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Current progress of nanotechnology in medicine: application in drug delivery, diagnostic, tissue engineering, and nanobots

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ABSTRACT

The integration of nanotechnology into medicine has resulted in rapid advancements, and revolutionized in the diagnosis, treatment and management of diseases. Through complex manipulation of materials at the nanoscale, nanotechnology has ushered in a new era of precision medicine. Their benefits include increasingly in earlier and more precise diagnosis, as well as in optimal treatment of diseases. This review explores the applications of nanotechnology in medicine, with a focus on drug delivery, diagnostic tools, tissue engineering, and the world of futuristic nanorobots. By investigating the complex workings of nanotechnology in medicine, we aim to highlight its innovative applications, the benefits it brings to diagnosis, and treatment, and its potential to reshape the landscape of contemporary medical practice.

ABSTRAK

Integrasi nanoteknologi ke dalam pengobatan telah menghasilkan kemajuan pesat dan merevolusi diagnosis, pengobatan, dan pengelolaan suatu penyakit. Melalui manipulasi material yang kompleks pada skala nano, nanoteknologi telah mengantarkan era baru pengobatan presisi. Manfaatnya antara lain dalam diagnosis awal yang lebih tepat, dan pengobatan penyakit yang optimal. Tinjauan ini mengeksplorasi penerapan nanoteknologi dalam kedokteran, dengan fokus pada penghantaran obat, alat diagnostik, rekayasa jaringan, dan dunia robot nano masa depan. Dengan menyelidiki cara kerja nanoteknologi yang kompleks dalam bidang kedokteran, tinjauan ini bertujuan untuk menyoroti penerapan inovatifnya, manfaat diagnosis, dan pengobatan, serta potensinya untuk membentuk kembali lanskap praktik medis kontemporer.

INTRODUCTION

Advances in technology have ushered the healthcare system into a new era called precision medicine, emphasizing personalized approaches based on individual genetic characteristics, lifestyle, and environment. This extends beyond treatment to include precise diagnostic methods. The focus is on molecular units, exploring the microscopic realm with tools like electron microscopes, building on humanity's historical fascination with the smaller entities of the world. Highlighting its innovative applications, benefits, and potential to reshape the landscape of modern medicine.[1] This continuous development has enabled scientists and researchers to investigate images of molecules and their bonds along with their properties, ultimately leading to the field of study known as nanotechnology.[2]

Nanotechnology refers to the study and application of small technology at the scale of 1 to 100 nm.[3] The small size of nanotechnology can be used in complex human tissue structures and yield various purposes, such as targeted molecular

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delivery, early and improved disease diagnosis, personalized medicine, and enhanced product efficacy. From those benefit, nanotechnology become the source of innovation in medical practice. In the other hand, researchers still have a long way to pave the breakthrough for many medical obstacles. Despite having little evidence of long-term side effects, nanotechnology has been at the forefront of many studies and is being extensively investigated.

This review delves into the application of nanotechnology in medicine, such as drug delivery, diagnostic tools, tissue engineering, and nanobots. Highlighting its innovative applications, benefits, and potential to reshape the landscape of modern medicine.

DISCUSSION

Nanotechnology in drug delivery system

Therapy typically involves administering pharmaceutical compounds to a specific target site to achieve a desired therapeutic effect(s). In drug design, absorption and distribution closely impact the efficacy of drug delivery to the target site.[4] Conventional drug delivery system has a disadvantage in which it takes longer to reach targeted areas thereby reducing the effectiveness of the drug.[2] Therefore, optimizing the drug delivery of a pharmaceutical compound may maximize therapeutic efficacy and minimize its side effects.[4] The solution to optimizing therapeutic efficacy, such as reduced side effects, and precisely targeted sites lies in the groundbreaking innovation of nanotechnology.

Nanotechnology in the field of pharmacology provides an exceptional toolkit for scientists and researchers to design pharmaceutical drugs with new devices, materials, and structures.[5,6] The use of nanotechnology hopes to address the issue of current drug delivery such as limited drug solubility, bioavailability, poor targeting, and off-target effects.[4,5] Many therapeutic compounds experience poor water solubility, hence obstructing their absorption and effectiveness in the body. Many studies have investigated the improvement in solubility and bioavailability of nanotechnology.[7,8]

Currently, the administration of pharmaceutical compounds is determined by their processes of adsorption, distribution, metabolism, and elimination. Frequently, drug dosages are increased in order to address issues related to low bioavailability, metabolism, elimination, or to achieve the intended therapeutic outcomes. Nevertheless, it is important to note that administering higher doses of medication or treatment may result in adverse consequences for healthy cells, which inadvertently become collateral damage for therapeutic interventions. Therefore, enhancing the solubility of medications and decreasing doses can contribute to the enhancement of their efficacy by selectively targeting specific cells without disrupting healthy cells. The enhancement of drug efficacy through the utilization of nanotechnology extends beyond the improvement of drug solubility, encompassing the capacity to control and delay drug release.

Conventional drugs may exhibit rapid release, leading to fluctuations in drug levels and reduced efficacy. Various nanoparticles can be designed to release drugs in a controlled manner over time, ensuring a steady supply of the therapeutic agent and potentially reducing the frequency of dosing. This controlled release not only improves patient compliance but also optimizes the therapeutic effect.[9] Nanoparticles refer to materials that have unique optical, electrical, and/or magnetic properties at the nanoscale. These particles are often used in medicine, specifically in pharmaceuticals to help optimize drug design. Their small size and unique properties make them into a pliant material to design various ways to reach their target.[4]

Several nanoparticles have been studied and approved for clinical use, among those are 1) micelles, 2) liposomes, 3) dendrimers, 4) carbon nanotubes,

5) metallic nanoparticles, 6) quantum dots, 7) magnetic nanoparticles, and 8) nanogels.

