CHAPTER 2

Nanotechnology and nanomedicine

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Brief history of nanotechnology

Nanoparticles have been around since the early universe, but the idea of designing and manipulating nanomaterials has emerged much more recently. Centuries ago, nanoparticles were already used in glassmaking, although the scientific details were not well-understood at the time. Important to the modern development of nanotechnology is atomic theory, which describes matter as very small discrete particles with definitive properties. While theories of quantum mechanics and relativity have since complicated this simplistic view, atomic theory has been deeply influential in the ideas of atoms and molecules that are fundamental to nanotechnology. A wide-ranging field that encompasses various scientific and medical disciplines, nanotechnology has the distinctive characteristic of engineering materials in the 1–100 nm range [1, 2].

The modern understanding of and interest in nanotechnology began about a century ago and skyrocketed in the 1980s. Nanoparticles were first observed and described by Richard Adolf Zsigmondy in the early 1900s [3]. In 1959, Richard Feynman introduced the concept of nanotechnology in a lecture entitled, "There's Plenty of Room at the Bottom," in which he envisioned the production of nanoscale machines [4]. Advances in microfabrication and microelectronics in the 1950s further fostered the development of nanoscale manufacturing. In 1974, Norio Taniguchi coined "nanotechnology" [5]. Worldwide interest in nanotechnology research increased in the 1980s when Eric Drexler published his ideas of molecular engineering and founded the Foresight Institute to promote nanotechnology [6]. The invention of the scanning tunneling microscope in 1981 enabled the visualization of individual atoms [7]. The atomic force microscope soon refined the imaging of organic molecules [8]. These innovations were instrumental in the progress of nanotechnology. In 1985, Richard Smalley's research group reported the

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synthesis of carbon fullerenes (buckyballs) [9]. These strong soccer ball-shaped particles were approximately 1 nm in diameter. They helped pave the way for the synthesis of carbon nanotubes in the following decade [10].

Rising public interest in nanotechnology led to new initiatives and regulations by the United States government. Representatives from different federal agencies began holding meetings about nanotechnology in 1996 and became the Interagency Working Group on Nanotechnology (IWGN) in 1998. The IWGN is managed by the National Science and Technology Council. The National Nanotechnology Initiative was launched a few years later to fund nanotechnology research. Over the past two decades, nanotechnology has been permeating into everyday consumer products, including but not limited to personal care products, sports equipment, and consumer electronics [11].

Brief history of nanomedicine

The intersection of nanotechnology and medicine arose in the early 20th century and their synergism has continued to the present. Nanomedicine began as parallel developments in many different fields, including biotechnology, cell and molecular biology, chemistry, engineering, and physics. By targeting specific pathogens using drugs, Paul Ehrlich pioneered chemotherapy and the concept of the "magic bullet" [12]. Ehrlich's development of Salvarsan in the early 20th century demonstrated the efficacy of targeted drug therapy, which had a lasting impact on the direction of drug synthesis with heavy emphasis on specificity. The field of biomaterials also made major breakthroughs in the following decades, including research into biopolymers through the use of electron microscopes and X-ray diffraction techniques [13, 14]. Watson and Crick's elucidation of the DNA structure in the 1950s and further investigations into the genetic code illustrated the precise molecular mechanisms underpinning life processes [15]. As early as the 1960–70s, scientists at ETH Zurich were experimenting with nanoparticles for pharmaceutical purposes [16]. On a different frontier, novel findings in cell membrane structure and function enabled a greater understanding of transport across membranes. One example was the study of ion channels using the patch clamp technique [17]. The discovery of membrane receptors and ion channels revealed the complexity of highly regulated signaling pathways in the body which could potentially be targeted by specific drugs. Another notable progress in the field was the discovery of reverse transcriptase in 1970 [18, 19]. As the field of immunology evolved, scientists began learning about the intricacies of the immune system, including its cellular and molecular components. In the 1970s, monoclonal antibodies were synthesized to allow for specific targeting of molecules [20]. These advances in the 20th century opened the doors for genetic engineering. There was a growing appreciation for the complexity of proteins as molecular machines. Diagnostic tools such as microchips and microsensors have been developed for fast, inexpensive, and high-throughput screening. Many potential applications of nanomedicine have been established and will be detailed in the following section.

