Review Article

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# Nanotechnology-enabled biomedical engineering: Current trends, future scopes, and perspectives

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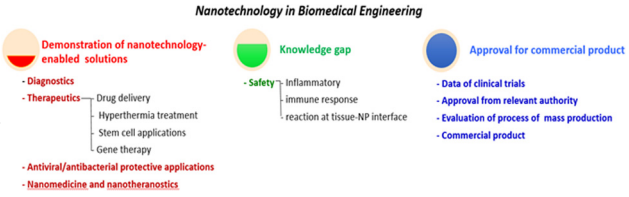
**Abstract:** Applications of nanotechnology in biomedical engineering are vast and span several interdisciplinary areas of nanomedicine, diagnostics, and nanotheranostics. Herein, we provide a brief perspective on nanotechnology as an enabling tool for the design of new functional materials and devices for medical applications. Semiconductor nanocrystals, also known as quantum dots, are commonly used in optical imaging to diagnose diseases such as cancer. Varieties of metal and metal oxide nanoparticles, and two-dimensional carbon-based nanostructures, are prospective therapeutics and may also be used in protective antiviral/antibacterial applications. Similarly, a number of nanomaterials have shown the potential to overcome the drawbacks of conventional antiviral drugs. However, assessing the adverse effects and toxicities of nanoparticles in medicine and therapeutics is becoming more critical. This article discusses the latest developments of nanomaterials in diagnosis, nanotheranostics, and nanomedicines, with particular emphasis on the importance of nanomaterials in fighting against coronavirus disease. Further, we considered the safety and toxicity of nanomaterials in the context of biomedical applications. Finally, we provided our perspective on the future of nanotechnology in emerging biomedical engineering fields.

**Keywords:** nanotechnology, biomedical engineering, nanomedicine, trends, scopes and perspectives




Graphical abstract

## 1 Introduction

Nanotechnology is an enabling tool for designing new materials and devices, which opens a new era of biomedical engineering. Biomedical engineering is an expeditious field that bridges the gap between technology, biology, and medicine. The potential use of nanotechnology in biomedical engineering includes the early detection and treatment of diseases. Cognizance in physical/chemical biology, fabrication principles, and the development of predictive methods to control them, are likely to lead the major advances in nanomedicine and nanodevices.

Paul Ehrlich, a medical doctor who expressed great interest in bacteriology and immunology, proposed the concept of targeted drug delivery that was mediated by nanoparticles in 1954 [1]. He called the delivery system "Zauberkugeln," which translates to "Magic bullets" in English. This concept gained momentum in 1950–1960 and the controlled release of drugs has since then attracted significant attention. The historical development of nanoparticles (NPs) for biomedical applications over the years is depicted in Figure 1. Professor Peter Paul Speiser and his group first investigated polyacrylic beads for oral administration and developed NPs for drug delivery purposes and vaccines in 1973 [1,2]. Several vaccinations, such as those for tetanus and diphtheria, require multiple injections to build up sufficient antibodies for protection. It was anticipated that the sustained release mechanism of NPs would provide constant immune stimulation, and hence, one injection would be sufficient to achieve the necessary antibody response. Within a short time, the Johns Hopkins

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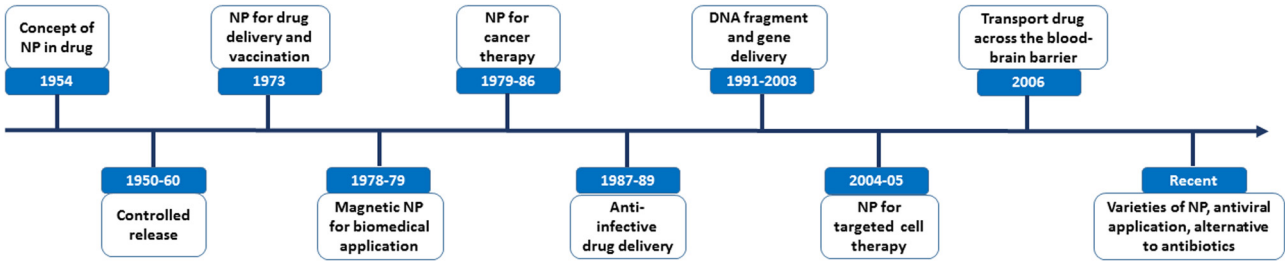


**Figure 1:** Historical development of nanoparticles for biomedical applications.

Medical Institutions invented albumin NPs and, in subsequent years, Kramer used a similar method to produce magnetic NPs. One of the most important applications of NPs, which is for the detection of tumor cells and cancer therapy, was developed between 1979 and 1986 [3,4]. Later, it was demonstrated that NPs could deliver anti-infective drugs [5], DNA fragments, and genes [6]. The covalent attachment of antibodies on human serum albumin NPs enabled drug transport across the blood–brain barrier [7]. NPs have been introduced in pharmaceutical and medical applications 67 years ago and have great potential for future biomedical applications.

Nanotechnology has revolutionized medical diagnosis, immunization, treatment, and even healthcare products. The coupling of biological agents with different types of NPs can be achieved either *via* chemical conjugation, physical encapsulation, or adsorption [8]. The suitable dosage of these nanosubstances depends on the application purpose. They can be used to deliver various chemicals (drugs, chemotherapeutic agents, or imaging substances) and biological substances (antigens, antibodies, RNA, or DNA) through endocytosis, and transmit light and heat to target cells in therapies [8]. The emerging field of nanotechnology for biomedical application is vast and can be classified into four categories, as shown in Figure 2. Diagnostic methods involve different imaging techniques. Drug delivery, tissue engineering, prosthetic orthopedic implants, and gene and stem cell therapies fall under the category of therapeutic applications. Other emerging fields include antiviral applications of NPs in conjunction with treatments used in combating drug-resistant bacteria, as well as immunization and vaccine production. Therefore, because of the growing importance and the need to draw the attention of current researchers towards the application of nanotechnology in biomedical fields, we hereby provide a brief account of the latest developments in the use of nanomaterials in diagnosis, nanotheranostics, and nanomedicines. The importance of nanotechnology in fighting against the coronavirus disease, safety, and toxicity of nanomaterials is also discussed. Finally, we propose possible future directions in the context of the current challenges.

## 2 Nanotechnology in diagnostics

NPs used in imaging applications, such as optical imaging and magnetic resonance imaging (MRI), are well established and widely used for diagnosis. Semiconductor nanocrystals, known as quantum dots (QDs), are also commonly used in optical imaging [10]. QDs are 100 times brighter than organic dye molecules. The number of NPs in the cell cytoplasm is critical to illuminate the cells within deep tissue. Although QDs are useful tagging materials, they have several disadvantages. There is a risk of an increase in toxicity due to the increased number of NPs required to illuminate the cell. Another drawback is the blinking behavior, which hinders the tracking of QD-targeted biomolecules [10]. Hence, the development of fluorescent NPs for *in vivo* imaging is still an open challenge. Compared to QDs, silicon nanocrystals are more appealing because they are nontoxic to the cells and do not require a thick surface coating to protect the nanocrystal core from the environment [10]. Table 1 shows the comparative advantages of silicon nanocrystals over QDs and organic dyes. Silicon nanocrystals are small and have high photostability and moderate quantum yield (a measure of the efficiency of photon emission, as defined by the ratio of the number of photons emitted to the number of photons absorbed).