Micelles

Micelles are surfactant molecules that possess amphiphilic properties. These unique properties are the result of the structure of its particles that are made up of a hydrophobic core and a hydrophilic end that self-assembles into spherical vesicles containing a hydrophobic drug. The hydrophobic core of this particle can be bound to a hydrophobic drug to accommodate the compound at the core of the assembled polymer, even under aqueous conditions. The use of micelles provides increased solubility, enhancement of drug stability and effectiveness. Furthermore, micelles provide up-scaled feasibility of production that is less costly, complex, and time consuming in manufacturing, compared to other nano particles. This in turn benefits to increase therapeutic efficacy and bioavailability; however, it does come with its challenges, such as poor stability of the polymeric micelles and low drug loading. Polymeric micelles are investigated for their use in the pharmacotherapy of cancer, as it provides the potential for a safe and effective carrier. The application of polymeric micelles is not merely reserved for drug delivery but also imaging agents, contrast agents, and therapeutic agents.[6,10]

A good example can be demonstrated in the use of micelles in the paclitaxel delivery system for the treatment of cancer. Several anticancer, including paclitaxel, are hydrophobic with limited solubility, and low bioavailability. Therefore, these anticancer drugs are only effective against cancer cells at higher dosages. Due to low selectivity and sensitivity, these anticancer cause serious adverse reactions. The use of micelles-coated paclitaxel promotes solubility, bioavailability, and controlled release. Notably, it also facilitates selective targeting through higher permeability and retention, enabling the preferential accumulation of paclitaxel in specific tissues.[11,12]

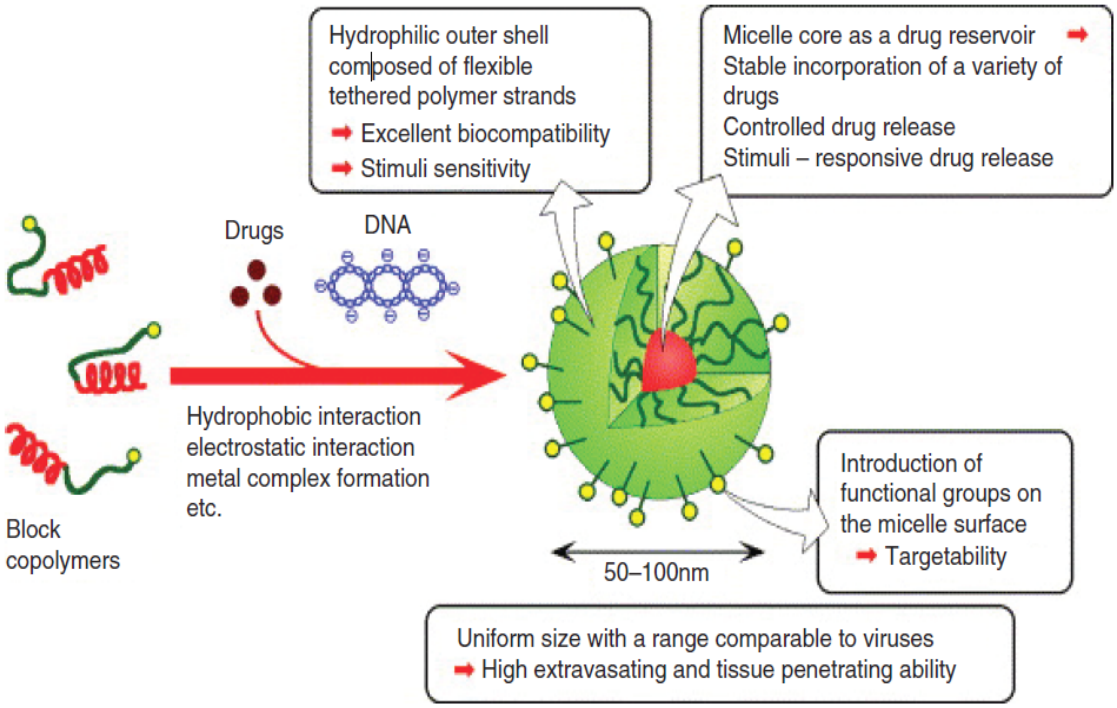

FIGURE 1. Polymeric micelles as nanocarriers for drug delivery and therapeutic agents.[10]

Liposomes

Liposomes are spherical vesicles formed by a self-assembled phospholipid bilayer enclosing an aqueous core. Due to the nature of their layers, liposomes can load and deliver molecules with different solubility. Hydrophilic molecules are enclosed in the aqueous core of the structure, while hydrophobic molecules are secured between the lipid bilayer, and amphiphilic molecules reside at the water/lipid bilayer interface (FIGURE 2).[15] Liposomes are considered a compelling breakthrough for the drug delivery system due to their structural versatility, biocompatibility, biodegradability, non-toxic, and non-immunogenic properties. The versatility of liposomes accounts for their modifiable characteristics, the surface of liposomes are adept to be integrated with polymers, antibodies, protein, and various macromolecular compounds.[6] Their bilayer structural properties prove to mimic the natural cell membrane, this allows for a liposome and mammalian cell interaction granting an efficient cellular uptake. Furthermore, their additional advantages include the ability to load larger molecules, ability for self-assembly, their vast range of physicochemical and biophysical properties, along with their vitality to modify biological characteristics.[13]

