Chapter 15
What Can Nanomedicine Learn from the Current Developments of Nanotechnology?

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15.1 Introduction

Nanotechnology is defined as the design, control, manipulation, synthesis, production and application of properties and functionalities of any structure, device, or system, which has one of its dimensions between 1 and 100 nm, by controlling its shape and size [1]. Expanding from its original definition, nanotechnology can be applied to and combined with various fields of science and gives rise to emerging sciences which greatly improves technology and, ultimately, the quality of life. An excellent example to this is the combination between nanotechnology and medicine – known as the emerging 'nanomedicine'. Therefore, nanomedicine can be defined, in general, as the application of nanotechnology to medicine to create advanced diagnostics and therapeutics for disease treatment and prevention from nanoscale, using knowledge, principles, and techniques from nanotechnology [1–4].

The starting point of nanotechnology in the human history began when Richard Feyman gave his infamous lecture in 1959 'There's Plenty of Room at the Bottom' stating the idea of manipulating individual atoms using larger equipment to produce relatively small matters. However, it was only in 1974 that the term 'nanotechnology' was first invented by Norio Tanaguchi and was accepted as an official, new scientific terminology. Nanotechnology and nanosciences has begun to grow at an incredible speed since then, and their applications started to branch out in various fields. However, proper and serious attention in nanomedicine has begun since only

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a few decades ago [5, 6, 7]. Table 15.1 below lists a brief summary of hallmarks relating to the evolution of nanotechnology and nanomedicine.

At nanoscale, substances exhibit unique properties and phenomena which are absent or different from when they are at macroscale [5]; based on the significance of this fact, versatile applications and implications can be made to find solutions to the related unsolved problems at macroscale. The application of nanotechnology in medicine has been brought to attention based on the fact that cellular components, activities and interactions, which are the essence and the most basic level of life, are at nanoscale (Table 15.2); hence working at the same scale might lead to solutions to current medical limitations or, at least, provide better understanding of the situation. Nanotechnology is widely applied to medical imaging, disease detection, medical analysis, drug manipulation, and modelling at nanoscale [5] to develop advanced diagnostic and therapeutic tools for curing and preventing diseases, and ultimately improve the quality of life.

Table 15.1 A brief list of nanotechnology and nanomedicine hallmarks [5]

Year	Event
1959	Richard Feyman's "There's Plenty of Room at the Bottom" lecture – the starting point of nanotechnology
1974	Establishment of the term 'nanotechnology' by Norio Tanaguchi
1979	World's first use of colloidal Au nanoparticles (NPs) in electron microscopy
1987	World's first cancer targeting using NPs coated with monoclonal antibodies
1990	World's first visualisation of atoms by the scanning tunnelling microscope (STM) invented by IBM Zurich Lab
1991	Discovery of carbon nanotube
1994	Establishment of the concept of NP-based drug delivery
1995	Liposome fabrication and usage in drug delivery
1998	Establishment of the term 'nanomedicine'

Table 15.2 Example dimensions of significant biological substances in the body [5]

Average dimensions (nm)	Substances
2,500	Human red blood cell
65–100	Exosome (vesicles from dendritic cells)
1–20	Proteins
2–4	Ribosomes
2.5	DNA (diameter)
1.2	The largest amino acid measured
0.4	A base pair in human genome
0.25	Average individual atom

From a general point of view, the scope of nanomedicine can be categorised into the following three main categories [8]:

- Medical imaging, diagnostics, and therapeutics using engineered nanoparticles and nanomaterials
- Regenerative medicine and other relevant innovative treatments
- Studies for in-depth understanding of activities, functions and mechanisms inside the body at nanoscale, and inside the cell

In this chapter, discussions about what nanomedicine can learn from the current developments in nanotechnology, and relevant topics, such as benefits, concerns, challenges and limitations, are explained. In addition, conclusions and suggestions on possible future opportunities and perspectives are stated.

15.2 From Nanotechnology to Nanomedicine

Achievement in nanotechnology opens the gate to the new era of medicine, creating opportunities for better understanding, development and invention from new perspectives. It moves medical challenges to the next step. However, everything has two sides: benefits and drawbacks. It is absolutely crucial, and it is always the aim, to minimise the adverse sides of the technology, and maximise its benefits.

Nanomedicine is a massive area, and is relatively new. Despite getting a lot of attention and funding over the past decade, the science and technology still have not been very well established and understood. Certainly, nanomedicine has been claimed to be capable of producing satisfying results and giving hopes for future medicine. However, the "negative" sides and its potential issues as well as the uncertainty have not been thoroughly studied and solved yet. As nanomedicine is closely linked to nanotechnology, it is a good idea to learn from what nanotechnology has already went through, to get a hinted starting point about what are to be marked for consideration when it comes to nanomedicine.

15.2.1 A Quick Look at the Current Development in Nanotechnology with a Critical View

Since its establishment, nanotechnology has been growing rapidly at an amazing rate. Extensive studies and experiments have been going on in various aspects of nanotechnology. Current major attentions are, for example, the development of nanoparticles and nanomaterials, nanofabrication techniques, nanoelectronics, precision engineering, nanofluidics, nanoreactors, advanced microscopy, nanometrology, nanotechnology for energy solution, nanophotonics, and nanotoxicity [9–15]. As studies and experiments go, investigators make discoveries of successful results, as well as problems and limitations. Discussion on how nanotechnologies

have been successfully applied into medicine will be made in the next section, while the problems and issues of the technologies from a nanotechnology perspective will be discussed in this section.

A classic example of problems raised which could be related to nanomedicine is the property inconsistency of products from nanofabrication. In the production of nanoparticles, this problem occurs very frequently, even with the best technique available which produces the finest nanoparticles. With current technologies, nanofabrication still exhibits variation of nanoparticle product sizes in a batch [14]. Having size inconsistency implies that the entire batch of the particle will also have inconsistent property – low production effectiveness and product quality. As a real-case example, Saito et al. carried out the synthesis of single-walled carbon nanotubes (SWCNTs) via gas-phase pyrolytic method using metal nanoparticles as catalysts [16]. In their experiments, particle size inconsistency occurred during fabrication of metal nanoparticles, hence creating SWCNTs size inconsistency. Problems with inconsistency does not confine to only particle sizes, but also other important parameters, such as surface chemistry and concentration, as demonstrated in the work conducted by França et al. [17].

Another example is related to micro- and nanofluidics which are very complicated concepts and are still under investigation [18]. A micro/nanodevice inevitably requires application of micro/nanofluidics. The concepts of micro/nanofluidics are complex and challenging even to engineers as it is, in effect, a scale-down, which is the opposite to their usual work – scale-up. There are several issues that have not been understood thoroughly yet, such as interaction between fluid flow, surface forces and molecular interaction. Uniquely, at these tiny scales, surface forces become dominant. This is one of the reasons which make micro/nanofludics so different from, and much more complicated than, fluidics at the normal scale. The flow regime in these devices has unique characteristics which cannot be considered as a laminar flow, and has to be classified as a separate regime called 'microhydrodynamics'. The flow also has complicated 3-D geometries [19, 20].

