Concluding Remarks and Future of Nanomedicines

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Abstract

Nanotechnology and nanoscience have a wide range of applications in drug development, drug delivery, and imaging and treatment of human diseases. Among several strategies, nanoparticle-based drug formulations, nanozymes, nanomaterials-based antimicrobials, scaffolds for tissue growth, and non-invasive cell imaging are some of the recently realized applications nanomedicines. Nanomedicines can be used as personalized medicines and offer reduced toxicity and side effects with concomitant enhanced therapeutic performance. This chapter comprehensively summarizes the recent advances of nanomedicine, associated challenges, and future expectations.

8.1 Nanomedicines

The combination of nanotechnology with biology has led to the novel aspects of approaching better human health and improved biomedical applications (nanomedicine). Recent developments in disease biology linked with genomics and proteomics have offered a significant advantage to nanotechnology to manage various human diseases. To realize the full potential of nanomedicine, research, and developments in several subdomains, such as targeted drug delivery, bio-inspired nanotechnology, cell/tissue imaging, catalytic nanomaterials, and cell/tissue engineering, has been progressed exponentially (Pelaz et al. 2017). Therefore, this book has been designed to comprehensively cover all the frontier areas of nanomedicine research written by global experts.

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Although it has been a few decades since the liposome-based delivery of an anticancer drug (Doxil) and other therapeutic drugs are reported; however, tissue-specific delivery of the intended agent is still infancy. The recent development in the area of molecular and cell biology of the disease has led to identifying specific proteins, nucleotides, and whole cell-based targets of diseased cells/tissues. Similarly, aptamers and siRNA-based approaches for targeting tissues and cell signalling pathways are some of the current and effective strategies that have given desired results when combined with nanotechnology. The route of administration of these nanomedicines in the human body is another point of debate. The oral route of delivery is considered safer than the intravenous; however, the latter is more effective. However, the formation of protein corona (from blood serum proteins) could lead to the alteration in the targeted delivery of drugs. Both of these methods share certain advantages and disadvantages over each other; however, being painless, the oral route of administration is the most preferred method. For chronic therapy and sustained delivery of various anticancer drugs such as Zytiga, Capecitabine, and Topotecan, the oral administration approach has been preferred (Gala et al. 2020). Oral delivery is also preferred for patients because of reduced visits of patients to clinics or venepuncture facilities. The gastrointestinal barrier remains one of the obstacles because the epithelial membrane hinders the permeability and absorption of drugs and the degradation of bioactive components from the formulations. Additionally, in the gastrointestinal tract, the pH variation could be broad from 1–2 (stomach) to 7–8 (colon and rectum). In this context, drugs are encapsulated in the form of nanoparticles, which offer protection of the drugs, leading to an increase in nanocarriers' pharmacokinetics. Some of the best strategies use pH-responsive coating over drugs, nanocarriers of mucoadhesive properties, gastrointestinal enzyme inhibitors, etc. (Zhang and Merlin 2018).

Nanomaterials displaying biological enzyme-like catalytic activities (Nanozymes) are being explored for performing better catalytic activities under the physiological conditions where natural enzymes exhibit compromised activity. Natural enzymes face several limitations: the high cost of synthesis, lower stability, very selective storage condition, poor recycling of catalytic activity, sensitivity to pH and temperature, heavy metals, etc. Based on catalytic activities, nanozymes can be classified into three major types, carbon-based, metal-based, and metal oxide-based nanozymes. These nanozymes are further categorized based on the mimicking activities they display, such as Superoxide dismutase, Catalase, Nuclease, Oxidase, Peroxidase, Phosphotriesterase, and Phosphatase, etc. The antioxidant nanozymes, such as cerium oxide, and platinum nanoparticles, are shown to be used to treat various disorders arising due to the inactivity of the related biological enzymes (Singh 2019).

Similarly, pro-oxidant nanozymes, such as graphene, quantum dots, and iron oxides are shown to produce free radicals, which could be used for several applications such as antimicrobial activity, anticancer effect, and regenerative medicine (Cormode et al. 2018). A combination of multiple materials has led to the development of multifunctional nanozymes equipped with multiple intrinsic properties such as various nanozyme activities associated with magnetism,

luminescence, or near-infrared absorbance. Such multifunctional nanozymes have opened up new industrial opportunities and biomedical applications (Liu et al. 2019). Nanozymes are also shown to be used to develop biosensors to detect biomolecules, disease markers, non-invasive imaging probes, and theranostics. Incorporating nanomaterials in sensors is also expected to create a multifunctional analyzer with enhanced sensitivity and superior performance. Due to these advantages, the incorporation of nanozymes is scheduled to facilitate to develop portable instruments enabling multiplexed analysis of samples even at extremely low concentrations.