The liposome was used in the doxorubicin delivery system for the treatment of breast cancer. Doxorubicin is a highly potent cytotoxic compound. Prolonged use of doxorubicin is associated with dose-dependent cardiomyopathy, characterized by irreversible damage to the heart muscle, as well as significant cardiac toxicity and potential liver impairment. The adverse effects of liposomes pose a hindrance to their utilization in clinical practice; nonetheless, the clinical application of liposomes has proven to be beneficial in mitigating the drug's side effects. Currently, there exist several liposomal anticancer drugs that have received approval from the Food and Drug Administration (FDA) USA. Since the mid-1990s, a liposomal formulation of doxorubicin known as Doxil®/Caelyx® has been commercially available for the treatment of several types of cancer. The liposomal formulation comprises liposomes coated with polyethylene glycol (PEG), which facilitates the targeted delivery of doxorubicin to tumor locations. Currently, liposomal doxorubicin is being used for the therapeutic management of AIDS-associated Kaposi's sarcoma, metastatic breast cancer, advanced ovarian cancer, and relapsed or refractory multiple myelomas.[14]

Dendrimers

Dendrimers derives from the Greek word "dendron" meaning tree or branch. Dendrimers are considered to be macromolecules with branched repeating units spouting from the central core and ends with interchangeable exterior functional groups. These functional groups could be anionic, neutral, or cationic terminals, thus giving it the freedom to modify the whole structure, and with that the chemical or physical properties of the dendrimers. The generation of a dendrimer refers to the number of recurrent branching series created during its creation (FIGURE 3.)[16] Therapeutic compounds can be loaded into the internal structure of the dendrimers, they are also able to be attached to the surface of the structure. These highly modifiable particles create dendrimers to be highly bioavailable and biodegradable. With the interchangeable surface properties of this highly adaptable particle, size, solubility, surface charge, and function can be controlled. Dendrimers have been used in many applications, one of which is drug delivery systems for cancer or as a delivery cargo for nucleic acid. However, despite the benefits that dendrimers offer, some challenges have yet to be solved. The size and surface chemistry of dendrimers correlate to the toxicity, pharmacokinetics, biodistribution, and clearance from the body.[6,17,18]

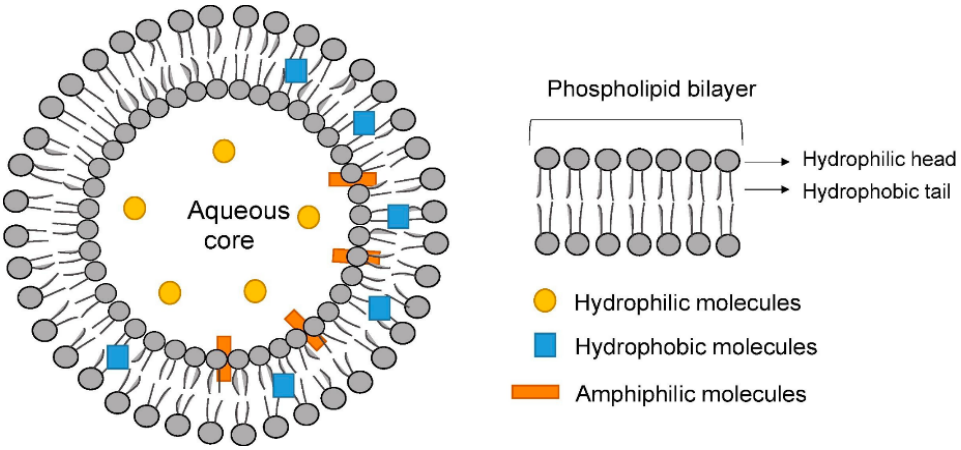

FIGURE 2. The general structure of liposomes.[15]

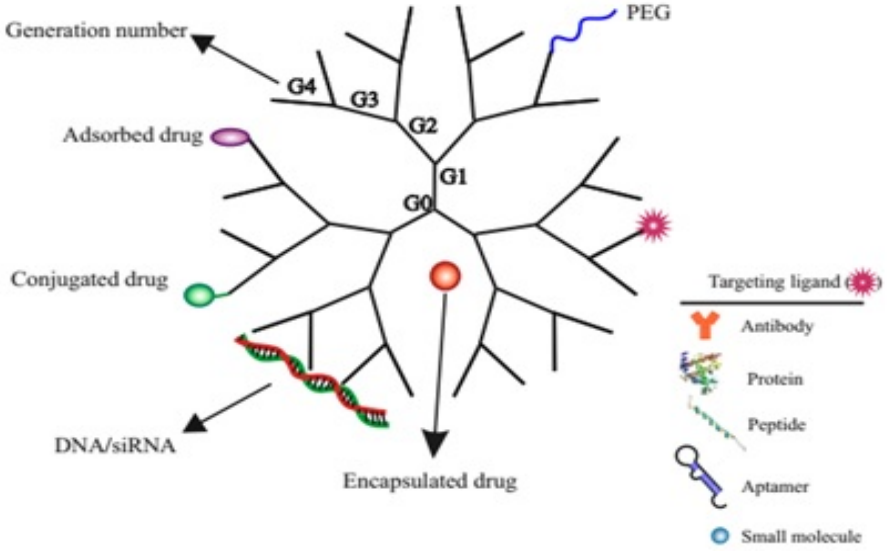

FIGURE 3. The general structure of dendrimer and different types of targeting ligands.[16]