A more general problem is that most of the products derived from nanotechnology currently rely on advanced technologies for their preparation and production, such as X-ray lithography for nanopattering; hence, production costs is undoubtedly expensive. Fabricating nanostructures involves several expensive technologies, for instance, as seen in the work of Liu et al. in producing palladium nanosprings [21]. Attempts have been made in trying to find alternative fabrication methods for nanotechnology related products, with the aim of reducing production costs. For example, Choi and Kim succeeded in developing an easy method to fabricate a dense nanoscale array on a large surface [22]. In addition, most of the products involving nanotechnology are still on a laboratory or pilot plant scale (i.e. still being processed in small batches), and their synthetic processes for industrial scale-up have not yet been established due to complexities and other several reasons (such as economics and profitability), which make mass production and commercialisation of these products still not practically and widely feasible.

15.2.2 A Glance of Current Advanced Nanomedicine

Before answering what nanomedicine can learn from nanotechnology so far, it is essential to understand and evaluate how nanomedicine has been making its progress. Several techniques and principles in nanotechnology, such as nanometrology, nanoparticles, nanomaterials, and nanofabrication, have been applied and implied to various medical fields. The technologies have greatly transformed medicine from its conventional practice both in diagnostics and therapeutics. It is worth noting that, several emerging medical concepts have been greatly made closer to clinical use through nanomedicine, such as regenerative medicine, theranostics, and gene therapy, as elaborated below.

15.2.2.1 Medical Diagnostics

Conventional medical diagnostic methods play important roles in medicine. However, they also have some noticeable drawbacks, such as time-consuming process and biological substance degradation. Table 15.3 shows some comparisons between conventional and nanomedical diagnostics in terms of their properties and performances. In addition to helping to modify and improve the conventional methods, nanotechnology has been applied in medical diagnostics to overcome some of their existing problems/drawbacks. Speaking in general, the major areas in nanomedical diagnostics are nanobiosensor, point-of-care (POC) medical diagnostic devices, and medical imaging.

Nanobiosensors Nanobiosensor is generally described as a biosensor at the nanoscale. A typical biosensor consists of three main parts: biological receptor element, physiochemical transducer, and detector. The first two components are critical parameters for a good biosensor. The biological receptor element should selectively and specifically binds to the desired analyte. Transduction process should be efficient so that the generated signal can be translated correctly and accurately. Hence, the design criteria for a good biosensor are selectivity, limit of

Table 15.3 Some comparisons between conventional and nanomedical diagnostics

Conventional diagnostics	Nanomedical diagnostics
Time consuming	Rapid diagnosis
Sample deterioration	Remove problems about sample deterioration
Requires a certain amount of sample to process, hence can be invasive	Requires only a very small amount of sample, hence less invasive
Difficulties from integrating parameters (resulting from various type of tests), hence requires personnel with special skills	Tends to be easy to use, hence does not require any special skill to operate
Can give inaccurate results at time, e.g. when the amount of sample is too small	Produce relatively accurate results instantly
High-cost	Low-cost

detection (LOD), response time, and signal-to-noise (S/N) ratio. Nanomaterials (e.g. nanoparticles) is one of the top candidates for the improvement of both above key components due to their unique physical and chemical properties and the ability to easily control those properties. Nanomaterials can be used to develop improved sensor coating, base, or circuit components. They can also be applied to improve the biological receptor element [23, 24].

Nanoparticles is the popular choice for studies in nanobiosensors due to several reasons, such as its unique optical property, high surface-to-volume ratio, tunable properties, high stability and biocompatibility, and non-complicated synthesis. When bound with an analyte, the overall physical and chemical property of the nanoparticle changes, thus producing detectable signal sent to the transducer. These changes, such as changes in surface plasmon resonance (SPR), electrical conductivity, or redox activity [25], could dramatically increases the sensor sensitivity. A recent example could be found from the work of Cao et al. where they reported that the plasmon shift produced from the sandwich system, having gold nanoparticles instead of secondary free antibody, was 28 times increased; hence, the signal was greatly amplified in such a manner so that it can detect the analyte at a picomolar level of concentration [26].

Several sensors can be integrated into an array called 'integrated biosensor' which is able to take different, parallel measurements simultaneously from one sample [27]. These nanobiosensors can also be combined with other nanotechnologies, such as atomic force microscopy (AFM) [28], fluorescence resonance energy transfer (FRET) [29, 30], and DNA technology [31], to improve the quality of contrast and/or add additional properties to the sensor. Recently, a novel paper-based nanobiosensor has been developed for medical diagnostic purpose by Parolo and colleagues [32].

Plastic antibody is a novel and powerful concept which greatly helps reducing several problems with biosensors. Plastic antibody is the synthetic and imprinted polymer with an affinity to bind with a specific analyte. It is produced by polymerisation of cross-linkers and functional monomer with a target molecule acting as a template. Popular templates in biological applications including proteins and small peptides. Plastic antibody has several advantages over natural antibodies. From a production point of view, it is cheaper and more stable. The product properties, such as particle size and molecular weight, can also be controlled easily during the production. For instance, [33] successfully created a nanoscale plastic antibody for the detection of a bee toxin called melittin.

Point-of-Care (POC) Medical Diagnostic Devices Compared with normal diagnostic tools, POC devices are for patients to be able to take measurement and see the results by themselves without having to visit the hospital and have their samples taken to the laboratory. Nanotechnology has made an impact on this area of medical diagnostics by offering micro/nanofluidics and nanoelectronics. POC devices tend to be of a portable size. One of the major POC principles is to take the sample from the patient as little as possible per measurement. A micro/nanofluidic system would be able to make this feasible and practical. The knowledge from nanoelectronics

could greatly help with circuit and circuit component fabrication for an electronic nanoscale device. There are many researches and studies on developing 'lab-on-a-chip' devices of which mixing, separation, identification and analysis of sample fluid can be done on a small, single device [34]. Attention has been paid to the 'lab-on-a-chip' concept due to its high possibility of providing early diagnosis and therapy monitoring [35]. POC development is unfortunately not in the main stream yet, but it is a good candidate in a long term strategy [2]. Good and encouraging examples in this area include the highly-integrated lab-on-a-chip which simultaneously analyses several parameters developed by Schumacher and colleagues [36] and an attempt to create an inexpensive POC microfluidic device for viscous sample [37].

