound healing ointment. This result suggested the widespread avenues of using selenium based nanomaterials in the wound healing therapeutics or could be used in combination with standard drug moieties for improved and faster would healing (Ramya et al. 2015). Earlier, *Origanum vulgare*-engineered titanium dioxide nanoparticles (TiO_2 NPs) exhibited promising wound healing properties as evidenced from excision wound model in Wistar albino rats. The wound healing efficacy of topically administered TiO_2 NPs could be attributed to their bioavailability and enhanced fibroblast deposition in the wounded tissue sites (Sankar et al. 2014). In the process of nanomaterial-based wound healing applications, an antibody-targeted magnetic nanoparticle was designed to achieve an accelerated wound healing process without causing tissue injury due to highly resistant *S. aureus* infections (Kim et al. 2013).

The FDA-approved PLGA is widely considered as promising antibacterial and wound healing agent. The contribution of PLGA based nanocarriers in the targeted

delivery of poorly soluble wound healing agents also gained considerable attentions in recent years (Chereddy et al. 2016). In this context, novel biodegradable nanocomposites were designed (containing PLGA, collagen, and selected antimicrobials) and developed to enhance the wound healing activity in *S. aureus*- and *E. coli*-infected wound in rat model. The novel nanocomposites have the inherent property of sustained release profile suggesting a long-term effect in accelerating the wound healing process with improved fibroblast concentration, sparse inflammatory cells, and reepithelialized epidermis in the dermis and subcutis at the wounded site (Chen et al. 2012). In a similar experiment, fusidic acid-encapsulated PLGA ultrafine fibers also exhibited an accelerated wound healing process by sustained delivery of fusidic acid at the wounded site protecting the wounded tissues from reinfection by eradicating the *S. aureus* infections (Said et al. 2012).

In nanomaterial-based drug delivery system, micellar nanocomposites hold a special emphasis owing to their unique physicochemical properties, targeted drug delivery efficacy, and biodegradability. In this context, curcumin-loaded micelles (Cur–M) in combination with desirable wound dressing in situ gel-forming hydrogel system (Cur-M-H) were designed to evaluate their wound healing potential in linear incision as well as full thickness excision wound model. The unique nanoformulations significantly improved the wound healing process by increasing the collagen content, improved granulation, enhanced wound maturity, and increased cutaneous wound repair (Gong et al. 2013). The encapsulation of bioactive curcumin into desirable nanomaterials significantly improved the wound healing efficacy of curcumin owing to their slow and sustained release profile and enhanced bioavailability (Hussain et al. 2017). In recent years, nitric oxide (NO) has emerged as a warrior in the fight against wound infections. In this context, nitric oxide releasing nanoparticle technology was designed to improve the conventional wound healing process. The NO nanoparticles (NO NPs) significantly accelerated the wound healing process in mice model by critically inducing the fibroblast migration and collagen deposition in the wounded tissue site (Han et al. 2012).

11.4.6 Radioprotective Activity

The inadvertent exposure of living organisms to the ionizing radiations such as ultraviolet (UV) rays in general and X-rays and gamma rays in particular proved to be detrimental to public health. The continuous exposure of ionizing radiations tends to generate severe deleterious effects and more often irreversible cellular damage in the living organisms (Painuli and Kumar 2016). Protecting the living system from the radiation-induced health consequences, a variety of potent chemical and biological compounds were screened for their ability to reduce the risk to the normal tissues or those that facilitate the healing of radiation injury. Antioxidants, phytochemicals, cytoprotective agents, immunomodulators, etc. have been screened extensively for their radioprotective potential (Arora et al. 2005; Aprotosoaie et al. 2015). In recent years, the nanotechnology-based radioprotective measures are being considered as next generation therapeutics as the nanomaterials not only possess intrinsic

radioprotective properties but also stringently improved the radioprotective effect of the encapsulated therapeutic drugs (Mohamed et al. 2013; Xie et al. 2018).

Selenium nanoparticles (SeNPs) exhibited promising radioprotective effect against gamma radiation induced nephropathy in mice model by critically altering the serum creatinine, urea, β2-microglobulin, as well as in-built antioxidant enzymes (Karami et al. 2018). Recently, graphdiyne, a new emerging carbon network material, was employed for promising biological activities. Xie et al. (2019) developed bovine serum albumin (BSA)-modified graphdiyne nanoparticles (graphdiyne-BSA NPs) for the assessment of their radioprotective efficacy. From the results, it was evidenced that graphdiyne-BSA NPs significantly attenuated the radiation induced DNA damage as well as maintained the superoxide dismutase (SOD) and malondialdehyde (MDA) level in the mice model without any systemic toxicity (Xie et al. 2019). Other carbon-based nanomaterials such as water-soluble fullerenes, grapheme oxide, and carbon nanotubes also proved to be influential in exhibiting radioprotective effect (Krokosz et al. 2016). Vesna et al. (2016) advocated the efficacy of fullerenol-based nanoparticles in mitigating the radiation-induced lesions in the spleen, lungs, and intestinal tissues of rats when exposed to X-rays (Vesna et al. 2016). The unique surface regenerative property of cerium oxide nanoparticles (CeO_2 NPs) could be utilized for their ability to mitigate the acute radiation mediated lung injury in CBA/J mice model suggesting their efficacy in controlling the endogenous level of highly reactive oxygen species (Xu et al. 2016). The mitigation of radiation induced lesions by CeO_2 NPs could be attributed to their inherent ability to absorb ionizing radiations as well as their potential to neutralize the radiation-induced oxidative stress as evidenced from their ability to protect the germ cells from radiation mediated cell death in C57BL/6J mice (Das et al. 2018).