In contrast, superparamagnetic iron oxide ($Fe_2O_3$) and manganese oxide (MnO) NPs are suitable for MRI. Further, research has shown that metal NPs, fullerenes, dendrimers, and polymer-coated copper sulfide nanocrystals are suitable for diagnostic imaging [9–12]. An example of the use of Au@MnS@ZnS core/shell/shell NPs with poly(ethylene glycol) functionalization, in the diagnosis of a tumor, is shown in Figure 1 [9]. The figure shows efficient accumulation and retention of NPs in the tumors of mice after intravenous injection. Moreover, exposure to X-rays can significantly inhibit the growth of tumors, which shows the possibility of using such NPs in therapeutic applications. In recent years, multipurpose nanosized sensors have been designed to detect

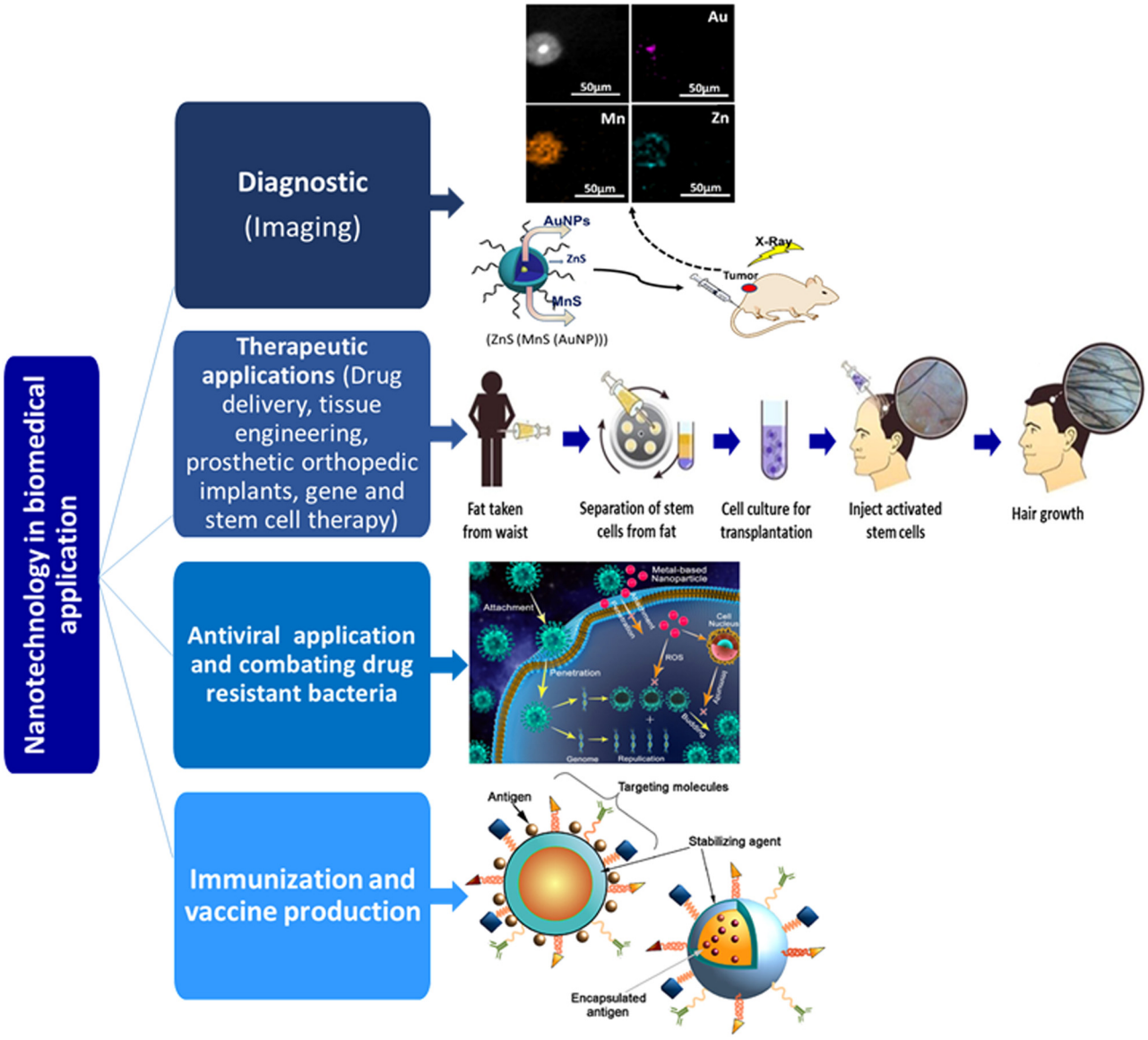


**Figure 2:** Application of nanotechnology for biomedical purposes [9,26,51]. Reproduced with permission from ref. [9], © American Chemical Society. Reproduced with permission from ref. [51], reproduced with permission from ref. [9], © 2011 Elsevier Science Ltd., and reproduced with permission from ref. [51]; © 2011 Elsevier Science Ltd.

different pathological parameters, antigens, and toxic substances.

Chen *et al.* [13] have reported a method that utilizes a small-molecule peptide, the asparagine-glycine-arginine (NGR), as a capture probe for the selective enrichment and isolation of circulating tumor cells (CTCs). The multi-scale $TiO_2$ nanofibers are obtained by electrospinning and calcination. Bovine serum albumin (BSA) is decorated

**Table 1:** Comparative properties of silicon nanocrystals with QDs and organic dyes [10]. Reproduced with permission from ref. [10]; this work is licensed under the Creative Commons Attribution 4.0

| Properties | Silicon nanocrystals | QDs | Organic dye |
|---|---|---|---|
| Average size | 1–4 nm (diameter) | 10–20 nm (diameter) | 0.5–10 nm |
| Photo stability | >6 month | No data | 1 day |
| Blinking | No data | Microsecond | No data |
| Quantum yield | <60% | >50% | >90% |

onto $TiO_2$ nanofiber surfaces to inhibit nontarget cell adhesion. At the same time, NGR peptides are conjugated onto the $TiO_2$–BSA surface through the glutaraldehyde (GA) to specifically capture the target cells.

# 3 Nanotechnology in therapeutics

## 3.1 Treatment of hyperthermia

Metallic NPs, being excellent conductors of heat, efficiently transmit heat generated within them to adjacent tissues. When administered intravenously, they can accumulate preferentially in tumors. Magnetic NPs, gold (Au) NPs, and carbon nanotubes (CNTs) have been used in therapeutic applications. Typical examples of magnetic NPs are $Fe_2O_3$ NPs, superparamagnetic $Fe_2O_3$ NPs, and doped $Fe_2O_3$ NPs. Magnetic NPs are activated in an alternating magnetic field to generate heat, which damages the tumor cells without harming the healthy tissues. Superparamagnetic $Fe_2O_3$ NPs are efficient heat generators that can be localized within the center of the tumor and have low toxicity [14]. The presence of dopants in $Fe_2O_3$ NPs increases their specific absorption rate and enhances the heat generation efficiency in an alternating magnetic field [14]. Recently, electrospun fibers containing NPs have received attention for postsurgical treatment. Superparamagnetic $Fe_2O_3$, graphene oxide, and doxorubicin-incorporated nanofibers are proven to eradicate breast cancer's regional recurrence and enhance tissue regeneration [15,16]. In contrast to magnetic NPs, Au NPs are activated photothermally. When Au NPs are illuminated by light, the light energy is converted into heat energy. CNTs absorb incident energy over a broad frequency spectrum, including visible light, near-infrared light, and even radiofrequency waves, and the absorption is considerably higher than that of natural chromophores such as melanin, hemoglobin, and water. Electrospun nanofibers composed of NPs (such as copper sulfide nanoflowers) can be used for postsurgical skin cancer treatment and skin tissue regeneration. While copper sulfide plays an important role in photothermal performance, the nanofibers enhance the adhesion, proliferation, and migration of cells [15].

## 3.2 Drug delivery

Various lipids are also used as antiviral drug carriers. Lipids are biodegradable, biocompatible, inert, nontoxic, nonimmunogenic, easily available, and cheaper. Moreover, their unique characteristics include a smaller size, larger surface area, high drug-loading capacity, improved interface interactions, controlled release, and enhanced overall performance of the drug they deliver [17].

A drug called antisense oligonucleotide (ASO) can inhibit the mRNA processing and translation that leads to many diseases. The disadvantages of ASO-based therapies include poor biological stability, short half-life in circulation, and limited cellular uptake of free ASO. Wartlick *et al.* [7] showed that NPs consisting of human serum albumin (HSA), cross-linked with glutaraldehyde and the drug ASO, enhances the cellular uptake of ASO. Confocal laser scanning microscopic images presented in Figure 3 confirm the presence of the NPs containing drugs in different types of cells (MDA-MB-468, MCF-7, and BT-474 are breast cancer cells; A549 is lung cancer cells). At an incubation temperature of 37°C (similar to our body temperature), NPs were spotted after 24 h, and rapid uptake of the NPs was observed in MDA-MB-468 and MCF-7 cells.

Drug delivery systems fabricated with functional electrospun fibers show promising results for local cancer therapy due to their porous structure, relatively large surface area, high drug loading capacity, and stimuli-responsive drug release [15]. For instance, pH-responsive electrospun fibers can be fabricated by direct blending or core–shell structures comprised of pH-responsive inorganic components or polymer chains and anticancer drugs. Similarly, thermo-responsive, magnetic-responsive, light-responsive electrospun fibers contain NPs of respective properties and the target drug to treat a specific disease.