Medical Imaging Nanoparticles, often with modified surfaces, have unique and useful properties which can be used to improve in vivo medical diagnostics by generating contrast through a selection of paths, such as radiation and magnetic field. They have been investigated and applied in various medical imaging technologies, such as magnetic resonance imaging (MRI), X-ray imaging and computer tomography (CT) to improve the efficiency of imaging tools and their contrast agents. The main purposes of the application are to make early diagnosis, track therapeutic efficiency, and obtain knowledge regarding disease development and pathology. Usually, the materials used for making contrast agents are those which are fluorescent, magnetic or paramagnetic. They can be used to localise and verify the current stage of tumour, identify the location of inflammation, verify stages of particular diseases, visualise structure of a blood vessel, and assess drug distribution and accumulation inside the body [38]. For a more advanced medical imaging, it is aimed for a method capable of detecting a single specified molecule or cell in the complex environment of human body. Since high dose of contrast agent is required for CT scan, inert materials, such as iodine-based, gold, lanthanide and tantalum nanoparticles have been chosen to make a suitable CT scan contrast agent [39]. The main focus of using nanomedical imaging technology currently is in cancer detection. Recently Chien et al. reported that administration of gold nanoparticle together with heparin produced contrast in X-ray imaging which was sufficient to see tumour microvessel (3–5 μm diameter) or extravascular diffusion [40]. For MRI contrast agents, the use of iron oxide nanoparticles is a classic example. Bae et al. developed carbon-coated iron oxide nanoparticles, improving the availability of the contrast agent [41].

15.2.2.2 Nanomedical Therapeutics

In general, the on-going research and development in nanopharmaceutics can be grouped into the following categories:

- Single, specific aspect: targeted delivery, stimuli responsive systems, controlled release, imaging, disease detection, and gene therapy
- Multifunctional nanoparticles (MFNPs): non-hybrid MFNPs and hybrid MFNPs
- Synthesis and fabrication method
- Therapeutic medical devices (e.g. cardiovascular stent)

There are further three main factors which make nanoparticles and other proper nanomaterials appealing to their application in therapeutics: very small size, unique behaviour and designable properties. Having a very small size means that they can reach sites which are previously unreachable, thereby increasing treatment effectiveness. Through several available modification techniques for nanoparticles, the particle biocompatibility, bioavailability, half-life can be increased, while the toxicity can be minimised. Apart from receiving the most attentions in cancer therapy, nanomedical therapeutic products have also been intensively investigated for providing solutions for some other major diseases, such as neurological diseases (e.g. Alzheimer's and Parkinson's diseases) cardiovascular diseases, respiratory diseases, infectious diseases (e.g. HIV and meningitis), and chronic diseases (e.g. diabetes). The field of nanomedical therapeutics generally involves nanoparticle/nanomaterial drug-delivery systems, nano-therapeutic medical devices, and special nanomedical treatments.

Nanoparticle/Nanomaterial Drug-Delivery Systems Conventionally, drugs are administered into the body and the drug molecules float around inside the body. However, not all drug molecules could efficiently arrive at the desired location: some degrade, some trapped and some cleared by the body defence mechanism. In order to cope with these problems, nanoparticles and some other nanomaterials have been widely investigated and studied. They have been successfully incorporated into the drug molecules to add or enhance properties such as biocompatibility, bioavailability, half-life, target specificity, payload, and controlled release mechanism, while minimising its toxicity effect. Coating the system with certain polymers, such as polyethylene glycol (PEG), has been shown to increase biocompatibility, bioavailability and half-life [42]. Very recently Liu et al. fabricated a complex of gold nanoshells on silica nanorattles showing increased permeability, enhanced permeability and retention (EPR) effect in tumour tissues and light conversion in vivo, while having less toxicity [43]. The concepts of antigen-antibody binding can further be applied to create target specificity by incorporating suitable ligands, such as antibody, DNA strands, and peptides, on the surface of the drug-nanoparticle complex [44]. In 2007, Hatakeyama et al. reported an anti-MT1-MMP immunoliposome complex carrying doxorubicin [45]. The complex greatly reduced tumour growth in vivo in mice. They suggested that the cellular uptake of the complex was increased due to a resulting immunoconjugation. In addition, several nanofabrication and nanoencapsulation techniques could be applied to create layers or appropriate structures so that the complex can be loaded with desired drugs of different properties, such as hydrophobicity and hydrophilicity, on a single complex, as demonstrated by Hammond [46]. In summary, the nanoparticles and other nanomaterials which have been commonly used for drug-delivery systems include [47–55]:

- Carbon nanomaterials (e.g. carbon nanotubes, fullerenes)
- Magnetic nanoparticles (e.g. iron oxide nanoparticles)
- Metal/inorganic nanoparticles (e.g. gold, silver, silica nanoparticles)
- Quantum dots
- Polymeric nanoparticles (e.g. PLGA nanoparticles)
- Solid-lipid nanoparticles

- Micelles
- Liposomes
- Dendrimers
- Multifunctional nanoparticles (MFNPs)

There are about 22 nanoparticle-content drugs which have been approved by the Food and Drug Administration (FDA) in the United States of America. Furthermore, there are about 25 nanoparticle-content drugs being investigated in clinical trials in Europe [2].

Nano-therapeutic Medical Devices Nanotechnology has been applied not only in medical diagnostic devices, but also in therapeutic devices by improving the device's therapeutic efficiency, biocompatibility, strength or flexibilty, while minimising its adverse effects. An excellent example is the cardiovascular stent. The knowledge of nanomaterial fabrication has been used in mechanical improvement of the material used to build the stent itself [56]. Certain fabrication methods are used to improve the structure of the stent body. For example, micro-wells can be created on the surface of the metal that is used to make a stent, in order to increase drug-loading capacity of the drug eluting stent (DES). Other fabrication methods can also be used to create thin layers of polymer coating on the metal surface in order to increase the stent's biocompatibility and reduce the side effects from restenosis and thrombosis, which are side effects as a result of the interaction between the body immunological response and the stent (considered as a foreign object inside the body) [56]. There further has been a report on a successful sustained and controlled release of a DES using the layer-by-layer thin-film coating consisting of different materials for different functions [46]. Layers of drugs with different opposite charges were coated. The properties of the materials in each layer govern the kinetics of layer degradation and drug release based on the principle of mass transfer. Moreover, the technology of making a particular nanocomposite, together with surface modification, could add desired properties onto a cardiovascular stent. For example, after coating the stent with a layer of polyhedral oligomeric silsesquioxane poly (carbonate-urea) urethane (POSS-PCU), which is a nanocomposite, endothelial progenitor cell (EPC) specific antibody was successfully grafted on the composite [57]. Consequently, this device could facilitate endothelialisation of the stent to blood vessel wall, reducing problems with restenosis and thrombosis.