Synopsis of recent advances in nanomedicine

As a relatively new field, nanotechnology has enormous potential in medicine, and novel applications are actively being explored. Nanoparticles in the 10–100 nm size range are useful for medical applications because they are small enough to avoid occluding vessels and other passageways in the body, while large enough to have adequately long clearance times for imaging enhancement [21–24]. In addition, nanoparticles are advantageous for drug delivery, because they accumulate in areas of inflammation due to leaky vessels [25–28]. Nanoparticles can be made of a variety of materials, including ceramics, polymers, or metals, which allow for functionalization. They exhibit physical properties that are conducive to imaging, such as fluorescence. Multiple functions can be combined into a single nanoparticle (Fig. 1). For medical use, nanoparticles need to be minimally toxic in the body, so biodegradability and clearance are valuable characteristics [29–32].

One application of nanotechnology in medicine is contrast enhancement in diagnostic imaging for a wide variety of modalities, such as ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI) [30, 33–37]. Nanoparticles provide excellent contrast in soft tissues and are, therefore, valuable in oncology and cardiology [38–41].

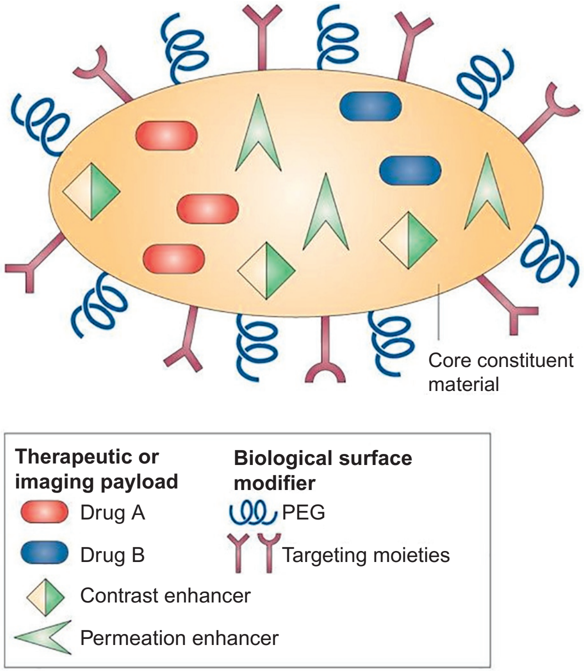

Fig. 1 Nanoparticles can have multiple functions and properties. They can carry various therapeutic agents, contrast agents, and permeation enhancers. They can also be modified with polyethylene glycol (PEG) and specific targeting moieties. *(Adapted from Ferrari M. Cancer nanotechnology: opportunities and challenges. Nat Rev Cancer 2005;5:161–71.)*

The functionalization of nanoparticles permits multimodal capabilities and selective targeting of specific tissues [42–46]. Magnetic nanoparticles functionalized with antibodies have allowed for early detection of cancer cells via sensitive blood tests and enhanced imaging [47–53].

In addition, nanoparticles can carry pharmaceutical agents for selective drug delivery [54]. Nanoparticles loaded with therapeutics can be directly administered into diseased tissues such as tumors [55, 56]. For circulating nanoparticles, markers are needed to increase their specificity to target tissues [57–59]. These markers include nucleic acid templates, antibodies, different metabolic levels, and unique aspects of the physiological environment (e.g., pH). An additional challenge is managing the clearance of these nanoparticles by the body's immune system and filtration mechanisms. Some advantages of nanoparticles for drug delivery are their ability to deliver multiple drugs, ease of passage across biological barriers, high affinity for target molecules, high payload capacity, pharmacokinetic properties that can be altered, and potential for controlled release [60–63]. Conjugation and encapsulation can enhance the properties of nanoparticles for drug delivery.