## 3.3 Stem cell applications

NPs are beneficial for regenerative medicine, stem cell growth, and differentiation. Pluripotent stem cells generally need to be cultured before they are transferred to the human body. Due to their large surface area and biocompatibility at low concentrations, two-dimensional nanostructures are proven to be felicitous for the fabrication of scaffolds suitable for the culture of pluripotent stem cells. Asil *et al.* [18] used graphene oxide (GO) and nanofiber scaffolds to culture neural stem cells, as shown in Figure 4. Moreover, GO allows the spontaneous differentiation of the stem cells. Superparamagnetic $Fe_2O_3$ NPs promote the proliferation of human multipotent stem cells found in the bone marrow [19]. Metal oxide NPs such as $Fe_2O_3$, zinc oxide (ZnO), and Au NPs are used to track the stem cells [20,21].

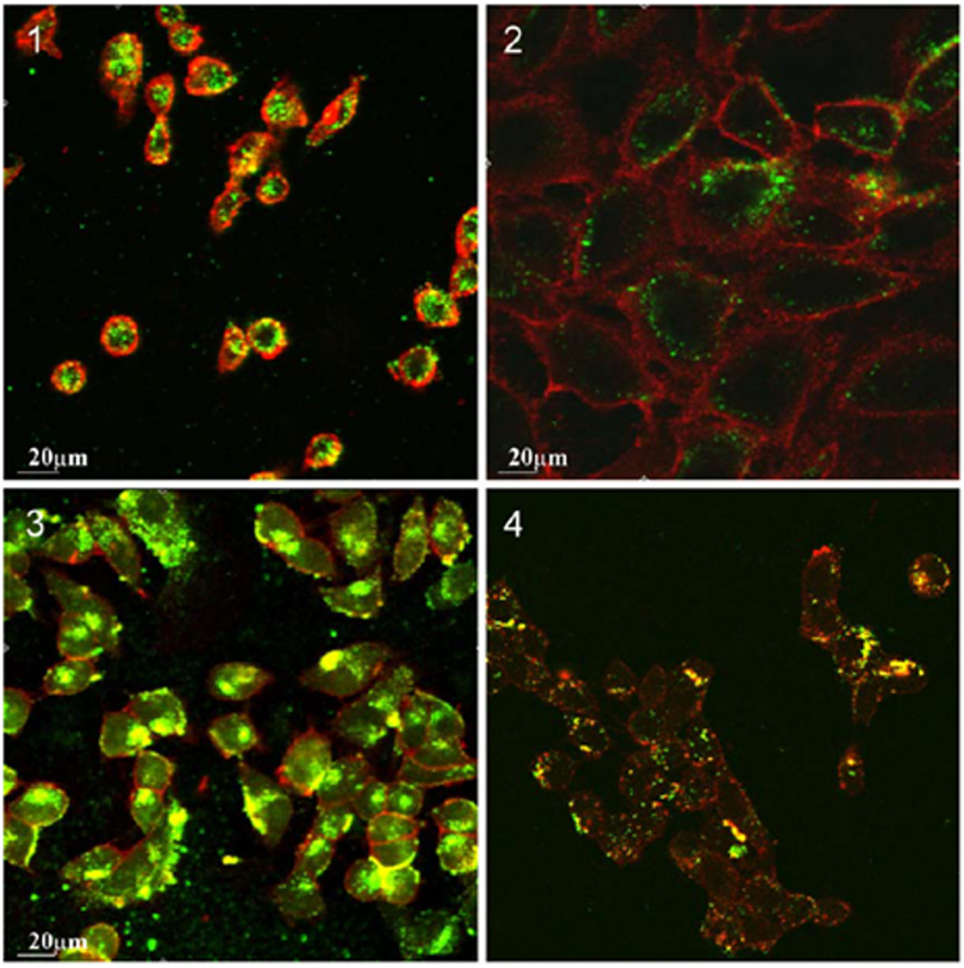


**Figure 3:** Confocal laser scanning microscopic images showing the presence of the nanoparticles containing the drug in different types of cells: (1) MDA-MB-468, (2) MCF-7, and (3) BT-474 are breast cancer cells, and (4) A549 is lung cancer cells. Reproduced with permission from ref. [7].

To treat patients with Batten disease, neural stem cells are administered to the brain by multiple subcortical or intraventricular injections. Batten disease, caused by a genetic defect, can cause loss of vision, and a progressive decline in motor and cognitive responses. A number of studies have shown that the number of neural stem cells injected can be tolerated with immunosuppressant therapy. The use of immunosuppressant drugs is common during organ and tissue transplants because they stop the immune system from overreacting and damaging transplanted organs and tissues. A similar procedure can be used for brain tumor diagnosis and therapy, provided that neural stem cells containing NPs are administered [22]. The characteristics of stem cells can be altered by using loaded stem cells. Chung *et al.* [23] recently showed that the migration of stem cells toward tumor cells improves when stem cells are loaded with $Fe_2O_3$ NPs. Figure 5 shows a schematic diagram of the proposed chronological order of events that take place during the intraoperative transplantation of stem cells carrying drug-loaded NPs into the human brain after tumor resection [22]. Nevertheless, the efficacy of this therapy is yet to be proven.

## 3.4 Gene therapy

Gene therapy introduces normal exogenous genes into the target cells to compensate for the defective and abnormal disease. Usually, viral vectors are used as transporters to deliver the desired gene to the cell. However, there are many limitations, including infection-related cell damage [24]. Nanoparticles bound to DNA have shown promising results when used for delivering genes into stem cell carriers [25,26].

A recent study showed that DNA-containing surface-modified Au NPs provide synergistic photothermal/gene

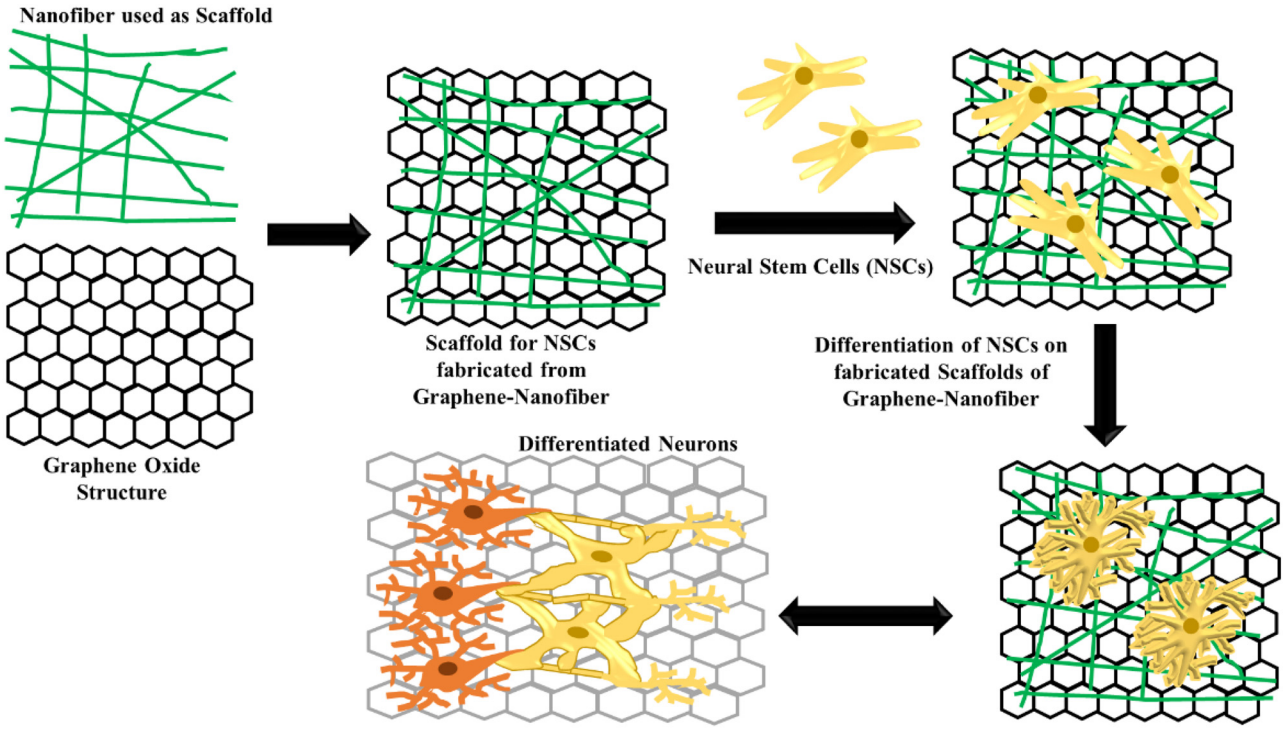


**Figure 4:** Schematic diagram of the scaffold structure fabricated from graphene oxide and nanofibers for the differentiation of neural stem cells [18]. Reproduced with permission from ref. [18].