Innovative Medical Treatment for Specific Diseases The unique behaviours of substance at nanoscale can be selectively used to enhance treatment efficiency. For example, there are several nanoparticles which respond to certain external stimuli. They could be applied in hyperthermia for cancer treatment. Hyperthermia literally means the condition where temperature is higher than normal. However, it can also refer to a method in cancer treatment using heat. Hyperthermia cancer treatment is a non-invasive medical treatment in which body tissue is exposed to higher temperatures to damage and kill cancer cells or to make cancer cells more sensitive to the effects of radiation and certain anti-cancer drugs. Since a too high temperature might also kill neighbouring normal cells; hence the heating process must be carefully

controlled. There were problems regarding keeping the heat at the suitable level and location (problems with consistency and accuracy). For the conventional hyperthermia, heating is supplied from an external source and has to struggle through several barriers, which can be considered as resistance to heat transfer. Heat is lost during the way and the amount of heat that reaches the target is obviously less than the heat originally emitted from the heat source. However, by utilising nanoparticles in hyperthermia, it has now become feasible to achieve better consistency and accuracy [58–60]. Bhayani et al. successfully developed a nanoscale complex of dextran-iron oxide nanoparticles which responds to a certain radio frequency [61]. The complex, activated by the certain radio frequency, provides the same changes to the tumour cells as seen from externally heating (43 °C for 60 min) in terms of cell morphology, proliferation patter, and measurement of protein associated with heat shock. Similarly, magnetic nanoparticles can also be used in hyperthermia where the magnetic nanoparticles generate heat after an alternating magnetic field is applied. For example, Sadhukha et al. successfully achieved a significant in vivo inhibition of lung tumour growth by using super-paramagnetic iron oxide nanoparticles (SPIONs) [62].

15.2.2.3 Multifunctional Nanoparticles: Diagnostics and Therapeutics in a Single System

Equipped and stimulated by the rapid development of advanced nanotechnology, it is able to fabricate a nanoscale complex which has multifunctionalities, such as both therapeutic and diagnostic features. A selection of techniques such as nanofabrication, nanoencapsulation, surface grafting and layer-by-layer coating can transform simple nanoparticles to all-purpose multifunctional nanoparticles or nanoplatforms. Multifunctional nanoparticles have been established aiming to improve the particle's stability, biocompatibility, half-life, and add miscellaneous properties (e.g. stimuli responsive, target-specific, disease detecting, or imaging). Particle functionalisation is normally achieved by surface modification [63, 64].

For cancer treatment, attempts have been made to try to create a stable, safe and biocompatible nanoscale system which is capable of (1) accurately targeting tumour cells or tissues; (2) releasing therapeutic agent or performing appropriate treatment in a controlled manner to destroy the tumour cells directly or inhibit their growth; and (3) safely self-degrading or getting itself out of the body through body clearance mechanism. Usually, the system (e.g. non-hybrid multifunctional nanoparticles) consists of a nanoparticle core, shell(s), and surface ligands. non-hybrid multifunctional nanoparticles. Recently, a new class of multifunctional nanoparticles has been created by combining more than one nanomaterials as the system's backbone [63]. They are classified as hybrid multifunctional nanoparticles which possess properties of different backbone materials. Furthermore, they seem to offer possible solutions to current limitation from the non-hybrid systems in terms of the suspension and size stability (once administered into the body), encapsulation effectiveness, controlled release mechanisms, and biocompatibility issues (multi drug resistance and blood compatibility).

Cheng et al. recently a multifunctional system of upconversion nanoparticles (e.g. nanoparticles of lanthanide elements) offering in vivo dual medical imaging: fluorescence and MRI [65]. The system also has the magnetic targeting ability which can increase its accumulation on tumour sites by approximately eight times when compared to the system without the presence of magnetic element. In addition, the system is capable for hyperthermia via near-infrared (NIR) light stimulating which is its therapeutic feature, specific to cancer. Another recent example of multifunctional nanoparticles for the treatment of other diseases was reported by Lee et al. who successfully fabricated targeted gold half-shell nanoparticles for chemo-photothermal therapy of rheumatoid arthritis [66]. Arginine-glycine-aspartic acid (RGD) was conjugated to the nanoparticles for its rheumatoid arthritis-specific targeting ability. The system was loaded with methotrexate, the most effective drug of choice for treating rheumatoid arthritis. The gold nanoparticles further provide hyperthermia ability. When stimulated with NIR radiation, those gold nanoparticles generate heat effectively. The generated heat acts as a trigger for both drug release and direct hyperthermia to cure the diseased sites inside the body. This system further greatly increased the therapeutic efficiency for arthritis using a dramatically reduced dose of methotrexate and its side effects.

15.2.2.4 Nanotechnology in Regenerative Medicine

Regenerative medicine has been increasingly exploited and developed where nanotechnology is utilised in cell therapy, in vivo real-time labelling and imaging, 2D-nanotopography, 3D-nanoscaffold, and growth factor delivery [67, 68]. Nanomaterials have been investigated for their effectiveness, in mechanical, chemical and biological aspects, for making regenerative scaffolds. Furthermore, nanotechnology is able to create opportunities for scientists to develop biomaterials which can mimic various types of extracellular matrices in tissues, generating suitable conditions for triggering cell repair or growth [2, 69].

However, further studies are still required to develop nanomaterials used for regenerative medicine and investigate if they possess the following conditions [2]:

- Non-toxic
- Biocompatible
- Simultaneously facilitate regeneration
- Maintain physical properties (even after being conjugated at the surface)
- Interact with desired target (protein or cell) but not disturbing its normal biological activities

The ultimate goals of regenerative medicine are to induce cell or tissue repairmen without causing other complication from immunological respond or dependence of donors [67].

15.2.2.5 Nanomedicine in Gene Therapy

Gene therapy is defined as a method which utilises appropriate genetic materials, such as fragments of DNA or RNA, to selectively repair faulty genes causing diseases [70]. It is seen as a promising solution as a cure to diseases which are currently incurable or difficult to be cured, such as genetically inherited disorders, certain types of cancer, and viral infections [71]. There are several approaches to cure diseases using different techniques in gene therapy. The most common approach is to replace a non-functional gene on a specific location with a normal gene. Therapy target can be set on the faulty gene too. Homologous recombination can be used to swap a problematic faulty gene with a normal healthy gene. Alternatively, selective reverse mutation on the faulty gene can result in gene repair and the gene is turned into a normal gene [70].

