Review Article

Nanomedicine - Impact and perspectives

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ABSTRACT

The use of nanoscale materials to develop entirely new class of therapeutics continue to receive increasing interest. Many of these developments are still at the early stages, but some have already been translated into viable clinical products. Here, we provide an overview of recent developments in nanomedicine and highlight several areas of opportunity where current and emerging nanotechnologies can address numerous medical and health-related issues.

Key words: Biomedical, diagnostics, drug delivery, nanotechnology, therapy

Nanotechnology has become a powerful platform to address the shortcomings of traditional disease diagnostic and therapeutic agents. Here, an overview of recent developments in nanomedicine, several areas of opportunity, and current challenges for translation to the clinic have been provided.

The application of nanotechnology for biomedical purposes such as diagnostics, drug therapy, and imaging has grown exponentially over the past few decades (Figure 1).[1-4] This is exemplified by approval given by the US Food and Drug Administration to several nanomedicines for various diseases, and more are on the verge of getting the requisite approval. The global market for nanomedicine is projected to reach USD 350.8 billion by 2025.[5] The key players in the market are GE Healthcare, Abbott Laboratories, Johnson and Johnson, CombiMatrix Corporation, Nanosphere, Inc., Merck and Company, Inc., Pfizer, Inc., Sigma-Tau Pharmaceuticals, Inc., Celgene Corporation, Mallinckrodt plc, Teva Pharmaceutical Industries Ltd., and Union Chimique Belge S.A.[6]

Located on an intersection of diverse fundamental disciplines including chemistry, biology, physics, material science, nanotechnology, and medicine, nanomedicine differs from conventional medicine.[7-10] It involves the development of nanomaterials, surfaces based on nanostructures and nanoanalytical tools for molecular diagnostics and therapy (theranostics).[10] Major emphasis of nanotechnology in biomedical field is in diagnostic techniques, drugs, and prostheses and implants.[1-4]

Nanoparticles are being widely utilized in diagnostic devices for higher sensitivity and selectivity to help diagnose patients in much earlier stages of disease.[11-14] Among the first applications, immunoassays with lateral flow technique (also known as a "dipstick") employed gold nanoparticles in the 1960s. Gold nanoparticles were utilized since they produce intense red color due to high molar absorptivity coefficient. In this method, immobilized primary antibodies and gold nanoparticle tagged with antibody labels interact with an antigen, to produce a red line, indicating a positive result. This platform where nanotechnology plays a very critical role is currently being used for diagnosing pregnancy, infectious pathogens, as well as diabetic and cardiovascular diseases. Similarly, over the past 15 years, the research community has focused on incorporating nanoparticles in diagnostic

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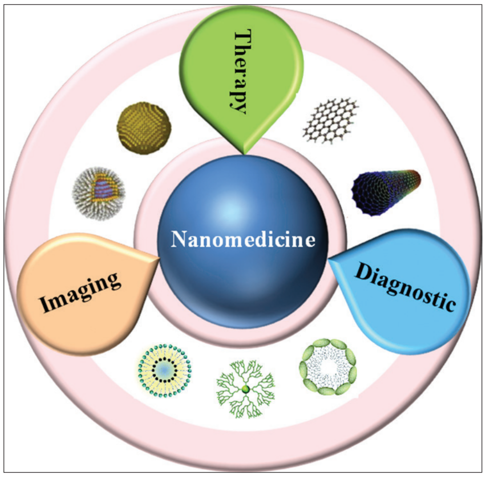

Figure 1: Schematic representation of major nanotechnology applications in biomedical field