Nanotechnology can also be utilized for delivering energy to destroy malignant cells by means of photodynamic and photothermal therapy. Radiation therapy can be administered with functionalized nanoparticles to increase therapeutic efficacy against cancers [64, 65]. Gold nanorods have shown immense promise in photothermal therapy [66, 67]. Nanoshells, which usually comprise a dielectric core surrounded by a gold shell, absorb heat when irradiated by infrared light and can be used to target cells [68, 69]. For photodynamic therapy, photosensitizer dyes are activated by light at specific wavelengths, which triggers the release of reactive oxygen species to kill tumor cells [59, 70, 71]. These dyes can be delivered to specific sites by liposomes or nanoparticles [72].

Nanomedicine has played a significant role in surgical applications as well. The ideas of nanotechnology have been incorporated into improving minimally invasive surgery, including endoscopic microelectromechanical systems (MEMS) and very small catheters [73–76]. The sensors and computer processors in robotic surgery and micro/nanorobotics for high precision microsurgery and other medical procedures are all based on nanotechnology concepts [77–79]. Capsule endoscopy and laser microsurgery are just some of the many examples of surgical applications involving nanotechnology [80, 81].

Recent breakthroughs in genomics and proteomics have also greatly benefited from nanotechnology. High-throughput DNA and RNA sequencing and protein analysis tools, along with headways into metabolomics, have been crucial in advancing personalized medicine [82, 83].

New advances in nanosensors have the ability to transform and improve the precision of medical diagnosis. Nanocantilevers are one type of nanosensor which can measure minuscule deflections and vibrations [84]. They can be employed for biomedical applications such as cancer screening by detecting miniscule changes like antigen binding to antibodies

[85–87]. Surface plasmon nanosensors are used to analyze proteins and DNA [88]. Sensors synthesized from magnetic nanoparticles, films, nanofibers, and nanotubes demonstrate the numerous avenues in which nanotechnology has become a central part of medical diagnostic tools [89]. Additionally, nanotechnology has facilitated the monitoring of medical conditions and health in real time, including the use of wireless biosensors and personal electronic devices [90].

Furthermore, restorative and regenerative medicines have seen rapid progress with the introduction of nanotechnology. Nanoengineering has made possible the development of nanoscale structures for restoring tissues and repairing wounds [91, 92]. Ceramics, glasses, and polymers are some of the materials used for nanotechnology-based regeneration [93]. Carbon nanotubes and titanium dioxide films are examples of nanomaterials used in scaffolds [94]. An advantage of nanomaterials is that they help support growing cells by facilitating their attachment to the structures. Biodegradable nanomaterials may further promote tissue recovery [95]. Besides providing scaffolds for attachment and support, nanomaterials can serve as barriers around tissues to prevent transplant rejection [96]. Nanoparticles also have antiseptic properties that promote wound healing [97]. Tissue engineering involving nanotechnology is another promising area of study in regenerative medicine [98–100]. Researchers are examining intelligent biomaterials which can detect and respond to changes in the local environment [101, 102]. Putting these ideas into practice are techniques like scaffold-guided tissue regeneration using bioactive materials, integration of nanotechnology into stem cell therapies, and nanoencapsulation to protect tissues [103].

Future of nanomedicine

Nanotechnology is at the forefront of helping to realize the concept of "theranostics," which combines therapy and diagnostics in medicine [104–106]. Ideally, multiple different functions can be united into single nanoscale devices to manage diseases. The precision of nanotechnology is also consistent with the idea of personalized medicine [107–109]. Specific biomarkers can be targeted by nanomaterials based on individualized cellular and molecular information. While nanotechnology provides immense potential to improve health, concerns have been raised about the safety of nanomaterials to human health and the environment [110–112]. Nanotoxicology is a new discipline which evaluates possible detrimental effects of exposure to nanomaterials, such as assessing their kinetics and dynamics [113]. Ongoing efforts are made to translate nanotechnology discoveries in the laboratory to clinical practice.