To carry out gene therapy, a messenger called 'gene vector' is required to deliver desired genetic material into the nucleus. Gene therapy starts with the transfection of the target cells by the gene vectors. Genetic materials inside the vectors are then released into the cell. After the genetic materials pass through nuclear membrane into the nucleus, the desired proteins can be synthesised, which will ultimately bring the cell back to its normal condition. There are usually two main types of gene vectors: viral vectors and non-viral vectors. At present, viral gene vectors have a much higher rate of successful delivery compared with non-viral vectors. However, there are issues and concerns using viruses inside the body, despite the fact that they are genetically modified to contain only the desired human genetic materials for the therapy. As a foreign body, it would activate the body's immunological response and even inflammation. Concerns have been raised regarding the fact that there has been no solid evidence to approve: after being administered into the body, the modified viruses would be able to resume their original pathogenic activities and not to cause complication to the patient [70]. As a result, efforts have been continuously made to apply safe and effective non-viral gene vectors. However non-viral vectors have several limitations which are needed to be overcome: stability in biological condition, extracellular obstructions, intracellular obstructions and targeted delivery [72, 73].

Recently nanotechnology has been applied to gene therapy in order to overcome these limitations by creating a stable, safe, and biocompatible non-viral gene vector for effective targeted intracellular gene delivery. Both inorganic and organic (biodegradable) nanoparticles/nanomaterials have been used to create non-viral gene vectors for gene therapy.

Labhasetwar and Panyam described a successful escape of gene-encapsulated PLGA nanoparticles from endosome into the cytoplasm [74]. Yamashita et al. made a photothermally controlled gene delivery system by conjugating double-strand DNA onto gold nanorods [75]. The system has a unique thermal conductivity in response to near-infrared radiation, causing the release of single-strand DNA in a controlled manner. A system of chloroquine-encapsulated polycationic mesoporous silica nanoparticles containing siRNA was shown to have successfully delivered both siRNA and chloroquine [76]. In addition, Chen et al. reported an up-to 50 % gene silencing ability after 48-h post-administration of chitosan-siRNA nanoparticles in

PLGA nanofibers [77]. An approximately 1 week of sustained therapeutic genetic expression was observed by Kwon et al. employing a complex of DNA and cationic lipid-based nanoemulsion [78].

15.3 What Lessons Nanomedicine Can Learn from Nanotechnology?

Nanomedicine incubates and develops from nanotechnology. Broadly speaking, nanomedicine could be regarded as one of the divisions of nanotechnology. Thus, all matters inherited and/or transferred from nanotechnology would certainly affect the progress of nanomedicine.

Lessons, depending on their nature, influence and impact, could be either positive or negative. In the previous sections of this chapter, detailed discussions and sufficient examples are given to demonstrate the positive lessons and results from nanotechnology. It has shown that nanotechnology has broken down several crucial barriers previously existed in medicine, bringing the chance and reality of curing hopeless diseases. It also has improved effectiveness of current medical technologies, such as medical imaging, by enhancing the efficiency of the contrast agents or creating a novel approach of multi-modal medical imaging. Furthermore, the appropriate use of unique physicochemical properties of nanoparticles/nanomaterials enables modulation and control of biological activity at nanoscale, which has been proved to be a promising approach in drug delivery, regenerative medicine, gene therapy and other innovative medical treatments. The following table (Table 15.4)

Table 15.4 Summary of current positive and negative aspects in nanomedicine

Positive aspects	Negative aspects
Smaller devices, hence they are less invasive	Smaller devices require sophisticated technology which may not be economically feasible to everybody
Nanomedical diagnostic devices and methods only require a small amount of sample	Several pre-analysis preparations of the sample are required
Comes in small size and operates at the same level as interaction inside the body	Early developed NPs might accidentally affect various biological barriers, hence results in unexpected toxicities
	Difficult to monitor exposure from outside
Drug delivery technology using nanoparticles protects the drug from being degraded inside the body	The used nanoparticle might be difficult to degrade or come out of the body via normal excretion pathways or mechanisms
NPs-based drugs come in small quantities but with increased efficiency	Damages could be done to healthy tissues or cells if NPs accidentally accumulate at the unexpected areas
Cheaper	More expensive
More accessible to general public	Limited access to affordable population only

summarises the current positive and negative aspects in nanomedicine, leading to a further discussion next on the constructive lessons that nanomedicine can learn from nanotechnology.

15.3.1 Inconsistency Issues in Nanofabrication

As mentioned earlier, there are issues and concerns with respect to the inconsistency of particle sizes and properties, even within the same batch production. The inconsistency could greatly reduce the product quality, and further especially affect the safety of product to be effectively used inside human bodies since it is difficult to confidently control or monitor the effectiveness of the treatment which is not uniform. Serious undesired complications might even occur from this uncontrolled variation.

15.3.2 Industrial Scale-up and Commercialisation Limitations

The techniques and methods evolving nanotechnology could be very specific and expensive. Some of them are also limited to only batch production. Furthermore, some synthetic routes of nanoparticles and other nanomaterials could be too sophisticated so that the product yield might be relatively low and that overall product cost is high. These issues have been preventing several nanotechnology related products from being industrially scaled-up and commercialised as they are not economically feasible with reasonable profitability. It is suggested that researches should be carried out in order to find better and optimised (scaled-up and economic) synthetic routes. Generally speaking, an ideal synthetic route of nanoparticles and other nanomaterials for industrialisation should have the following features:

- Safe
- Easily accessible raw materials
- Including sophisticate steps or equipment as least as possible
- Reasonable capital and operating costs
- Reasonable yield
- Reasonable production timescale
- Useful by-products (if any)

15.3.3 Complex Nature of Biological Phenomena: Additional Complication to the Complex Concept of Nanoscience, Nanotoxicity and Related Matters

Biological phenomena are much more complicated than physical phenomena. Several activities occur simultaneously in a set manner in the biological environment. This is an additional complication to the study of nanoscale phenomena.

Nanotechnology is already a very broad, emerging and extensive field. As discussed earlier, it is somehow difficult to set topics or areas of nanomedicine into discrete categories since everything seems link together.

A critical limitation to the development of nanomedicine at present is the lack of thorough and well-established knowledge regarding interaction between nanomaterials and biological environment inside and outside the body. It has raised public concerns about safety issues regarding the use of nanotechnology in health care, and this is why the study of nanotoxicology will play an more and more important role [2, 79, 69]. The classic examples regarding the nanotoxicity issues include the cases of using silver nanoparticles and carbon nanotubes. Silver nanoparticles have many interesting properties involving the anti-bacterial property which has received extensive interests and investigations. However, it was discovered later that silver nanoparticles has undesired adverse effect in vivo [80]. For carbon nanotubes, it was once at the centre of attraction as a promising drug delivery method and platform. However, it was also discovered later that it could become harmful [81]. Concerns have also been raised with respect to the nanomaterials' fate inside the body and body clearance. In theory, nanomaterials for clinical application has to undergo absorption, distribution, metabolism and excretion (ADME) studies first. However, since it is heterogeneous in content with size distribution, it is difficult to describe ADME properties of nanomaterials [79].