therapy during photoacoustic imaging [27]. Figure 6 shows a schematic illustration of synergistic photothermal/gene therapy for breast cancer. The procedural sequence used to study the efficacy of this NP is presented in Figure 7 [27]. Tumor-bearing mice were divided into four groups: (i) control, (ii) gene therapy group (J-ACP/p53, where J-ACP represents the surface-modified Au NPs and p53 is DNA), (iii) photoacoustic imaging group (J-ACP + NIR; NIR stands for near-infrared radiation), and (iv) complementary photothermal/gene therapy J-ACP/p53 + NIR (refer to Figure 7(a)). It is evident from Figure 7(b) that the volume, average weight, and size of the tumors in the control group grew rapidly over time. For monotherapy groups (Groups ii and iii), the growth of tumors was inhibited by the photothermal killing effect, the high transfection efficiency of J-ACP, and the excellent antitumor function of p53. However, the monotherapy was not sufficient because the average volume of tumors was still ≈3.5 times as large as the tumors before the treatment. The tumor growth of the complementary photothermal/gene therapy group (Group iv) was completely inhibited and the tumors were significantly smaller than the monotherapy groups after treatment. Therefore, such synergistic therapies seem promising for use in the treatment of cancer.

Gene transfer is a new mode of cancer treatment that introduces new genes into a cancerous cell or the surrounding tissue to cause cell death or slow cancer's growth, or correct genetic errors to reverse the malignant state. Typical therapeutic approaches include angiogenic gene therapy, suicide gene therapy, immunotherapy, small interfering RNAs (siRNA) therapy, pro-apoptotic gene therapy, oncolytic virotherapy, and gene directed-enzyme prodrug therapy [28]. Angiogenic gene therapy (angiogenesis) promotes the formation of new capillary blood vessels from existent microvessels. Suicide gene therapy uses a drug to kill cancer cells. siRNA therapy refers to the transient silencing of a gene of interest. Pro-apoptotic gene therapy prevents apoptosis, a process of programmed cell death. Oncolytic virotherapy uses viruses to infect and destroy cancer cells. Gene for a nonendogenous enzyme is directed to target tissues in gene-directed enzyme prodrug therapy, which activates subsequently administered prodrug. Development of safe and effective vectors for gene delivery and understanding

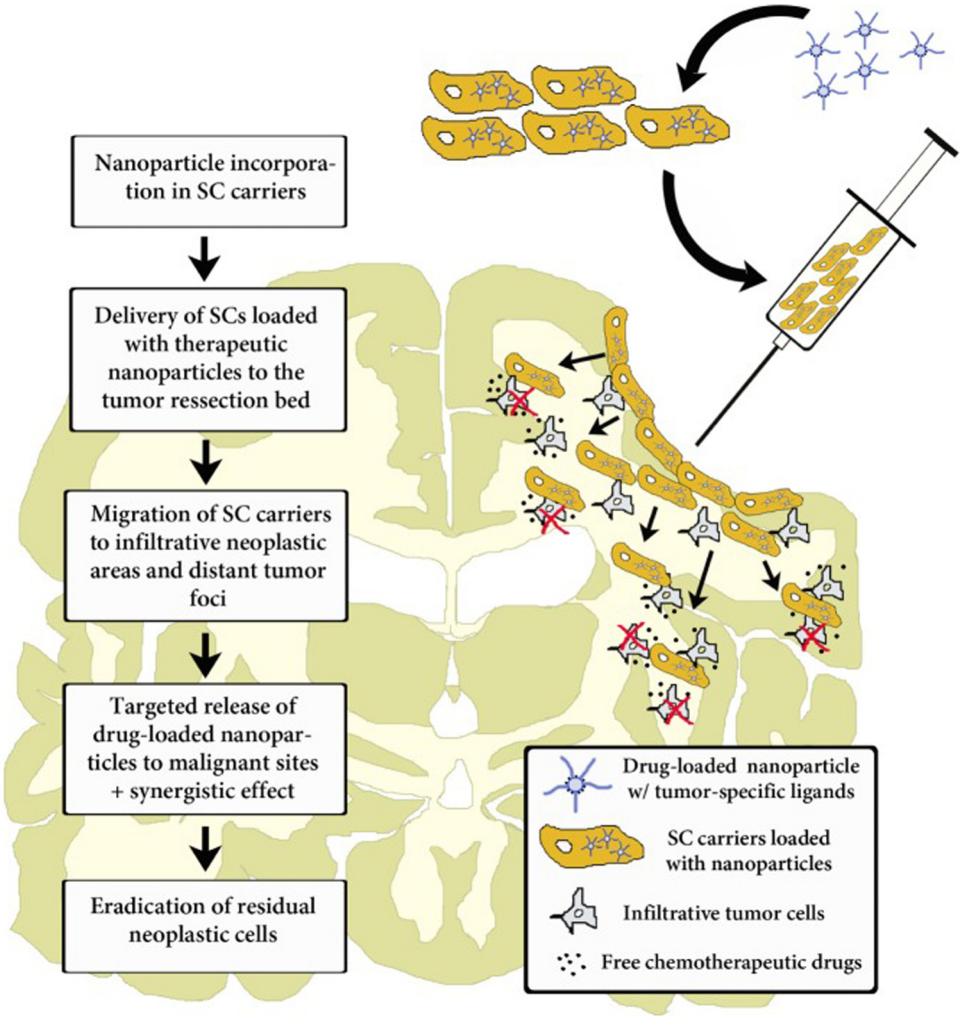


**Figure 5:** Intraoperative transplantation of stem cells carrying drug-loaded NPs into the human brain after tumor resection [22]. Reproduced with permission from ref. [22].

the activity of nucleases will facilitate future genome editing as new treatment approaches for cancer.

## 4 Nanotechnology in antiviral/antibacterial protective applications

Infectious diseases caused by viruses pose a significant risk to human health worldwide. Aerosol particles play a critical role in the spreading of airborne viruses. Different sizes of aerosol particles infect the host's respiratory tract through different mechanisms, as shown in Figure 8 [29,30]. Aerosol particles are released while breathing, speaking, sneezing, or coughing. Smaller particles (<0.2 µm) infect the lungs *via* diffusion and particles that are <2.0 µm in diameter can infect the respiratory tract as well as the lungs. Pathogen inactivation and protection depend on filtration efficiency, face seal, and infrastructure to reduce cross-infection and minimize environmental contamination.

One common protective tool is a facemask. Medical protective masks are typically made of a functional wet-resistant spun-bonded nonwoven layer, a melt-blown nonwoven layer, and a skin-friendly spun-bonded nonwoven layer, as depicted in Figure 9(a) [30]. Facemasks allow gas/steam perspiration but prevent the penetration of aerosols, blood, or fluids. Facemasks are mandatory to fend off the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and the development of innovative self-sterilized and re-useable facemasks has been stipulated. Sunlight-mediated sterilization of facemasks appears to be a promising avenue for recyclability [31–33]. Meanwhile, photothermal materials such as carbon dots, graphene, and silver (Ag) NP-based