Overview of nanotechnology in cardiology

Nanomedicine has a profound impact on cardiology in all the aforementioned ways (Fig. 2). Nanoparticles can enhance images of cardiovascular tissue to monitor disease

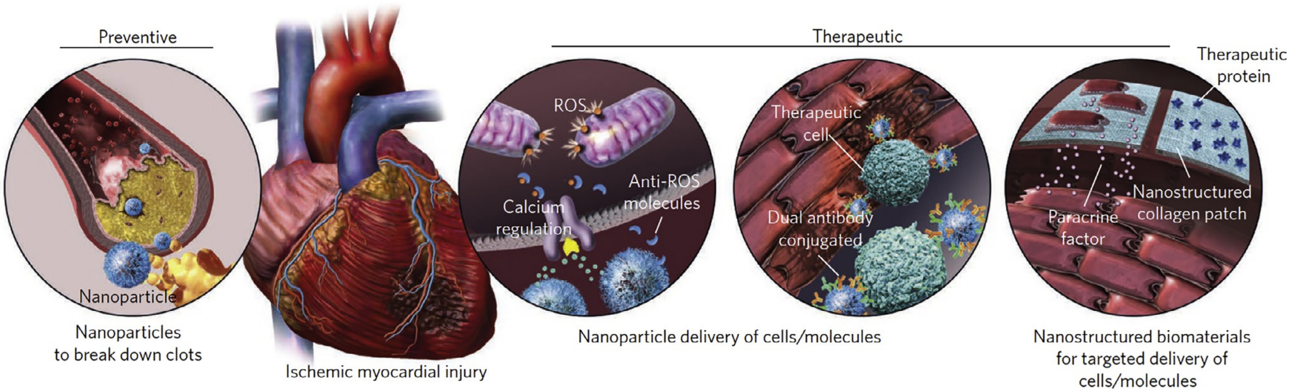

Fig. 2 Nanoparticles have numerous applications in cardiology. They can break down clots and prevent ischemic injuries. In addition, they can deliver cells and biomolecules to specific locations. *(Adapted from Mahmoudi M, Yu M, Serpooshan V, Wu JC, Langer R, Lee RT, et al. Multiscale technologies for treatment of ischemic cardiomyopathy. Nat Nanotechnol 2017;12:845.)*

progression and deliver drugs to specific tissues [114–117]. One application of nanoparticles is detecting and treating atherosclerosis, which involves reducing plaques and decreasing inflammation [118]. An active area of research is understanding the complex interactions at the nanoparticle-biological interface, known as the protein corona, to increase drug delivery [119–121]. Another focus is on improving targeting of nanoparticles to coronary arteries and cardiac tissue. Passive targeting strategies that take advantage of the enhanced permeability and retention effect in myocardial infarcts and active targeting strategies using specific ligands are helping to address these obstacles [122].

In addition, investigators are utilizing stem cell therapy to treat cardiovascular diseases [123]. Given the limited regenerative capacity of cardiomyocytes, continuing efforts are made to overcome cell cycle checkpoints and stimulate mitosis to restore cardiomyocyte proliferation [124–126]. Some researchers have proposed using embryonic or induced pluripotent stem cells to regenerate cardiac tissue [127]. Directly reprogramming other cells into cardiac cells incorporating nanotechnology is another promising approach that is in the early stages.

Aside from the examples mentioned earlier, nanomedicine is making numerous other contributions to cardiology. Vascular stents coated with nanomaterials can aid in wound healing [128]. Using nanoparticles to prevent restenosis is being examined [129]. Surgical robotics are being utilized for catheterization and cardiothoracic procedures [130, 131]. Creating nanoscale surgical tools will help facilitate minimally invasive cardiac surgery [132]. Nanoscale scaffolds can potentially be used in conjunction with stem cell therapy to promote myocardial tissue regeneration [133, 134]. Fabricating scaffolds using 3D printing technology to increase precision at the nanoscale level is being explored as well [135, 136]. Nanotechnology has increased the biocompatibility and efficiency of cardiac pacemakers [137]. Medical simulation software for training physicians is an additional example of the impact of nanotechnology on cardiology and medicine in general [138].

New applications of nanotechnology in cardiology to improve medical diagnosis and treatment are continually being discovered and refined. The focus of this book is to provide a detailed account of innovative developments in this burgeoning area of interdisciplinary research.

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