15.3.4 Establishment of Standards and Protocols for Nanomaterial Characterisation

Despite the amazing developments in nanotechnology, there are still limitations of achieving accurate and reliable characterisation of the physical and chemical properties of nano-products. Furthermore, there is no solid standards and protocols for a full/comprehensive and reliable nanomaterial (medical nanomaterial in particular) characterisation mainly due to the diversity, complexity and uncertainty of nanomaterials. There have been suggestions to first develop ex vivo studies of activities of nanoparticles and the body thoroughly from the possible ways of administration, their routes and journey inside the body, and their fate, before performing in vivo studies [11]. However, more issues will rise due to the complexity in fabricating ex vivo system for the study. It is also essential to trace if the nanoparticles are degraded, excreted or accumulated inside the body, as it will affect the toxicity of such particles [79].

15.3.5 Nanomedicine Regulating Bodies: A Demand for Proper Regulations

Nanomedicine has recently come into our visions attributed to the rapid and exciting development of nanotechnology. Researchers are even more optimistic for the future of nanomedicine but it also consequently brings us a new task of determining

how to best regulate it so that it is both safe and effective. Similarly occurred during the development of biotechnology, the national governments/bodies worldwide are now struggling with balancing the competing benefits and risks of nanotechnology in the medical and other sectors. It is becoming increasingly clear that reasonable, effective and predictable regulatory structures will be critical to the successful implementation of nanotechnology [82]. When it comes to developing a regulation plan for nanomedicine, the focus needs to be on who will be given the responsibility to oversee regulation and whether to operate under the current regulations or write new regulations [83].

Hence, there have been some discussions on the challenge and suitable role of regulatory bodies such as FDA [84, 85]. It was suggested that whether the FDA should at least look at nanoproducts on a case-by-case basis and should not attempt regulation of nanomedicine by applying existing statutes alone, especially where scientific evidence suggests otherwise. Incorporating nanomedicine into the current regulatory scheme is a poor idea. Hence, regulation of nanomedicine must balance innovation and R&D with the principle of ensuring maximum public health protection and safety. The FDA should also consider implementing several reforms to ensure that it is adequately prepared to regulate nanomedicine.

Chowdhury further recently discussed the regulation of nanomedicine in Europe [86]. Due to the fact that the nanomedicine market in EU is poised at a critical stage wherein clear regulatory guidance is lacking in providing for clarity and legal certainty to manufacturers of nanomedicine, it is imperative to establish suitable regulatory structures for nanomedicine. It was suggested that both the pediatric and the advanced therapies medicinal products regimes offer important regulatory guidance that could be adopted for the regulation of nanomedicines in the EU first.

15.3.6 Ethical Issues

For nanomedicine, an evolved area from nanotechnology receiving increasing attentions from our society, it is crucial to proactively address the ethical, social and regulatory aspects of nanomedicine to minimize its adverse impacts on the environment and public health and to avoid a public backlash [87]. The most significant concerns involve risk assessment, risk management of engineered nanomaterials, and risk communication in clinical trials. Other concerns have been raised regarding privacy violation from generating genetic data of the patient and social justice. Accessibility to health care is also an important issue. Due to generally high-cost of the nanotechnology related products, economic and equity issues have also been pinpointed that only a few people who are financially capable can access this high-end health care but the diseases do not selectively occur in rich population [2, 87]. Educating members of society about the benefits and risks of nanomedicine is thus important to gain and maintain public support.

15.4 Conclusions and Future Outlook

Nanomedicine bridges the gap between nanotechnology and medicine. It is a truly interdisciplinary science which requires cooperation and contribution from engineers, scientists and medical staffs to appropriately, effectively, safely and successfully apply nanotechnology in medicine to move to the next generation of health care. Several discoveries and achievements in nanomedicine have been made, making significant medical advancement and bringing medicine closer to the new era. However, in order to drive nanomedicine further in the right direction with confidence, lessons from nanotechnology must be considered and should be learnt and used wisely to overcome problems and limitations. Complete knowledge and understanding of nanoscale phenomena, such as interaction between nanoparticles and biological environment, nanotoxicity, and nanomaterial physical and chemical properties characterisation are all needed to better refine and catalyse the successful implementation of nanomedicine. It is also very crucial to establish suitable regulating bodies for controlling and monitoring the use of nanotechnology and its products, as well as for providing clarity and legal certainty to manufacturers. The new era of nanomedicine is coming and the potential of nanomedicine seems infinite along with more public awareness and support.

References

1. Logothetidis S (ed) (2012) Nanomedicine and nanobiotechnology. Nanoscience and nanotechnology. Springer, Heidelberg
2. Boisseau P, Loubaton N (2011) Nanomedicine, nanotechnology in medicine. C R Phys 12:620–636
3. Fattal E, Tsapis N (2014) Nanomedicine technology: current achievements and new trends. Clin Transl Imaging 2(1):77–87
4. Tong S, Fine E, Lin Y et al (2014) Nanomedicine: tiny particles and machines give huge gains. Ann Biomed Eng 42(2):243–259
5. Jain K (2008) The handbook of nanomedicine, 1st edn. Humana Press, Totowa
6. Kalangutkar P (2014) The evolution of nanomedicine with the re-evolution of nanotechnology. Int J Eng Sci Invent 3(5):12–16
7. Zarzycki A (2014) Editorial: at source of nanotechnology. Tecno Lógicas 17(32):9–10
8. Vogel V (ed) (2009) Volume 5: Nanomedicine. Nanotechnology. Wiley, Weinheim
9. European Technology Platform on Nanomedicine (2009) Roadmaps in nanomedicine towards 2020 (version 1.0). www.etp nanomedicine.eu/public/.../091022_ETPN_Report_2009.pdf. Accessed on 14 Jan 2014
10. European Technology Platform on Nanomedicine (2013) Roadmaps in nanomedicine towards 2020 (version 1.0). www.etp-nanomedicine.eu/public/.../091022_ETPN_Report_2009.pdf Accessed on 14 Jan 2014
11. Engstrom D, Savu V, Zhu X et al (2011) High throughput nanofabrication of silicon nanowire and carbon nanotube tips on AFM probes by stencil-deposited catalysts. NanoLett 11(4):1568–1574
12. Lieber C (2011) Semiconductor nanowires: a platform for nanoscience and nanotechnology. MRS Bull 36(12):1052–1063
13. Smith GB & Granqvist CGS (2010) Green Nanotechnology: Solutions for Sustainability and Energy in the Built Environment. CRC Press Print ISBN: 978-1-4200-8532-7. eBook ISBN: 978-1-4200-8533-4. http://www.crcnetbase.com/isbn/9781420085334