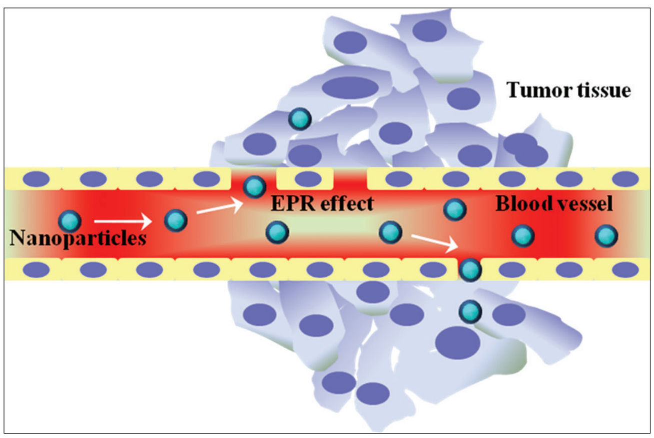

Figure 2: Enhanced permeability and retention effect. Nanocarriers can enter through the gaps between endothelial cells and accumulate in the tumor due to poor lymphatic drainage

assays or devices.[11-14] Many desirable properties that nanoparticles possess such as tunable optical, magnetic, and electrical properties have been exploited in diagnostics. Iron oxide nanoparticle surfaces modified with targeting moieties such as proteins and antibodies have been used in many bead-based assays.[15,16] It allows to target cells having complementary groups on the surfaces and other biomarkers which are indicative, for example, of cancer or other severe diseases. Their magnetic properties play a vital part in isolation and purification of biomarkers.[15,16] Furthermore, to significantly increase the resolution and sensitivity, nanoparticles have been utilized in several imaging methods such as infrared or nuclear magnetic resonance methods.[17-19] Increased resolution and sensitivity will lead to faster and cost-effective clinical measures in therapy as lengthy turnaround times and requirement for costly chemicals/instruments have restricted the availability of these technologies to a wider pool of patients.[11,20]

In the field of drug delivery, nanoparticles have been developed for various diseases, but cancer has been the most prominent disease of focus.[21,22] Clinically, it has been confirmed that therapeutic index of anticancer drugs improves when delivered by nanocarriers. This is due to change in pharmacokinetics and tissue distribution as nanocarriers utilize the enhanced permeability and retention (EPR) effect. According to the EPR hypothesis, due to leaky tumor vasculature and poor lymphatic drainage, nanoparticles experience higher permeation and retention in the interstitial space of tumors (Figure 2).[23] As a result, nanocarriers accumulate more in tumors than in tissues with normal vascular permeability and lymphatic circulation. The first anticancer nanomedicine approved by the Food and Drug Administration (FDA) in 1995 was liposomal doxorubicin (Doxil™/Caelyx™).[24,25] In patients, Doxil™ showed nearly 300-fold rise in doxorubicin concentration at the target sites as compared to free doxorubicin, although this contains free (bioavailable) as well as liposome-encapsulated (non-bioavailable) doxorubicin. Many other nanomedicines have also been approved by the FDA for clinical use in cancer treatment such as Depocyt™, DaunoXome™, Abraxane™, Myocet™, Genexol-PM™, and most recently, Onivyde™.[22] Now, many drugs that were previously considered unsuccessful due to delivery-related issues such as poor solubility or stability in biological environments have again generated interest among academic and industry investigators due to the advantages that nanotechnology offers.

However, few notes of concern related to nanomedicine are emerging that could limit its future evolution, particularly if they are not appropriately addressed.[26] First, complete understanding of potential toxicity and properties of nanomaterials such as physicochemical and cell binding that influences biological and therapeutic activity is lacking.[27] Second, developing nanosystem-based formulations are a challenge as they are complicated, and thus, scale-up becomes difficult and costly. Furthermore, developing newer nanodrug delivery system which includes targeting moiety to promote association with a particular cell type or tissue is technically challenging. Especially, anchoring targeting moieties on nanosystems without compromising their activity