A dendrimer specifically designed to target bone tissue was developed as a delivery system of methotrexate to treat bone metastases. Conventional formulation of methotrexate have limitations in terms of its distribution in the bone, mostly due to the presence of the blood-bone barrier. This barrier restricts the passage of sizable foreign substances to the surface of the bone. The researchers employed alendronate (ALN), a bone-targeting agent, that was chemically linked to a PEG-conjugated polyamidoamine (PAMAM) dendrimer (PEG-PAMAM-ALN). The utilization of a bone-targeting dendrimer facilitates the selective targeting of certain cells, hence restricting the non-specific dissemination of the anticancer.[19]

Carbon nanotubes

Carbon nanotubes are a part of the nanoparticles that can be applied in the drug delivery systems. Carbon nanotubes are structured as cylindrical molecules that are produced by rolled-up sheets of single-layer carbon atoms (graphene).

The nature of the high external surface area of carbon nanotubes makes its ability to hold relatively large capacities for various compounds as drug carriers. Many promising properties hold this particular particle in high regard, not only its high surface area, but the needle-like structure, strength, malleable interaction with cargo, high loading capacity, chemical and physical properties, stability, biocompatibility, and precision. However, they do lack in biodegradability and toxicity. Toxicity concerns mainly ascribed to their hydrophobic and shape patterns and resulting in inflammation and alteration of the cellular redox state. Despite the limitations they possess, carbon nanotubes show an excellent application in medicine specifically in drug delivery systems, gene delivery and therapy, vaccine delivery, and many more applications yet to be discussed.[6,20]

A study employed a hybrid material consisting of carbon nanotubes and chitosan as a carrier with pH-sensitivity properties for the methotrexate delivery system for the treatment of lung cancers. Chitosan has demonstrated notable attributes in terms of biocompatibility, chemical adaptability, and its affinity for tumor tissue. Additionally, it possesses favorable characteristics for nanoparticle delivery systems, allowing for convenient administration by multiple routes, particularly the pulmonary route. Chitosan exhibits hydrophilic and cationic properties, making it a promising candidate for surface functionalization of carboxylated carbon nanotubes. This functionalization process results in the creation of stable nanocarriers in aqueous solutions. Additionally, because it is unable to dissolve at pH 7.4 (the normal conditions of the body) but can dissolve in environments with a pH below 6.5 (the environment of a tumor), it may respond to changes in pH. This means that the carrier can hold onto the payload until it reaches the desired location, with very little release happening beforehand.[21]

Metallic nanoparticles

Metallic nanoparticles are made up of iron oxide and gold nanoparticles. Iron oxide nanoparticles are composed of a magnetic core with hydrophilic polymers, while gold nanoparticles are composed of a gold atom core that is surrounded by negative reactive groups on the surface. The surface of this polymer of this sort can be modified to fit the target site.[6]

Metal nanoparticles demonstrate the capacity to inhibit viral adhesion to the surface of host cells, hence hindering viral internalization and inactivating the virus. Various types of silver, zinc, and gold nanoparticles have demonstrated noteworthy therapeutic efficacy against several viral infections, including herpes simplex virus (HSV), influenza A, HIV, human parainfluenza 3 (HPIV-3), zika virus, monkeypox virus, and gastroenteritis virus. Silver nanoparticles (AgNPs) have the ability to degrade virion proteins, hence inhibiting primary infection caused by Kaposi's sarcoma-associated herpesvirus. The interaction between AgNPs and either the nucleus or the membrane hinders the ability of the virion to connect to the host. Metal nanoparticles are also currently being utilized in the field of vaccine production. The small dimensions of these particles result in a high surface area to volume ratio, which in turn enhances their potency and tunability. Consequently, metal NPs hold significant potential as platforms for the advancement of future vaccines. At present, there are 26 ongoing clinical trials for nanoparticle-based vaccines.[22]

Quantum dots

Quantum dots (QDs), alternatively referred to as semiconductor nanocrystals, are a type of nanoparticle characterized by a shell-core structure consisting of elements from the II-VI or III-V groups of the periodic table. Quantum dots have demonstrated

promise in various clinical domains, including drug delivery system, live imaging, and medical diagnosis. It possesses intriguing characteristics such as small particle size, customizable composition and properties, higher quantum yield, high brightness, and intermittent light emissions, rendering them very flexible for a wide range of applications. Quantum dots have been employed in the fields of drug delivery and cellular imaging due to their unique optical and electrical characteristics, as well as their size.[6,23] Despite the promising attributes exhibited by QDs, their practical applications remain distant, with only a limited number of ongoing clinical trials. As of 2021, there exists a limited quantity of clinical trials in phase I and II that focus on the utilization of QDs for the purposes of detection and diagnosis. Despite being distant from current reality, QDs hold significant potential to alter the field of biomedicine.[24] However, *in vitro* research has found that the use of QDs in the delivery of methotrexate for a selective pH delivery affectively terminated cancer cells.[25]

Magnetic nanoparticles

Magnetic nanoparticles are made up of metals such as iron, cobalt, nickel, or other metal oxides or mixed metals. They possess super-paramagnetic momentum, magnetic resonance, and effective biological interactions between molecules and cells. They have the potential to revolutionize the study to improve many aspects of medicine, including the drug delivery system. The magnetic force of this certain nanoparticle carrier led to the specific target binding of a drug utilizing magnetic absorption or strong interaction between the ligand and the receptor.[26]