Chlorogenic acid-encapsulated chitosan nanoparticles showed significant antioxidant potential by mitigating the oxidative stress-inducing reactive oxygen species thereby suggesting their potential in combating radiation-induced health hazards (Nallamuthu et al. 2015). Tea polyphenols are known for their widespread biological activities. However, their poor bioavailability issues hinder their pharmacological potential. In this context, encapsulating the tea polyphenols into chitosan nanoparticles where BSA was used as matrix could be of promising aspect in mitigating radiation-induced hematological injuries as well as radiation-induced lesions in Swiss albino mice suggesting their ability to improve the radiotherapeutic efficacy of tea polyphenols (Kumar et al. 2016). The radioprotective efficacy of poorly bioavailable vascular endothelial growth factor (VEGF) could be improved by impregnating into chitosan nanoplatforms. The VEGF-chitosan nanocomposites significantly improved the radioprotective efficacy by critically improving the local microcirculation and mitigating the effect of radiation-induced skin damage (Yu et al. 2016).

The specially designed α-tocopherol polyethylene glycol 1000 succinate (TPGS)-functionalized mesoporous nanocarriers with bamboo charcoal nanoparticles (TPGS-BCNPs) not only improved the bioavailability of curcumin in cancer cells but also critically improved the radical scavenging potential of curcumin (Xie et al. 2017). No doubt melanin can protect the cells from oxidative stress by scavenging the highly reactive oxygen species. However, the radioprotective efficacy of melanin

could be improved by designing melanin nanoparticles (MNPs), which critically protected the cells from radiation induced DNA damage, restored the SOD level, and reduced the MDA level in the mice model (Rageh and El-Gebaly 2018). The *Withania somnifera* extract-mediated synthesis of gadolinium III oxide nanoparticles (WSGNC) was evaluated for their radiosensitizing potential. The engineered nanomaterials exhibited promising radiosensitizing properties thereby promoting the efficacy of radiation therapy against cancer cells (Abdallah et al. 2016).

11.4.7 Anti-Diabetic Activity

Through the development of high-throughput technological advancement as well as healthcare settings, the incidence of diabetes remains a global public health issue. Diabetes is a form of metabolic disorder characterized by different interlinking parameters and biochemical conditions such as hyperglycemia, altered carbohydrate, and lipid and protein metabolism (Shanker et al. 2017a). The nanotechnological intervention in the field of biomedicines has paved the way for their explicit role in combating diabetic conditions. In this context, *Psoralea corylifolia* seed extract-mediated synthesis of AgNPs was developed. The biogenically synthesized AgNPs exhibited promising anti-diabetic effect by characteristically inhibiting the protein tyrosine phosphatase 1B (PTP1B), a negative regulator of insulin signaling pathway (Shanker et al. 2017a, b). The anti-diabetic properties of biogenically synthesized AgNPs could also be attributed to their effect on non-enzymatic glycosylation of hemoglobin with reduced of blood glucose level in streptozotocin-induced diabetic rats (Prabhu et al. 2018). The anti-diabetic properties of *Solanum nigrum*- and *Punica granatum*-synthesized AgNPs could be attributed to their efficacy in modulating the dyslipidemic condition and also inhibiting the α-amylase and α-glucosidase activity in diabetic rats (Sengottaiyan et al. 2017; Saratale et al. 2018). The biogenically synthesized AuNPs showed promising anti-diabetic effect by improving the insulin resistance and blood glucose level in Wistar albino rats (Dhas et al. 2016). Earlier, *Gymnema sylvestre*-mediated AunPs also exhibited potential anti-hyperglycemic properties suggesting the anti-diabetic role of engineered AuNPs in alloxan-induced diabetic rats (Karthick et al. 2014). *Sambucus nigra* L. extract-functionalized AuNPs exhibited significant anti-hyperglycemia properties by mitigating the hepatic inflammation and oxidative stress conditions suggesting their potential role as promising adjuvants in diabetes therapeutics (Opris et al. 2017).