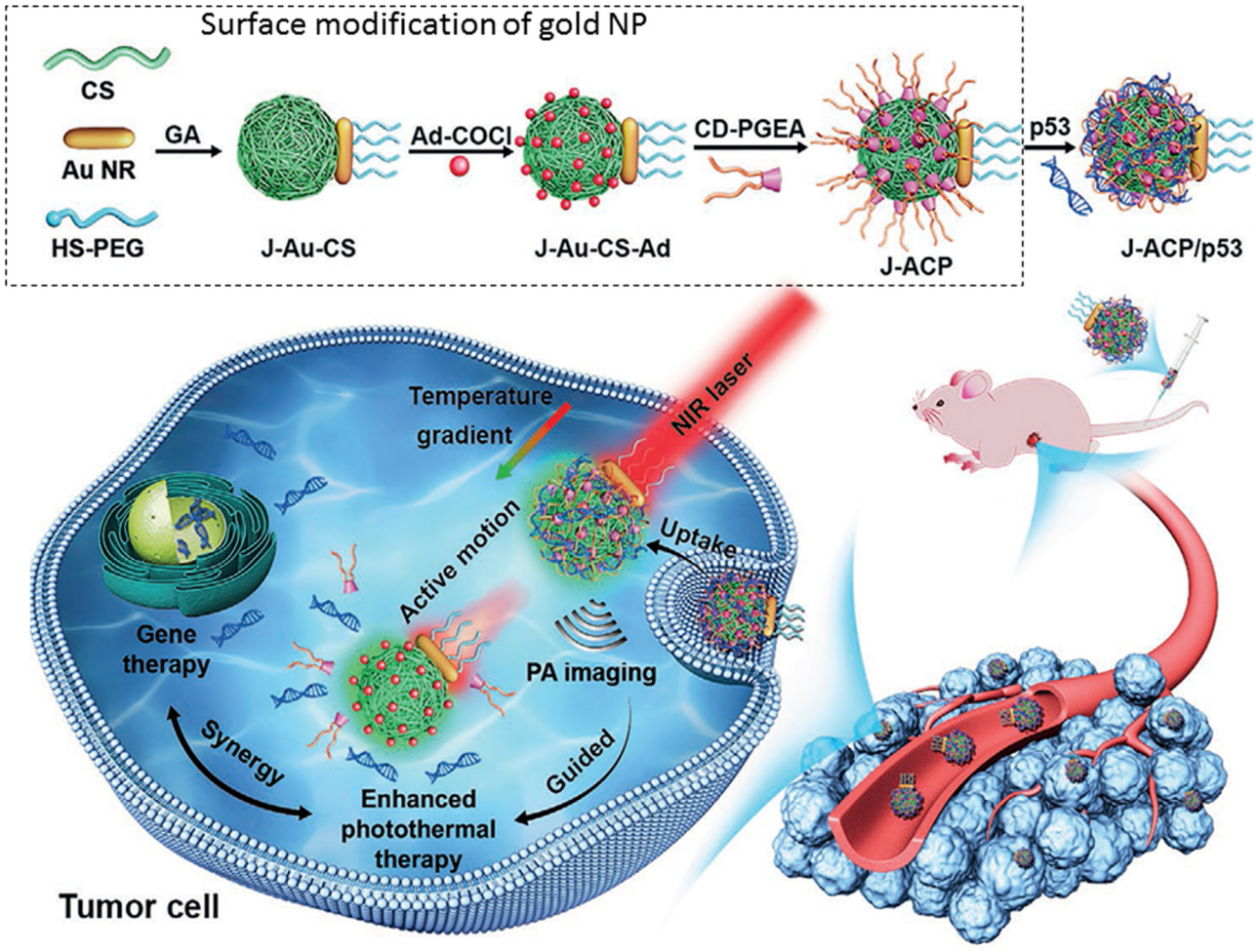


**Figure 6:** Schematic illustration of synergistic photothermal/gene therapy for breast cancer. J-ACP: surface-modified gold NP and J-ACP/p53: DNA containing surface-modified gold NP [27]. Reproduced with permission from ref. [27].

materials are being designed for facemasks. Figure 9(b) shows a schematic diagram of nanoporous membranes comprising carbon dots and a polymer [33]. The resulting composite film exhibits a hydrophobic surface, which prevents moisture accumulation. A compact nanopore network allows both breathability and effective filtration of particles above 100 nm in diameter.

Moreover, self-sterilization occurs upon simulated solar irradiation as the embedded carbon dots absorb visible light and concurrently increase the temperature through heat dissipation. Figure 9(c) shows the temperatures of the polymer-containing membrane and the membrane composed of carbon dot/polymer composite at different irradiation times. The authors tested the bacterial proliferation of *E. coli* to simulate the SARS-CoV-2 (due to safety precautions) and found that *E. coli* does not survive at elevated temperatures (<60°C) [33]. Hence, such a composite can be considered for facemasks.

The viral infection process involves attachment, penetration, uncoating, replication, assembly, and release, as illustrated in Figure 10(a). Viruses enter host cells through specific receptors on the host cell membrane using attachment proteins in the viral capsid [34]. Self-disinfecting devices, therefore, can prevent infections to a certain extent. Metal oxide NPs (*e.g.*, copper oxide, nickel oxide, and titanium dioxide), QDs, GOs, carbon dots, and Ag NPs can reduce the virus' viability on surfaces when associated with polymers and textiles [34,35]. Metal oxide NPs produce reactive oxygen species when exposed to illumination [30,35]. Metal-based NPs inhibit viral activities in three stages, as shown in Figure 10(b). First, NP attachment to the virus prevents the penetration of the virus into the cell. It then produces reactive oxygen species (ROS), ions, and radicals to destroy the structure and function of viral proteins and nucleic acids. Finally, it is simulated that the nucleus increases the immune response of the host cell and inhibits the budding and spreading of the virus. GO

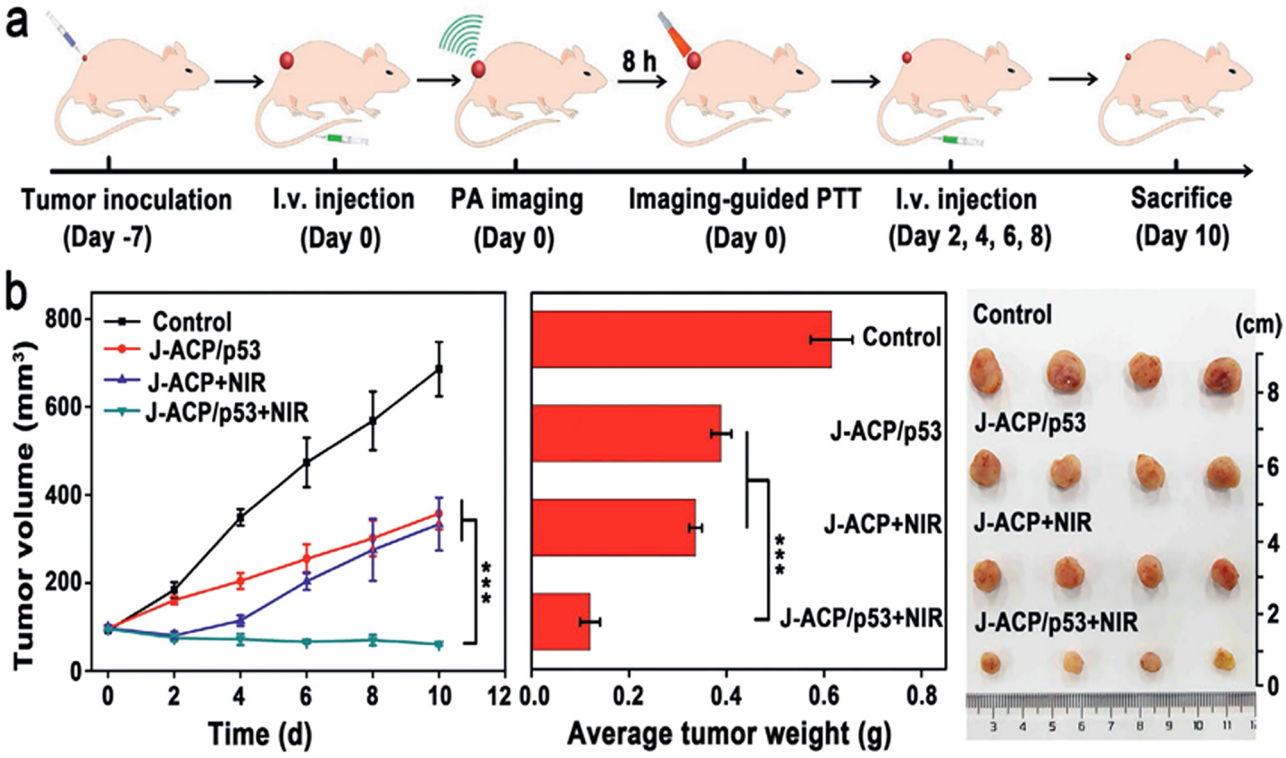


**Figure 7:** (a) Schematic illustration of the treatment process of photoacoustic-imaging guided therapy and (b) time-dependent growth curves of tumors, average weights, and representative photographs of excised tumors of mice [26]. Reproduced with permission from ref. [26].

can inactivate viruses due to its ability to destroy the viral envelope and capsid (protein shell of a virus) [30]. For instance, Au NPs could significantly reduce viral infections (a reduction of 92% after a 6 h interaction) by preventing the penetration of the virus into the cells.