A study was undertaken to solve the problem of early release of drugs from carriers. The study focused on the issue of initial burst release in drug delivery of doxorubicin. To tackle this, a triple-sensitive nanogel hydrogel composite was created. The researchers introduced magnetic nanoparticles into a polymer called poly(N-isopropylacrylamide)-co-((2-dimethylaminoethyl) methacrylate) (PNIPAM-co-PDMA), which was then attached to the biocompatible polymer sodium alginate. Upon arriving at the targeted location, the compound was subjected to a stagnant magnetic field. Subsequently, an alternating magnetic field was applied to release the doxorubicin molecules from its carriers. Once the compound has been released, the carrier can be retrieved using a static magnetic field.[27]

Nanogels

Nanogels refer to the nanosized network of crosslinked hydrogel nanoparticles. Nanogels commonly consist of polymeric nanoparticles, lipid nanoparticles, and inorganic nanoparticles. They have a very promising potential to be applied in drug delivery and tissue engineering. Due to the constituents that make up the polymer, nanogel possesses the properties of not only nanoparticles but also hydrogels. These crosslinked hydrogel nanoparticles have a three-dimensional network structure, allowing them to absorb and retain a significant amount of water or biological fluids within their porous structure. This unique property makes them particularly suitable for encapsulating and delivering therapeutic agents. The structure of nanogels also benefits in high drug loading capacity, the ability for a controlled release, ability to hold multiple therapeutic compounds, stability of compounds, as well as targeted deliveries using targeting ligands.[28,29]

Nanogels have been used in the combination of hydrogels as wound healing and delivery of antibiotics. Interestingly, nanogels are capable to be used in the delivery of insulin as well. In a study, insulin was incorporated into a pH sensitive methyl methacrylate (MMA)/

itaconic acid (IA) nanogels to combat the incapability of insulin administered via oral.[30]

Nanotechnology in diagnostic

Recently, many kinds of nanomaterials are used for the development of nanotechnology-based rapid tests, such as metallic nanoparticles, QDs, silica nanospheres, magnetic nanoparticles, carbon nanotubes (CNTs), silicon nanowires (SiNWs), nanopores, graphene, nanostructured surfaces, and metal films. Nanomaterials have a major contribution in diagnosing diseases accurately and precisely due to their unique physicochemical and optical properties.[31] There are many diseases that can cause epidemics and pandemics with high morbidity and mortality rates, so the development of nanotechnology-based diagnostic methods is very important. Nanodiagnostics is a field that analyzes single molecule systems and platforms for use in clinical diagnostics, of course by utilizing the nanoscale.[32] In fact, nanodiagnostics is the best choice for diagnosing infectious diseases because of its advantages such as fast detection, high sensitivity, and can be tested simultaneously on the spot. However, the implementation of affordable/cheap diagnosis point-of-care (POC) development in developing countries is still constrained by many effectiveness challenges such as single-use, easy-to-use, portable devices, mass production and quality control.[33] Measurement of changes in glucose levels using nanofiber fluorescent nano-optodes was carried out by Balaconis *et al.*[34] which is measured by monitoring changes in the optical signal. The glucose concentration changes and affects the competitive binding between the hydrophobic boronic acid recognition molecule, a chromophore and glucose. Nano-optodes have proven to be very sensitive, because they can detect small molecules, so they are very functional.[34]

In the diagnosis and treatment of cancer, nanotechnology has been widely used in detecting cancer biomarkers, including cancer-associated proteins, circulating tumor DNA (ctDNA), circulating tumor cells (CTC), and exosomes.[35–38] Nanomaterials/nanoparticles can improve biosensors and increase interaction ratios with markers which make them more sensitive to the detection of certain biomarkers.[39] The three most frequent nanoparticle probes employed in cancer diagnosis are QDs, gold nanoparticles (AuNPs), and polymer dots (PDs).[40] Among them are QDs with specific interactions of antigens and antibodies that will be converted into measurable signals, antibody fragments, or aptamers that have been used for various types of protein detection for colorectal cancer, liver cancer, prostate cancer and ovarian cancer.[41]

In the midst of the COVID-19 pandemic that occurred several years ago, nanomaterials played a major role in assisting the development of biosensors for rapid tests. The nature of transmission and the relatively fast spread of COVID-19 and the potential for it in the future. There is a huge unmet need in the clinical field in providing test platforms that can be mass-produced and inexpensive (low cost), laboratory-based tests, and direct tests at screening points.[42] For example, a protein-SWNT nanosensor that can bind to the receptor binding domain (RBD) domain in SARS-CoV-2, which can detect up to 12.6 nM spike protein with a reading range of up to 90 min.[43] Then, Cho *et al.* developed corona phase molecular recognition (CoPhMoRe) using a layer of amphiphilic polymer bound on a carbon nanotube. This nanotube layer will later bind to the nucleocapsid or SARS-CoV-2 spike protein and will fluoresce to produce an optical curve (reading). This is based on changes in the SWNT and the results can detect up to a concentration limit of 2.4 pg/mL protein in a relatively fast time of 5 min.[44]