Microbial infections with multidrug-resistant species have become a common threat to public health worldwide. Due to antibiotics' excessive use, microbial genome evolves mechanism to survive the antibiotic exposure by developing resistance against it. Due to antibiotics' chemical nature, microbes quickly develop resistance against them; however, exposure of metal-based antibacterial nanomaterials, such as AgNPs, are found to be more effective. Mechanistically, AgNPs bind with the microbial cell wall through noncovalent interaction, and upon entry in the cytoplasm, irreversibly react with "S" and "P" containing biomolecules. Additionally, the biosynthesis of AgNPs leads to the cost-effective and eco-friendly method to synthesize biocompatible AgNPs used for several biomedical applications such as antibacterial, anticancer, antifungal, antiparasitic, antidiabetic and wound healing activities (Wang et al. 2017). Current medical diagnosis requires adequate molecular imaging to facilitate early disease diagnosis, type and stage of the disease, and fundamental information about pathological processes. Non-invasive imaging and diagnosis of the disease is today's need for medical science. This paradigm shift exploits nanomaterial-based imaging probes, which are shown to be better than traditional single molecule-based contrast agents. Quantum dots, fluorophore-doped nanoparticles, radioactively labelled agents, and other nanomaterials have been found to offer excellent results; however, novel nanomaterials as a non-invasive imaging probe for animal/human organ imaging with X-ray based computerized tomography, ultrasound, and magnetic resonance imaging are still being developed (Li et al. 2015). Regenerative medicine and tissue engineering deal with the development of functional human tissues with either model, repairing or replacing the damaged body part to restore, maintain, or improve damaged tissues and organs. Nanomaterials encapsulated in these models and scaffolds have shown excellent outcomes from the in vitro and in vivo experimental studies; however, further thorough research is required for their bench to bedside application. In this context, tissue replacement, such as bone and tooth, and regeneration of damaged tissues/organs with metal or ceramic-based implants and scaffolds are some of the most successful surgical procedures worldwide. Several strategies have been followed to limit the implant failures, such as the type of material, use of composite materials, surface texture, and functional coatings. These strategies are found to have improved the integrity of the implant and normal functioning of the tissues by offering the higher longevity, optimum drug-eluting ability, quicker recovery, limited side effects, etc. The surface coating of implant material with biocompatible functional molecules such as dendrimers has been found to offer minimum implant

failure with improved integrity and tissues' natural functioning. The coating material enhances the implant properties and avoids the identification of implants to the immune system leading to prevent the probability of immune rejection. The globular shape, multivalent nature, presence of a dendrimeric cavity, and the functional versatility of dendrimers are some of the essential factors that allow the formation of a stable soft coating on implants and increase their utility for various biomedical applications (Bai and Liu 2012).

Scaffolds represent a three-dimensional network or structure mimicking the natural extracellular matrix properties and provide structural support to cells/tissues to regenerate. Nanofiber-based scaffolds composed of synthetic polymer biomaterial-based 3D scaffolds have been found to display promising tissue engineering scaffolds that mimic the native extracellular matrix's properties. The encapsulated nanoparticles within the fibers favor cell adhesion, proliferation, and differentiation, which are much needed for the success of tissue engineering applications. Nanofibers have been investigated in multiple tissue engineering applications, including bone, cartilage, ligament, skeletal muscle, skin, and vascular tissue engineering. The scaffolds are also shown to act as carriers for the controlled delivery of drugs, proteins, and genes (Cortez Tornello et al. 2016).

Although there have been several biomedical applications shown by the use of nanomaterials, the associated toxicity must also be unraveled before these nanomedicines are approved for human use. Several research groups have already investigated the toxic potential of various nanomaterials; however, there is no common consensus on synthesis method, capping molecules, test concentration, colloidal stability, aspect ratio, and mono/polydispersity of nanoparticles, etc. Depending on the size of the nanoparticles, they can either be internalized by macrophages (if >100 nm) or taken up into the cell cytoplasm (if <100 nm) by endocytosis and thus associated with higher toxicity risks than the nanomaterials with >100 nm size (Behzadi et al. 2017).

8.2 Associated Challenges and Future Aspects

For delivery applications, nanomedicines are required to be in blood circulation for an extended time so that the effective concentration of the encapsulated compound remains higher. Stealth nanomedicines, coated with biocompatible biomolecules, could offer such advantages without the activation of opsonins. The surface of nanocarriers coated with targeting antibodies or moieties could lead to the selected location delivery of the desired therapeutic molecule. Scaling-up and batch-to-batch reproducibility is another challenge for nanomedicines manufacturing. It is well known that the synthesis of nanomedicines involves multiple steps, such as sonication, emulsification, drying, re-hydration, chemical reaction, and organic solvent evaporation, etc. These processes are easy to control, synthesize, and optimize the formulation at a low volume and small scale level. However, when performed at large scale, slight variations during the manufacturing process may lead to significant changes in the physicochemical characteristics of the nanomedicines with

compromised quality, safety, and therapeutic efficacy. Therefore, a deep understanding of the critical steps of the synthesis and controlled process will be of a great need for the synthesis of nanomedicines at large scale. Similarly, the reproducibility of the physicochemical properties of synthesized nanomedicines is must be ensured by extensive characterization of the product (Soares et al. 2018).

The last decade has witnessed tremendous developments in the translational aspects of several nanomedicines into medical devices and pharmaceuticals. Several nanomedicine discoveries are at the different phases of the clinical trials and are expected to be available for commercial use in a few years. One of the significant limitations in that the discoveries and approvals are country-specific and lack any universally accepted protocol for the characterization, evaluation, and approval for nanomedicines. In this context, the European Medical Agency (EMA) has highlighted the need for suitable recommendations for nanomedicines to facilitate their synthesis, testing, and approval. Further, it is expected that the experts of related fields, including material scientists, biologists, policy and guidelines experts, engineers, managers, and government representatives, must work closely to unravel the real biomedical application potential of nanomedicines.

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