Carbon-based NPs, such as graphene or GO, bind with a virus, as shown in Figure 11 [36]. As a result, the virus loses its structural integrity with the destruction of the spike structures and the leakage of RNA. The extracted RNA can then be used to detect the virus. Graphene decorated with copper(I) oxide, silicon carbide, manganese dioxide, and molybdenum sulfide exhibits antibacterial properties in a similar manner [37,38].

Recent advances in borophene technology have demonstrated the potential for combined photothermal chemotherapy to treat cancer [39]. As graphene is a two-dimensional planar monolayer of carbon, borophene is a two-dimensional planar monolayer of boron. Because of its unique physical, chemical, optical, and electronic properties, it can be used as a biosensor in a variety of bioimage-guided therapies. It can also be used in boron neutron capture therapy, provided its biocompatibility, cytotoxicity, and stability are investigated.

## 5 Importance of nanotechnology in nanomedicine and nanotheranostics

There is a continuous effort to discover new antiviral drugs and therapies to improve the quality of life of patients suffering from viral infections. However, long-term treatment with antiviral drugs has toxic side effects. Other challenges with conventional treatments include the development of drug resistance, the inability to deal with critical diseases, patient noncompliance, as well as the issue of bioavailability and having a short half-life ($t_{1/2}$) [40]. The smaller size and high surface-to-volume ratio of NPs result in characteristics such as increased bioavailability, targeted drug delivery, and increased therapeutic efficacy. As a result, nanotechnology can revolutionize nanomedicine and nanotheranostics.

It is noteworthy to mention that according to StatNano, up until February 2020, 9,217 patents were registered as having the coronavirus disease, and 5.2% of these are being treated based on the application of nanotechnology in diagnostics, therapeutics, vaccines, and filters [40]. Nanoparticulates

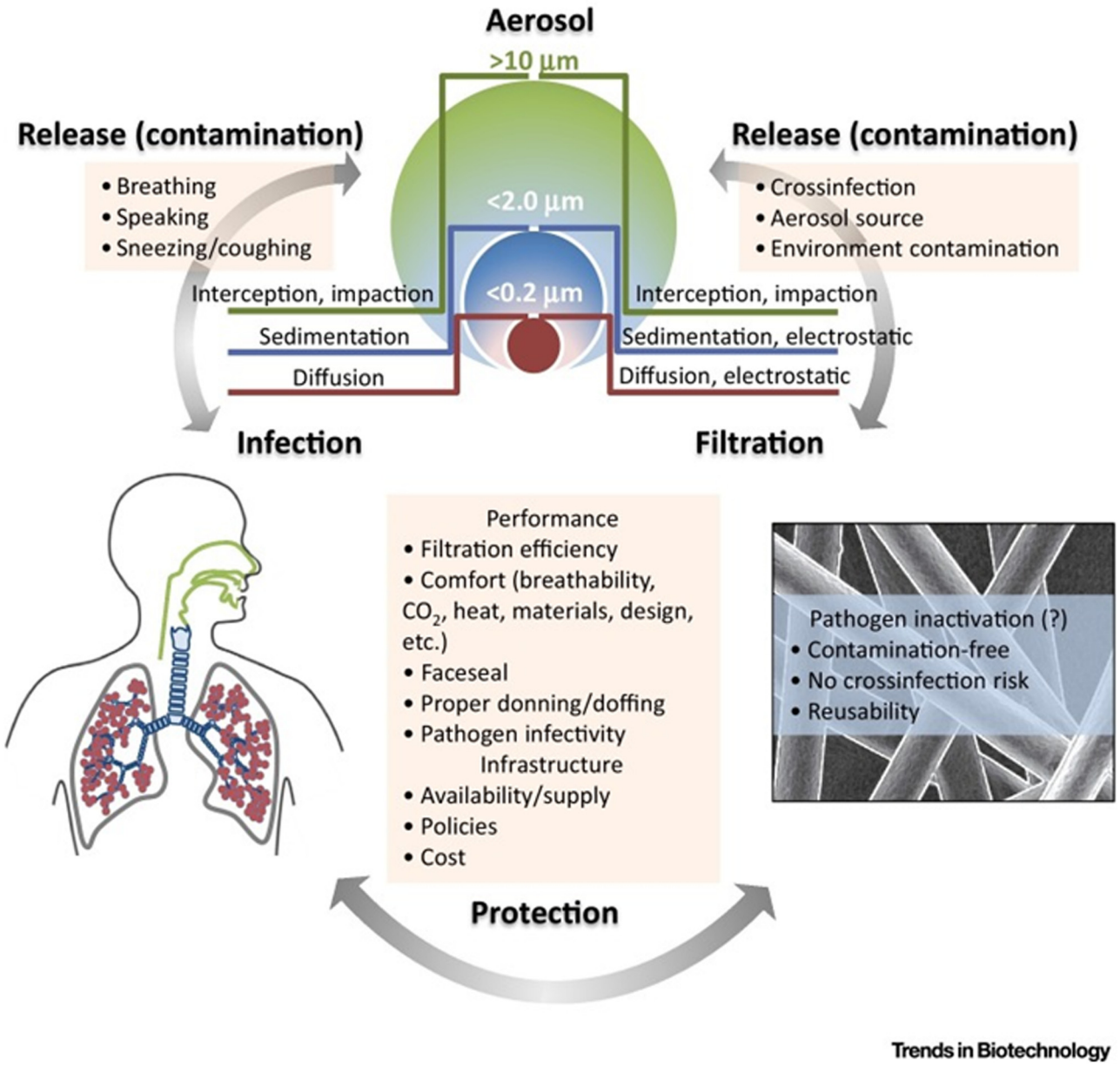


**Figure 8:** Respiratory protection and airborne transmission intertwine system [29]. Reproduced with permission from ref. [29].

composed of naturally occurring inflammatory compounds and fat as a core, and vitamin E as an envelope, were developed to reduce hyperinflammation [41]. Arcturus Therapeutic in San Diego as well as Duke-NUS Medical School and a research-intensive medical school in Singapore collaborated to develop an mRNA-based vaccine against the coronavirus disease [40]. Lipid-based NPs encapsulate the mRNA to trigger rapid and prolonged antigen expression within host cells, resulting in protective immunity against infectious pathogens. Scientists at the University of Waterloo, Canada, proposed the delivery of therapeutic DNA to target tissues through the nasal spray to produce antigenic proteins for the SARS-CoV-2 (virus-like particles), which are harmless but produce an immunogenic response against the virus [40]. Respilon Group incorporated copper oxide into nanofibers to produce a mask that can trap and destroy the virus [40]. The Advanced Institute of Science and Technology (KAIST) in Korea, developed nanofiber-based nanofilters that maintain their filtering efficiency even after 20 washes with ethanol. An MIT spin out start-up company has developed strips, based on AU NPs, which could give a color reaction within 20 min of the start of the test. The strip is coated with antibodies that bind to the specific viral protein of the SARS-CoV-2 and the second