Nanotechnology has greatly

influenced advances in imaging, early detection, diagnosis and prognosis of diseases by enhancing clinically relevant technologies. The unique biophysical properties of nanoparticles enable contrast enhancement to enhance biomedical imaging while our ability to manipulate nanoparticles for molecular level specificity enables tissue-specific diagnosis. This nanotechnology has been used in various tools such as magnetic resonance imaging (MRI), computed tomography (CT).[45]

Nanotechnology in tissue engineering

Hydrogels are a promising class of biomaterials for cartilage engineering and are characterized by bioactivity, degradability and elasticity as well as provide water content and mechanical support. However, the selection of suitable types of stem cells and hydrogels is difficult. Currently, various types of stem cells, such as embryonic stem cells (ESCs), mesenchymal stem cells (MSCs), induced pluripotent stem cells (iPSCs), and peripheral blood mononuclear cells (PBMSCs), and various types of hydrogels, including natural polymers, chemically modified natural polymers and synthetic polymers, have been explored based on their potential for cartilage tissue engineering.[46] Hydrogels are a series of ECM-mimicking polymeric biomaterials that have a high water content, porosity, biocompatibility and biodegradability. Hydrogels based on natural polymers can be divided into two groups: polysaccharides, such as hyaluronic acid (HA), chitosan, alginate and agarose; proteins, such as collagen, gelatin, and fibroin.[47] A variety of hydrogels based on synthetic polymers, such as polyethylene glycol (PEG), poly N,N-dimethylacrylamide (PDMAAm) and polyvinyl alcohol (PVA), have been reported.[48]

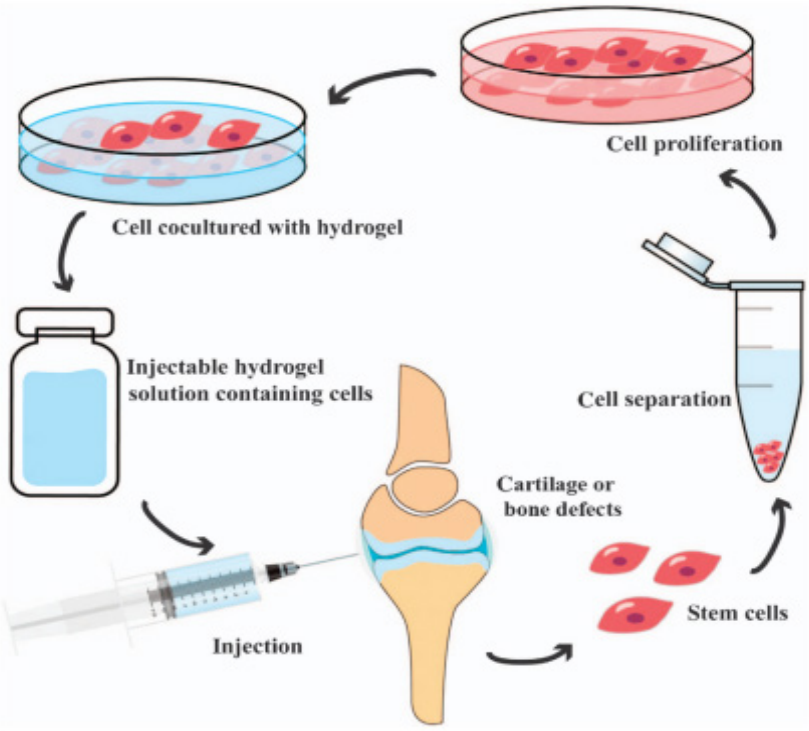

FIGURE 4. Schematic illustration of approaches to make injectable hydrogels for cartilage and bone tissue engineering applications.[46]

Hyaluronic acid is the most abundant native component in cartilage and an important component in organizing the cartilage ECM into resilient structures. It is able to stimulate the synthesis of chondroitin6-sulphate, collagen type II, glycosaminoglycan, hydroxyproline, and DNA in chondrocytes. Hence, an effort has been made to develop chondrocyte-laden HA hydrogels for the regeneration of cartilage tissues.[49] Advances use of stem cell-laden hydrogel biomaterials for engineering cartilage tissue. injectability, mechanical properties, outstanding biocompatibility, and proper biodegradability, stem cell-laden hydrogels have attracted increasing attention as promising tissue-engineered biomaterials for the repair of full thickness cartilage defects. Various types of stem cells encapsulated in hydrogels have been shown to be able to differentiate into chondrocytes via induction by growth factors and to promote chondrogenesis *in vitro* and *in vivo*. The combination of natural and synthetic polymer hydrogels takes advantages of both types of hydrogel, including their higher biocompatibility and cell viability, widely tunable mechanical properties and proper biodegradability for effective cartilage regeneration, which is promising for future studies and especially clinical trials.[50]