14. Juliano R (2012) The future of nanomedicine: promises and limitations. Sci Public Policy 39(1):99–104
15. Xu B, Yan X, Zhang J et al (2012) Glass etching to bridge micro- and nanofluidics. Lab Chip 12(2):381–386
16. Saito T, Ohshima S, Xu W et al (2005) Size control of metal nanoparticle catalysts for the gas-phase synthesis of single-walled carbon nanotubes. J Phys Chem B 109(21):10649–10652
17. França R, Zhang F, Veres T et al (2013) Core–shell nanoparticles as prodrugs: possible cytotoxicological and biomedical impacts of batch-to-batch inconsistencies. J Colloid Interface Sci 389(1):292–297
18. Segerink L, Eijkel J (2014) Nanofluidics in point of care applications. Lab Chip. doi:10.1039/c4lc00298a
19. Stone H, Kim S (2001) Microfluidics: basic issues, applications and challenges. Am Inst Chem Eng J 47(6):1250–1254
20. Wang L, Fan J (2010) Nanofluids research: key issues. Nanoscale Res Lett 5:1241–1252
21. Liu L, Yoo S, Lee S et al (2011) Wet-chemical synthesis of palladium nanosprings. Nano Lett 11:3979–3982
22. Choi C, Kim C (2006) Fabrication of a dense array of tall nanostructures over a large sample area with sidewall profile and tip sharpness control. Nanotechnology 17(21):5326–5333
23. Huefner S (2006) Nanobiosensors. http://www.chem.usu.edu~tapaskar/Sara.ppt. Accessed on 1 July 2013
24. Topal C (2011) Nanobiosensor. http://bionanotech.uniss.it/wpcontent/uploads/2011/09/biosensori.ppt. Accessed 1 July 2013
25. Saha K, Agast S, Kim C et al (2012) Gold nanoparticles in chemical and biological sensing. Chem Rev 112:2739–2779
26. Cao X, Ye Y, Liu S (2011) Gold nanoparticle-based signal amplification for biosensing. Anal Chem 417(1):1–16
27. Pumera M, Sanchez S, Ichinose I et al (2007) Electrochemical nanobiosensors. Sens Actuators B 123:1195–1205
28. Steffens C, Leite F, Bueno C et al (2012) Atomic force microscopy as a tool applied to nanobiosensors. Sensors 12:8278–8300
29. Tang B, Cao L, Xu K et al (2008) A new nanobiosensor for glucose with high sensitivity and selectivity in serum based on fluorescence resonance energy transfer (FRET) between CdTe quantum dots and Au nanoparticles. Chem Eur J 24:3637–3644
30. Lad A, Agrawal Y (2012) Optical nanobiosensor: a new analytical tool for monitoring carboplatin–DNA interaction in vitro. Talanta 97:218–221
31. Elahi M, Bathaie S, Mousavi M et al (2012) A new DNA-nanobiosensor based on g-quadruplex immobilized on carbon nanotubes modified glassy carbon electrode. Electrochim Acta 82:143–151
32. Parolo C, Merkoci A, Mousavi M et al (2013) Paper-based nanobiosensors for diagnostics. Chem Soc Rev 42:450–457
33. Hoshino Y, Takashi K, Yoshio O, & Kenneth JS (2008) Peptide imprinted polymer nanoparticles: a plastic antibody. J Amer Chem Soc 130(46):15242–15243
34. Foudeh A, Didar T, Veres T et al (2012) Microfluidic designs and techniques using lab-on-a-chip devices for pathogen detection for point-of-care diagnostics. Lab Chip 12(18):3249–3266
35. Medina-Sanchez M, Miserere S, Merkoci A (2012) Nanomaterials and lab-on-a-chip technologies. Lab Chip 12:1932–1943
36. Schumacher, Soeren, Jörg Nestler, Thomas Otto, Michael Wegener, Eva Ehrentreich-Förster, Dirk Michel, Kai Wunderlich et al (2012) 'Highly-integrated lab-on-chip system for point-of-care multiparameter analysis." Lab Chip 12(3):464–473
37. Govindarajan A, Ramachandran S, Vigil G et al (2011) A low cost point-of-care viscous sample preparation device for molecular diagnosis in the developing world: an example of microfluidic origami. Lab Chip 12(1):174–181
38. Carmode D, Skajaa T, Fayad Z et al (2009) Nanotechnology in medical imaging: probe design and applications. Arterioscler Thromb Vasc Biol 29:992–1000

39. Lee N, Choi S, Hyeon T (2013) Nano-sized CT contrast agents. Adv Mater 25(19):2641–2660
40. Chien C, Chen H, Lai S et al (2012) Gold nanoparticles as high-resolution X-ray imaging contrast agents for the analysis of tumor-related micro-vasculature. J Nanobiotechnol 10:10
41. Bae H, Ahmad T, Rhee I, Chang Y, Jin SU, Hong S (2012) Carbon-coated iron oxide nanoparticles as contrast agents in magnetic resonance imaging. Nanoscale Res Lett 7:44
42. Gupta A, Arora A, Menakshi A et al (2012) Nanotechnology and its applications in drug delivery: a review. WebmedCentral Med Educ 3(1):MC002867
43. Liu H, Liu T, Wang H et al (2013) Impact of PEGylation on the biological effects and light heat conversion efficiency of gold nanoshells on silica nanorattles. Biomaterials 34(28):6967–6975
44. Wang M, Thanou M (2010) Targeting nanoparticles to cancer. Pharmacol Res 62:90–99
45. Hatakeyama H, Akita H, Ishida E et al (2007) Tumor targeting of doxorubicin by anti-MT1-MMP antibody-modified PEG liposomes. Pharm Nanotechnol 342(1–2):194–200
46. Hammond P (2010) Thin films: particles release. Nat Mater 9:292–293
47. Dubey V, Mishra D, Nahar M et al (2010) Enhanced transdermal delivery of an anti-HIV agent via ethanolic liposomes. Nanomed Nanotechnol Biol Med 6(4):590–596
48. Mulik R, Mönkkönen J, Juvonen R et al (2010) Transferrin mediated solid lipid nanoparticles containing curcumin: enhanced in vitro anticancer activity by induction of apoptosis. Int J Pharm 398(1–2):190–203
49. Goldberg D, Vijayalakshmi N, Swaan P et al (2011) G3.5 PAMAM dendrimers enhance transepithelial transport of SN38 while minimizing gastrointestinal toxicity. J Control Release 150(3):318–325
50. Guo J, Gao X, Su L et al (2011) Aptamer-functionalized PEG–PLGA nanoparticles for enhanced anti-glioma drug delivery. Biomaterials 32(1):8010–8020
51. Makadia H, Siegel S (2011) Poly lactic-co-glycolic acid (PLGA) as biodegradable controlled drug delivery carrier. Polymers (Basel) 3(3):1377–1397
52. Sahni J, Baboota S, Ali J (2011) Promising role of nanopharmaceuticals in drug delivery. Pharma Times 43(10):16–18
53. Savla R, Taratula O, Garbuzenko O et al (2011) Tumor targeted quantum dot-mucin 1 aptamer-doxorubicin conjugate for imaging and treatment of cancer. J Control Release 153(1):16–22
54. Taghdisi S, Lavaee P, Ramezani M et al (2011) Reversible targeting and controlled release delivery of daunorubicin to cancer cells by aptamer-wrapped carbon nanotubes. Eur J Pharm Biopharm 77(2):200–206
55. Saad Z, Jahan R, Bagal U (2012) Nanopharmaceuticals: a new perspective of drug delivery system. Asian J Biomed Pharm Sci 2(14):11–20
56. McDowell G, Slevin M, Krupinski J (2011) Nanotechnology for the treatment of coronary in stent restenosis: a clinical perspective. Vasc Cell 3:8
57. Tan A, Alavijeh M, Seifalian A (2012) Next generation stent coatings: convergence of biotechnology and nanotechnology. Trends Biotechnol 30(8):406–409
58. American Cancer Society (2011) Hyperthermia. http://www.cancer.org/treatment/treatmentsandsideeffects/treatmenttypes/hyperthermia. Accessed 29 June 2013
59. Baronzio G, Parmar G, Ballerini M et al (2014) A brief overview of hyperthermia in cancer treatment. J Integr Oncol 3(1):1–10
60. Di Corato R, Espinosa A, Lartigue L et al (2014) Magnetic hyperthermia efficiency in the cellular environment for different nanoparticle designs. Biomaterials 35(24):6400–6411
61. Bhayani K, Rajawade J, Paknikar K (2013) Radio frequency induced hyperthermia mediated by dextran stabilized LSMO nanoparticles: in vitro evaluation of heat shock protein response. Nanotechnology 24(1):015102
62. Sadhukha T, Wiedmann T, Panyam J (2013) Inhalable magnetic nanoparticles for targeted hyperthermia in lung cancer therapy. Biomaterials 34(21):5163–5171
63. Morales C, Valencia P, Thakkar A et al (2012) Recent developments in multifunctional hybrid nanoparticles: opportunities and challenges in cancer therapy. Front Biosci 4:529–545
64. Lee D, Koo H, Sun I et al (2012) Multifunctional nanoparticles for multimodal imaging and theragnosis. Chem Soc Rev 41:2656–2672