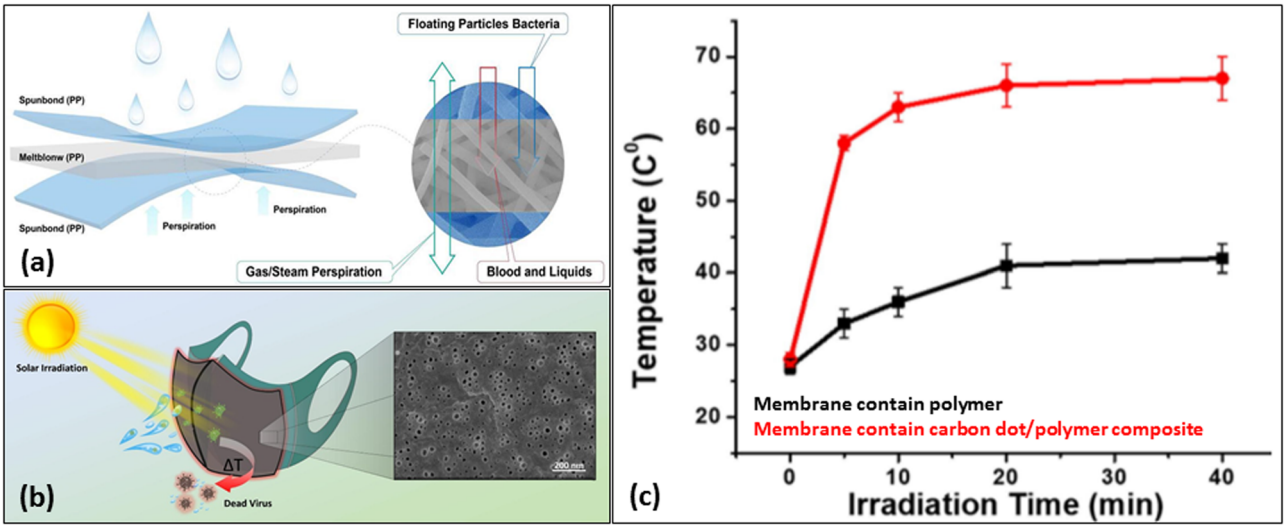


**Figure 9:** (a) Schematic diagram of facemasks [29]; (b) schematic structure of self-sterilization facemasks containing carbon dot/polymer composite [33]; and (c) temperatures of the polymer-containing membrane and the membrane comprising carbon dot/polymer composite at different irradiation times [32]. Reproduced with permission from ref. [32].

antibody is attached to AU NPs. The patient's sample is placed on the strip, and if it has a viral antigen that binds to both these antibodies, a colored spot appears on the strip.

## 6 Safety of NPs

The unique characteristics of NPs, such as their optical, fluorescent, and magnetic properties, impart new device capabilities for disease diagnosis. With the advancement in nanotechnology, including nanomedicine and nanotheranostics, assessment of its adverse effects and toxicities is becoming more important. The mechanisms by which NPs exhibit toxicity include the following:

(i) The direct association of NPs with an organism's cell surface causing damage to the cell membrane.
(ii) Dissolution of the material by releasing toxic ions that affect the organism by impairing through direct interaction with a cell's DNA or important enzyme functions.
(iii) The generation of ROS and subsequent oxidative stress in an organism, which can also damage an organism's genetic material or important enzymes [42].

NPs can generate oxidative stress and inflammation in various tissues, which damage the biological molecules (*e.g.*, proteins, lipids, and DNA) of the cell [40]. The most important organs in our study are the liver, lungs, spleen, kidneys, and heart. Hence, NPs may cause

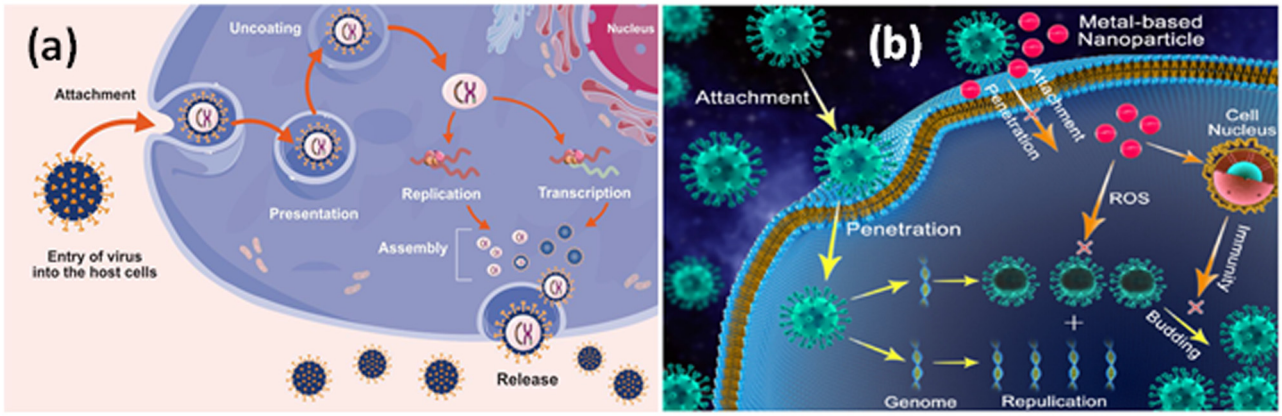


**Figure 10:** (a) Mechanism of entry of the virus into the host cells [34] and (b) schematic diagram of an antiviral mechanism of metal-based NPs [30]. Reproduced with permission from ref. [30] and [34], respectively.

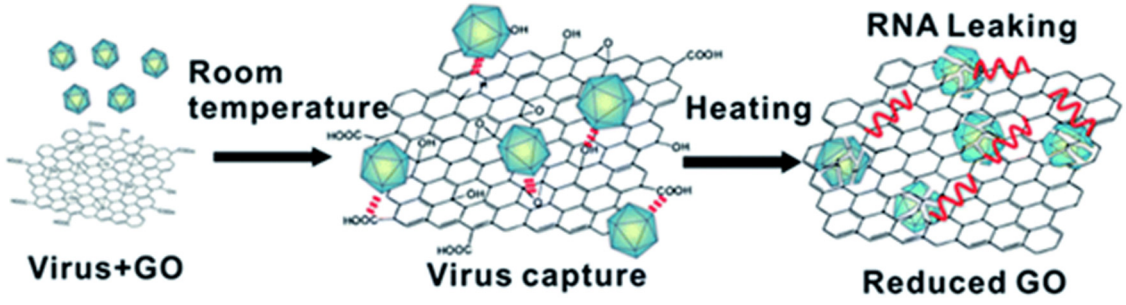


**Figure 11:** Schematic diagram of the antiviral mechanism of carbon-based NPs, such as graphene or graphene oxide [36]. Reproduced with permission from ref. [36].

hepatotoxicity, nephrotoxicity, cardiotoxicity, immunotoxicity, and genotoxicity [40]. Additionally, Au NPs can undergo cyanidation and oxidation in the body and generate toxic products. These products are heavily absorbed in the kidneys and may cause nephrotoxicity [43]. Sun *et al.* [44,45] studied the shape-dependent toxicity of Au NPs and found that rod-shaped Au NPs are more toxic than cube-shaped Au NPs. The spherical Au NPs exhibited the best biocompatibility [44,45]. Similar to the biodistribution of other nanomedicines, traces of Au NPs can be found in the blood, brain, lungs, heart, kidneys, liver, and spleen [46,47]. The unprotected QDs showed the release of toxic cadmium upon exposure to ultraviolet radiation [45]. Yoisungnern *et al.* [48] reported that Ag NPs are a potential cytotoxic agent for sperm cells and exert adverse effects, possibly *via* the induction of oxidative stress. Copper oxide NPs have shown the highest level of DNA damage and cytotoxicity *in vitro* [49]. In general, carbon-based nanostructures are biocompatible but metal-based impurities and the agglomeration state are considered to be the major factors responsible for the toxicity of CNTs [46,47]. Furthermore, long-term retention of long CNTs leads to severe inflammation and progressive fibrosis in mice [50]. Figure 12 shows the histological examination of chest wall samples from mice injected with NTtang1 (CNTs measuring 15–20 μm in diameter and 1–5 μm in length) and NTlong2 (CNTs measuring 20–100 μm in diameter and 56 μm in length) at day 1 and day 7 following injection [50]. It can be seen from the figure that the aggregates of inflammatory cells are present in both NTtang1 and NTlong2 samples at day 1. However, they were present only in NTlong2 samples at day 7. The