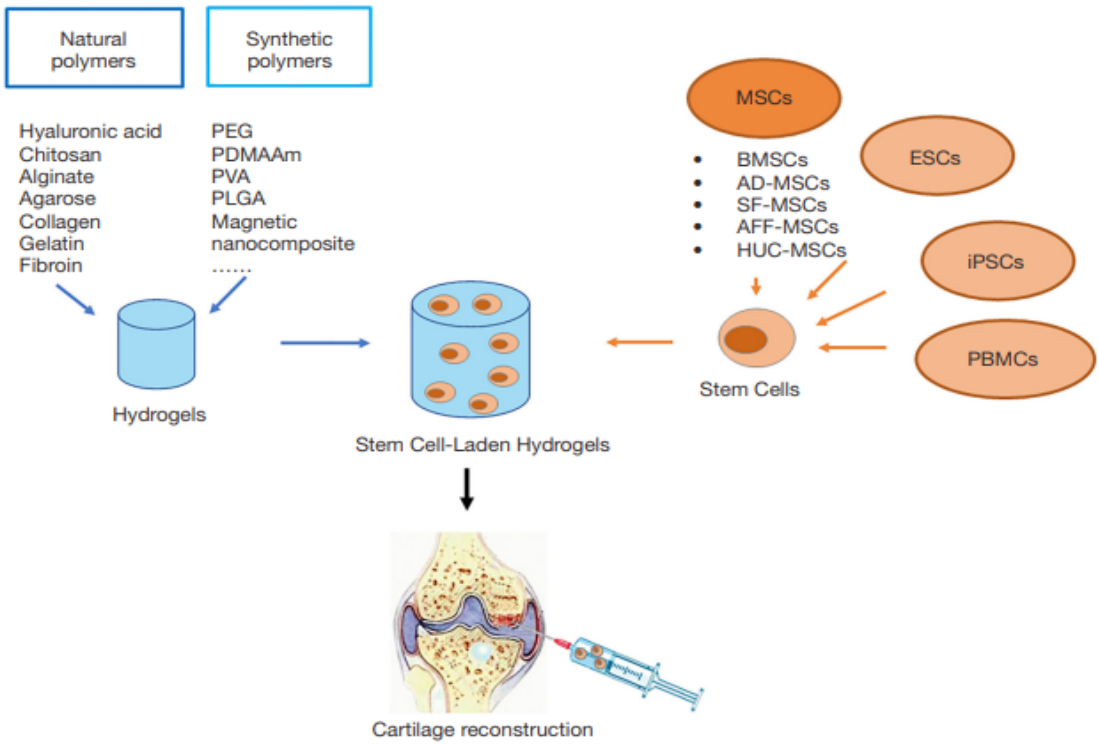

FIGURE 5. Types of the hydrogels and stem cells used for cartilage tissue engineering.[50]

Cell sheet technology involves the fabrication of a confluent monolayer of cells that can be harvested as a sheet. Various methods have been developed for cell sheet fabrication, including temperature-responsive polymer-based techniques, surface modification-based methods, and methods that do not require surface modifications. function can be improved through strategies such as electrical and mechanical stimulation, building 3D structures, and co-culturing with other cell species. One of the key challenges in tissue engineering is the development of perfusable blood vessels within cell-dense tissues to prevent necrosis and maintain cell viability. Different approaches, including *in vivo, ex vivo*, and *in vitro* methods, have been explored to introduce perfusable blood vessel structures into cell tissues fabricated using cell sheet technology. Development of cell sheet technology holds great potential for various bioengineering applications in tissue engineering.[51]

Cell sheet fabrication technologies can be classified into three categories: temperature-responsive polymer-based methods, other surface modification-based methods, and methods that do not use surface modifications.[52] Improving the function of cell sheets can be achieved various strategies, including electrical and mechanical stimulation, building 3D structures, and co-culturing with other cell species.[53] Electrical stimulation has been shown to enhance the functionality of muscle-type cell sheets. Mechanical stimulation, such as stretching or cyclic stretching, can also enhance the function of cell sheets. Building 3D structures using multiple layers of cell sheets is another strategy to enhance tissue function. Layering cell sheets can create complex tissue structures and promote tissue maturation. Strategies these aim to mimic the physiological environment and enhance the functionality of cell sheets for various tissue engineering applications.[54]

Clinical applications of regenerative technologies are already being used in practice, with tissue engineering-related products generating significant revenue. In 2017, Kim *et al.* reported 21 companies made an estimated $9 billion in sales of tissue engineering-related products, and the field is projected to continue growing in the coming years.[55] These technologies have the potential to address the growing clinical needs of an aging population, as well as provide solutions for major diseases such as Alzheimer's and certain cancers.[56] Bioprinting has the potential to revolutionize tissue engineering by enabling the fabrication of complex structures that incorporate important growth factors and multiple cell types.[57] Additionally, extracellular analog technology has been developed to measure cell-extracellular matrix dynamics and electrical stimulation has been explored as a tool for tissue engineering.[58] Innovations development in diabetes treatment, osteoarthritis approaches, and cardiovascular tissue replacement.[59]

Nanobots

Nanobots (nanorobots) are the study of robots on a scale of hundreds of nanometers or smaller, and can be controlled by a program.[60] Technologies that are incorporated into this field are known as nanotechnology.[61] The nanotechnology include in design, produce, program, and control a robot at the nanoscale; combining sensing, actuating, signaling, processing information, artificial intelligence, or creating a set of nanoscale actions.[61,62] The idea of developing nanorobots was first coined by Feynman and K Eric Drexler, up to now it's used in various field of human life, including in the medical field.[62]

The most common mechanism of nanobots in the medical field is for drug delivery, to the target location, which aims such as tissue repair, cleaning of blood and air passages, and transportation of drugs to infected cells.[61,63] For those

mechanism, nanobots must be small enough to not damage tissue physically and big enough to handle endogenous and exogenous signal from multiple sensing system.[64] For that reason, at least 2 main components are needed in nanobots: sensors for automatic control on a certain scale/target and the assembly of nanorobots.[62]