The anti-hyperglycemic potential of SeNPs also gained considerable attention in recent times owing to their ability to reduce the glucose-6-phosphatase activity, hepatic function markers, and low-density lipoprotein cholesterol (LDL-C) levels. On treatment with SeNPs, there is a marked increase in the levels of glucose-6-phosphate dehydrogenase and hexokinase activity, high-density lipoprotein cholesterol (HDL-C) levels, and liver glycogen levels suggesting their prolific anti-diabetic properties (Al-Quraishy et al. 2015). Owing to the widespread biomedical applications of ZnO NPs, biosynthesized ZnO NPs using *Hibiscus sabdariffa* leaf extract was employed to determine the anti-diabetic activity using mice model system. On

treatment with ZnO NPs, the blood glucose level was restored by modulating the expression of pro-inflammatory cytokines including tumor necrosis factor (TNF-α), interleukin-6 (IL-6), and IL-1β. Besides, the expression of IL-4 and IL-10 was also normalized when treated with ZnO NPs suggesting their characteristic anti-diabetic properties (Bala et al. 2015). The anti-hyperglycemic potential of biogenically synthesized ZnO NPs from *Momordica charantia* extract was evaluated against streptozotocin-induced diabetes in Wistar rats (Shanker et al. 2017b). The anti-diabetic properties of ZnO NPs could be attributed to their ability to deliver zinc which is essential for the synthesis, storage, and secretion of insulin and structural integrity of insulin (Jiang et al. 2018).

Myricitrin, an antioxidant-based solid lipid nanoparticle, also exhibited promising anti-diabetic activities by critically modulating the hyperglycemia-related complications in mice model (Ahangarpour et al. 2018). A pH-sensitive polyurethane-alginate nanoparticle was developed which eventually controls the blood glucose level by critically modulating the release of insulin (Bhattacharyya et al. 2016). *Stevia rebaudiana* leaf extract was encapsulated into chitosan nanoparticles and evaluated for its anti-diabetic efficacy. The novel nanocomposites critically improved the serum levels of serum glutamic-oxaloacetic acid (SGOT), serum glutamic pyruvic transaminase (SGPT), reduced glutathione (GSH), catalase, and SOD thereby promoting the reduction in blood glucose level as compared to diabetic Wistar rats (Perumal et al. 2016).

11.5 Current Trends and Future Perspectives

The advent of nanotechnology in the biomedical sectors has revolutionized the current understanding of therapeutic strategies. The widespread biomedical applications especially antimicrobial potential of biogenic nanoparticles are considered to be influential as compared to their bulk counterparts or the conventional antimicrobial strategies. The advantages of nanomaterials in the treatment of microbial infections could be attributed to their insensitivity toward the drug resistance shown by pathogenic microorganisms. The unique properties and ease of modification approaches also significantly improved the therapeutic index of nanomaterials with a long-term effect. In addition, being small in size, the nanomaterials could bypass the biological barriers and could be impregnated deep into the cellular sites for effective therapeutics (Khan et al. 2016). The nanoparticles could also be attributed toward their efficacy in controlling the vector-borne diseases in infected mice models suggesting their widespread avenues. In this context, benznidazole nanoparticles (BNZ-nps) were developed to target the Chagas disease caused by *Trypanosoma cruzi*. The results suggested the effectiveness of engineered nanomaterials in increasing the survival rate of *T. cruzi*-infected mice and thereby controlling the Chagas disease (Scalise et al. 2016).

The nanotechnology-based platforms could also be used for enhancing the biological activities of old drug moieties suggesting their role in deciphering the undue potential of these repurposed drugs for various biological functions (Patra et al. 2018). The recent concept of antimicrobial photodynamic therapy (aPDT) also

proved to be influential in targeting recalcitrant microbial biofilms and associated drug resistance phenomenon. The combinatorial concept of aPDT along with a promising nanocarrier greatly improves the photodynamic inactivation of highly tolerant biofilms suggesting their widespread venue in the near future (Biel et al. 2011; Sharma et al. 2014). The advent of photothermal therapy and efflux pump inhibitors in combination with appropriate nanoplatforms could be influential in sequestering the widespread avenues of nanotechnology in biomedicines (Millenbaugh et al. 2015; Vyshnava et al. 2016).

11.6 Conclusion

The nanotechnology-based platforms have provided novel avenues in understanding the current therapeutic strategies. The engineered nanomaterials also characteristically improved the biological efficacy of various drug candidates as well as antibiotics. In understanding the extensive biomedical applications of different engineered nanomaterials, it is highly important to select an appropriate model system. In this context, murine models have provided the horizons to understand the physiological, biochemical, and metabolic processes during the therapeutic approaches and could also decipher the impregnable responses made after the administration of drug candidates. Though ethical consideration limits their extensive exploitation, the established murine models remain highly essential to understand the various biological functions as no promising alternative models are available. In this regard, it is important for the scientific community to quest for alternative model systems sequestering the mechanism of biological activities of engineered nanomaterials without affecting the information gained from murine models including the biodistribution profile, pathophysiological processes, and physiological responses.

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