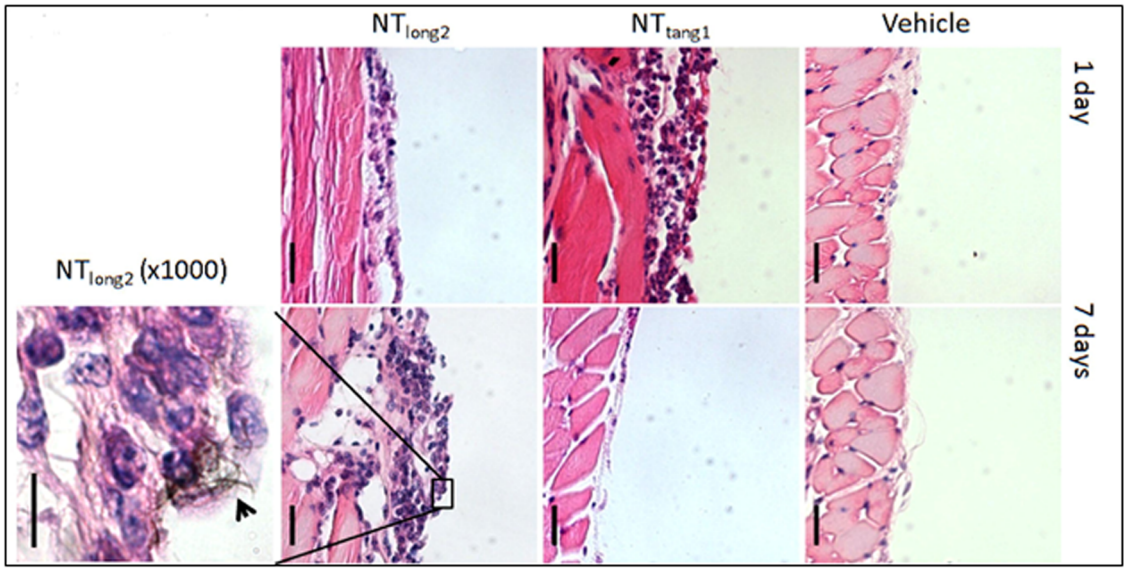


**Figure 12:** Histological examination of chest wall samples from mice injected with NTtang1 and NTlong2 at day 1 and day 7 following injection. The diameters of NTtang1 and NTlong2 are approximately 15–20 and 20–100 μm, respectively; while the length of NTtang1 and NTlong2 are approximately 1–5 and 56 μm, respectively. The arrowhead indicates long CNT aggregates in ×100 magnification of NTlong2 (7-day sample). Scale bar = 20 μm [50]. Reproduced with permission from ref. [50].

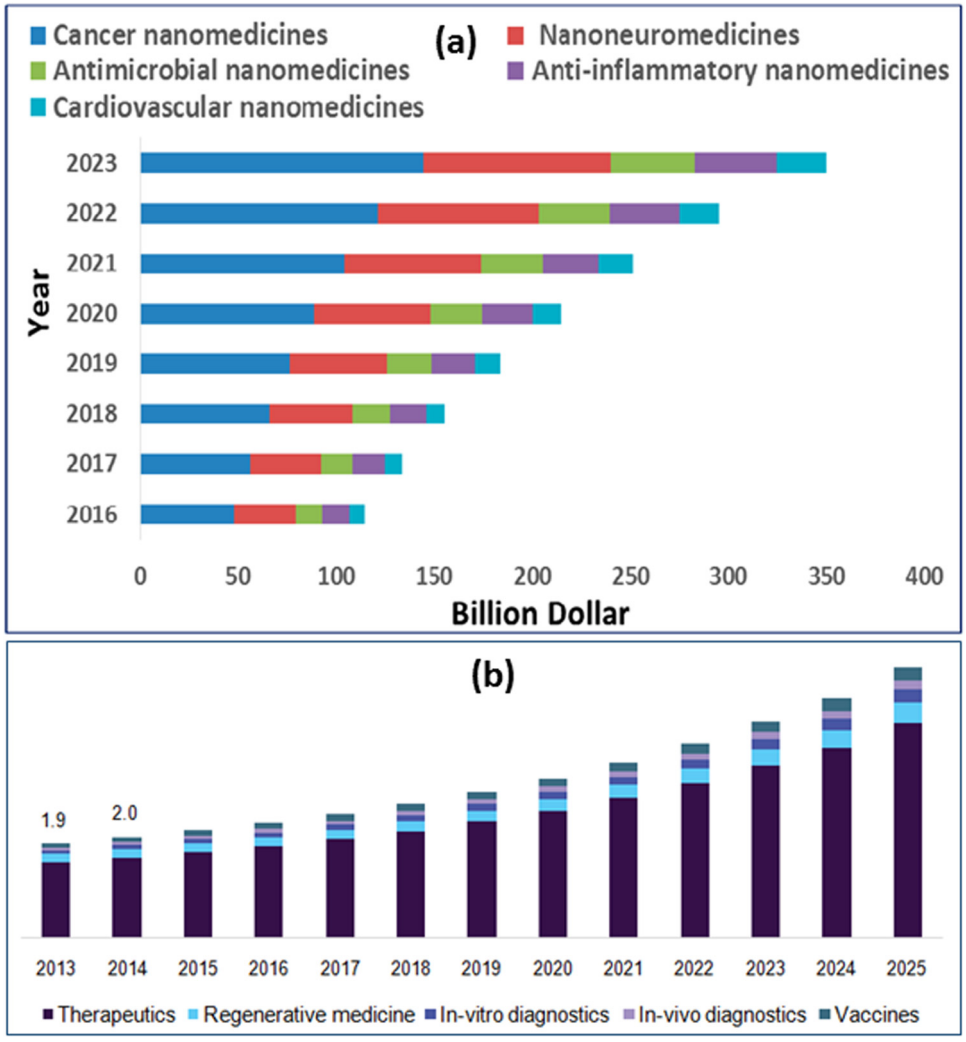


**Figure 13:** (a) The global nanomedicine market revenue trends [53] and (b) US nanomedicine market size for by-products [54]. Reproduced with permission from ref. [53].

authors have concluded that short nanofibers either resolve no inflammation or modestly resolve inflammation, with no parietal pleural pathological features. Furthermore, surface-modified CNTs create more toxic effects than pristine CNTs [51]. The toxicity of NPs depends on the dose and duration of exposure. Understanding the mechanism of toxicity will guide the redesign strategies based on the major modes of toxicity.

## 7 Future scopes

In many ways, nanotechnology can shape the future of biomedical engineering and medical treatments. For instance, the FDA-approved "pill cam" technology can be expanded to monitor when medication is taken, based on the response of the body, and may also assist with aspects such as the adjustment of the prescribed drug dosage [52]. Globally, researchers are working on controlled drug release to target cancer cells as an alternative to chemotherapy [52]. The global nanomedicine market revenue trends illustrated in Figure 13(a) indicate that the market is growing [53]. The US nanomedicine market size for by-products (including diagnostics, therapeutics, and vaccines) is also showing a growing trend, as depicted in Figure 13(b) [54]. In order to produce the vaccine, antigens can either be conjugated to the surface of the nanoparticles or encapsulated in the core of the particles [55]. The potential pipeline of nanotechnology-based products and associated nanotechnology-based devices is anticipated to drive the market with potential avenues for growth. The presence of approximately 40% of the products in phase II of clinical development is anticipated to

result in a number of key commercialization opportunities over the coming decade.

Nanoscale sensors embedded directly into the implant or surrounding area can reduce the risk of post-surgery inflammation and infection through early detection [52]. Based on the advancements made in understanding type 2 diabetes, the possibility of devising a smart therapy for the reversal of type 2 diabetes in the near future can save many lives [45]. The correlation and reproducibility between the toxicity testing methods, and adequate knowledge of *in vivo* and *in vitro* findings, are necessary to implement nanotechnology in biomedical applications. Biopharmaceutical and toxicity regulation agencies are moving forward rapidly to new metrics to keep pace with the changing paradigms introduced by nanomedicines. Through the realization of the challenges of the recent coronavirus disease in the health care system, nanotechnology can ameliorate the breathability, antiviral capabilities, and entrapping potential of personal protective equipment.

# 8 Conclusion

In this article, we have presented the recent developments in a variety of nanotechnology-based solutions for emerging biomedical engineering fields. A number of applications, namely pharmaceutical engineering (*e.g.*, drug engineering and targeted drug delivery), tissue engineering (*e.g.*, creating artificial organs), genetic engineering (*e.g.*, gene slicing and modification/manipulation), medical devices, imaging, and antiviral use, which have been reported in the recent literature, were discussed. However, the effectiveness of any such application is determined through clinical evaluation, its compliance with performance standards, or demonstrations of substantial equivalence with an already marketed device. Currently, a number of nanomedicines are undergoing phase II of clinical trials for practical applications. Moreover, the current challenges associated with the use of nanomaterials in biomedical fields were discussed, and suitable directions for future research were proposed. Despite the fact that recent research showed superior performance of stimuli-responsive electrospun fibers for local cancer therapy, several issues must be resolved before clinical trials. A deeper understanding is required of the inflammatory and immune response, consequence of reaction at the interface of tissue/blood and the fibers, concentration of drug and the consequence of burst release, and so on. In summary, the authors believe that the various research contributions summarized in this article will help to accelerate the application of nanotechnology in different challenging biomedical engineering fields.

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