Some of the applications of nanobots in the medical field are: cancer treatment, surgery, precision medicine, diabetes monitoring, dentistry, blood monitoring, drug delivery, targeting and early diagnosis of cancer, tissue engineering, gene delivery systems, cardiology, analysis of body vital signs, as well as capabilities visualization and detection.[60,66-70] In the development of nanobots, normally will confronting with issues, such as: complicated design and programming, high cost, potential of stray electrical field, terrorism issue, molecular collision as a result of Brownian effect, dan toxicity; that become challenging to deal with to invent new technology of medical nanobot.[71]

From various utilities of nanobots, drug delivery became one of the most researched issues. Especially in the most concealed and difficult to reach tissue. In this application, diversified cargo can be loaded to nanobot, such as drugs, inorganic therapeutics, living cells, and biologics.[72] Then the cargo-loaded nanobots can be driven to the target using magnetic field, and the cargo unloaded using pH shift or external infrared.[71,73,74] Gao's group design magnetically driven cargo-towing nanobot, free fuel, to carries drug. This two-three-segment flexible nanowire consists of a magnetic nickel head (±1.5 μm) along with a flexible silver segment (±4 μm). For loading cargo, the drug (doxorubicin) must be encapsulated with iron oxide and then magnetically stick on nickel head. In vitro, this nanobot design were tested in the PLGA particle delivery experiment to HeLa cell. The flexible nanomotor approaches the target iron oxide/doxorubicin-encapsulated PLGA particle in a cell-free well via precise magnetic guidance and the particle is magnetically attracted and picked up. The nanomotor is then guided to a target HeLa cancer cell and the flexible silver segment of the nanowire nonspecifically bound to the HeLa cell to enable localized drug release from the PLGA particle. It shows targeted bound and drug release to HeLa cell.[75]

In other research conducted by Park's group, a biodegradable magnetically attenuated hyperthermia microbots (DHM) were used to drug delivery and hyperthermia therapy. It contains EGDA-pentaerythritol triacrylate (PETA), Fe 3O4 MNPs, and 5-fluorouracil (5-FU) as a stealth polymer matrix, magnetic material, and anticancer drug, respectively. To release the carried drug and control the released heat, it needs external alternating magnetic field; along with rotating magneting field to navigate the nanobot.[76]

In vivo test using HCT116 cell shows no different against control group, indicate the biocompatibility of the nanobot. Other benefit using DHM lies in different release mode of drug depends on the application, from normal release, constant release, to high-burst release.[76]

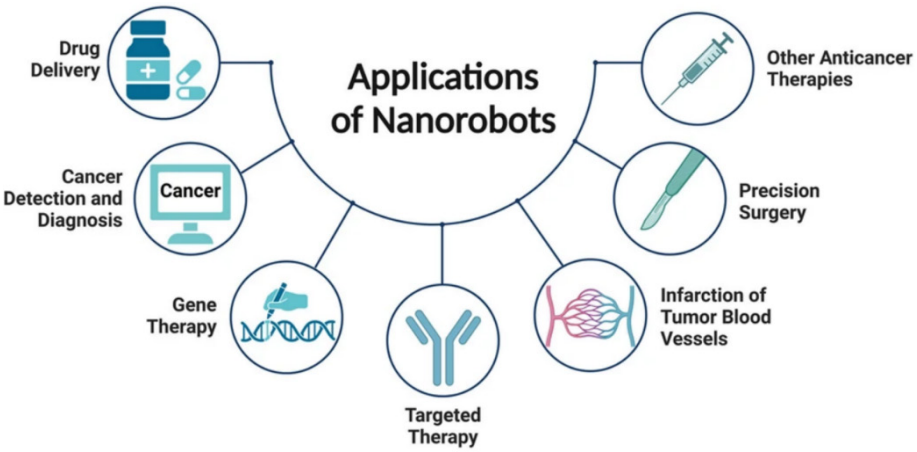

FIGURE 5. Various application of nanobots.[65]

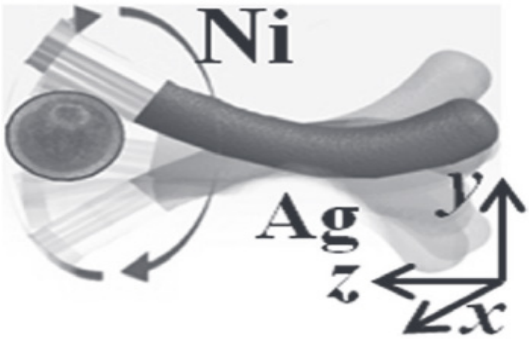

FIGURE 6. Schematic nanobots model and movement direction.[75]

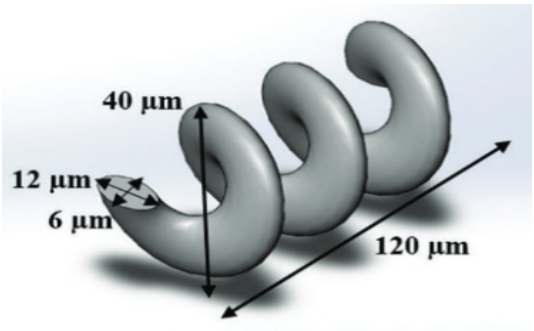

FIGURE 7. DHM structural dimension. [66]

CONCLUSION

Nanotechnology has vast potential to resolve various medical problem in curing common and rare diseases. Developing new technology or optimizing the current nanotechnology need deep insight on how the technology work or the disease interrupted, to maximize capability and minimize the side effect of nanotechnology. One of the biggest homework is to make the new technology from benchside to bedside.

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