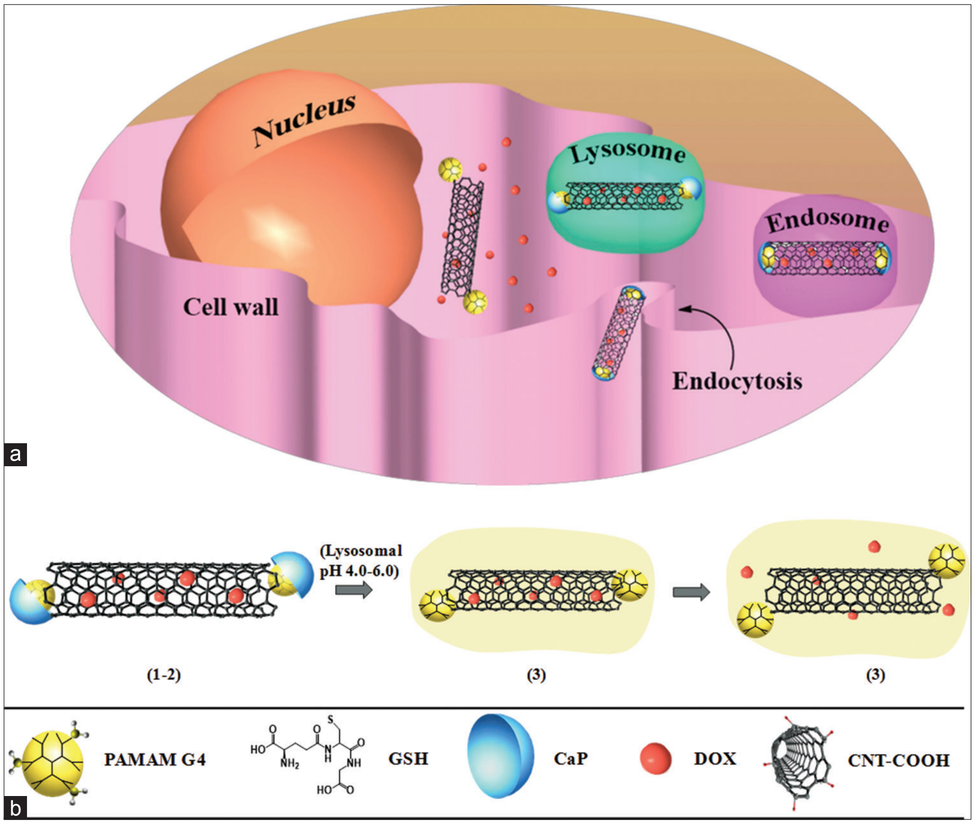

Figure 3: (a and b) Schematic illustration of triggered doxorubicin release from calcium phosphate nanocapsule gated carbon nanotube based nanosystem loaded with doxorubicin under intracellular endo/lysosomal conditions.[23]

are difficult. Furthermore, the presence of targeting moiety reduces the nanosystem lifetime in the circulation.[26]

In up-coming years, research focus of nanotechnology usage will expand to other medical challenges and newer areas of application.[21] Nanocarriers are now being explored for drug delivery to the eye, where penetration of the corneal epithelium and blood-retinal barrier is a challenge. Nanotechnology also offers to open up potential areas in neurological disease as more is understood in brain-related disorders. Nanomaterials with optimum size are also being investigated to deliver long-term release of drugs for pain and inflammation or regeneration of tissue by stimulation. Transdermal delivery using nanomaterials that penetrate different layers of skin offers an alternative route for both localized and systemic treatments, particularly given the access that skin provides to the inflammatory host system.[11] Nanoparticle-based therapies can also help in the coming era of personalized medicine. For this, nanoparticle-based formulations with varying sizes and surfaces can be made. Nanoparticles with custom-designed surfaces can help to subdue interactions with serum proteins and/or the immune system. Moreover, suitable surface change can facilitate conjugation of targeting moieties for higher uptake by cells of interest. This remarkable properties associated with nanoparticle-based agents give them vast potential in the coming era of personalized medicine.[28] Moreover, nanosystems that can simultaneously perform several functions such as diagnose, treat, and even control therapeutic release are being designed (Figure 3).[29,30]

With growing and expanding range of opportunities for nanomaterials systems, these are exciting times for nanomedicine research. The pace of scientific discovery in nanomedicine to overcome new challenges is gaining momentum; this may lead to discoveries that will ultimately benefit patients.

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