65. Cheng L, Yang K, Li Y et al (2012) Multifunctional nanoparticles for upconversion luminescence/MR multimodal imaging and magnetically targeted photothermal therapy. Biomaterials 33(7):2215–2222
66. Lee S, Kim H, Ha Y et al (2013) Targeted chemo-photothermal treatments of rheumatoid arthritis using gold half-shell multifunctional nanoparticles. ACS Nano 7(1):50–57
67. Bean A, Tuan R (2013) Stem cells and nanotechnology in tissue engineering and regenerative medicine. In: Ranalingam M, Jabbari E, Ramakrishna S et al (eds) Micro and nanotechnologies in engineering stem cells and tissues, 1st edn. Wiley, Hoboken
68. Kingham E, Oreffo R (2013) Embryonic and induced pluripotent stem cells: understanding, creating, and exploiting the nano-niche for regenerative medicine. ACS Nano 7(3):1867–1881
69. Thierry B, Textor M (2012) Nanomedicine in focus: opportunities and challenges ahead. Biointerphases 7(19)
70. Human Genome Project Information (2011) Gene therapy. http://ornl.gov/sci/techresources/Human_Genome/medicine/genetherapy.shtml. Accessed 2 July 2013
71. Genetics Home Reference (2013) What is gene therapy? http://ghr.nlm.nih.gov/handbook/therapy/genetherapy. Accessed 2 July 2013
72. Labhasetwar V (2005) Nanotechnology for drug and gene therapy: the importance of understanding molecular mechanisms of delivery. Curr Opin Biotechnol 16(6):674–680
73. Gascón A, Pozo-Rodríguez A, Solinís M (2013) Non-viral delivery systems in gene therapy, gene therapy – tools and potential applications, Dr. Francisco Martin (Ed.), ISBN: 978-953-51-1014-9, InTech, DOI: 10.5772/52704. Available from: http://www.intechopen.com/books/gene-therapy-tools-and-potential-applications/non-viral-delivery-systems-in-gene-therapy
74. Labhasetwar V, Panyam J (2003) Biodegradable nanoparticles for drug and gene delivery to cells and tissue. Adv Drug Deliv Rev 55(3):329–347
75. Yamashita S, Fukushima H, Akiyama Y et al (2011) Controlled-release system of single-stranded DNA triggered by the photothermal effect of gold nanorods and its in vivo application. Bioorg Med Chem 19:2130–2135
76. Bhattara S, Muthuswamy E, Wani A et al (2010) Enhanced gene and siRNA delivery by polycation-modified mesoporous silica nanoparticles loaded with chloroquine. Pharm Res 27(12):2556–2568
77. Chen M, Gao S, Dong M et al (2012) Chitosan/siRNA nanoparticles encapsulated in PLGA nanofibers for siRNA delivery. ACS Nano 6(6):4835–4844
78. Kwon S, Nam H, Nam T et al (2008) In vivo time-dependent gene expression of cationic lipid-based emulsion as a stable and biocompatible non-viral gene carrier. J Control Release 128(1):89–97
79. Nystrom A, Fadeel B (2012) Safety assessment of nanomaterials: implications for nanomedicine. J Control Release 161:403–408
80. Han DW, Woo YI, Lee MH, Lee JH, Lee J, Park JC (2012) In-vivo and in-vitro biocompatibility evaluations of silver nanoparticles with antimicrobial activity. J Nanosci Nanotechnol 12(7):5205–5209
81. Zhao Y, Xing G, Chai Z (2008) Nanotoxicology: are carbon nanotubes safe? Nat Nanotechnol 3(4):191–192
82. Marchant GE, Sylvester DJ, Abbott KW, Danforth TL (2010) International harmonization of regulation of nanomedicine. Stud Ethics Law Technol 3(3):1941–6008
83. Shanna H (2009) The Regulation of Nanomedicine: Will the Exisiting Regulatory Scheme of the FDA Suffice?, XVI Rich. J.L. & Tech. 4 http://law.richmond.edu/ jolt/v16i2/article4.pdf
84. Miller J (2003) Beyond biotechnology: FDA regulation of nanomedicine. Columbia Sci Technol Law Rev 4:E5
85. Bawa R (2011) Regulating nanomedicine – can the FDA handle it? Curr Drug Deliv 8(3):227–234
86. Chowdhury N (2010) Regulation of nanomedicines in the EU: distilling lessons from the pediatric and the advanced therapy medicinal products approaches. Nanomedicine 5(1):135–142
87. Resnik DB, Tinkle SS (2007) Ethics in nanomedicine. Nanomedicine 2(3):345–350