Nanomedicine: Integrating the advances in nanoscale technology into novel medical practices

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Nanomedicine is among the most prolific fields of current scientific research. By harnessing the technological progress that has characterized the past 50 years, this discipline is augmenting the visualization of nano-scale cellular processes with the goal of modulating nano-scale cellular interactions. This rapidly developing field spans nearly all scientific disciplines and medical specialties, and it presents significant promise in the struggle against some of the most pernicious human diseases. The main domains in which medical nanotechnology in particular has shown promise thus far are: imaging techniques, drug delivery platforms, and selective cellular targeting.

The origins of nanotechnology can be traced to the early-20th century. In this time, Max Planck and Albert Einstein theorized the existence of small particles that must obey their own sets of physical laws. Soon afterward, structures smaller than 4 nanometers were identified in ruby glasses via a microscope developed by Richard Zsigmondy and Henry Siedentopf (1). This discovery launched an era of microscopy that culminated with the discovery of the atom, cells, intracellular structures, and eventually DNA and RNA in the 1950s and 60s.

Richard Feynman is credited as the first scientist to describe the concept of nanotechnology without specifically using the word "nano." In a 1959 lecture entitled "There's Plenty of Room at the Bottom," he described the potential of manipulating matter at the atomic level and the impact it could have on scientific research (2). Norio Taniguchi is attributed with coining the term "nanotechnology" in a 1974 paper in which he described the fledgling field as "the processing of separation, consolidation, and deformation of materials by one atom or one molecule" (3).

Today, nanomedicine is a burgeoning area of research with modalities being implemented across medical specialties. In the field of pulmonology, for example, nanoparticle complexes and carriers have been engineered in order to better address the immune dysregulation that occurs in asthma. The technology has also been applied to treat Chronic Obstructive Pulmonary Disorder (COPD), cystic fibrosis, and various pneumoconioses (4). In anesthesiology, attempts are in progress to develop ultrasensitive nanosensors that can detect plasma biomarkers indicative of pain so that physicians can better address chronic pain syndromes (5). In cardiology, gold and silica nanoparticles have been developed to improve the supply of the vasoactive

compound nitric oxide (NO) to blood vessels in order to address systemic effects of cardiovascular disease such as hypertension (6). Additionally, in neurology, the use of Multiwalled Carbon Nanotubes (MWCT), which cross the blood brain barrier and are taken up by malignant brain cells to induce cell death, has shown promise as an effective therapy against glioblastoma multiforme, a brain malignancy with an extremely high mortality rate (7). Several examples in other specialties abound.

Key Points: Types of Nanoparticles

Protein-drug conjugated nanoparticles
- Proteins are directly conjugated to drug molecules
- This link is usually biodegradable once it has entered cell
- Because the link is so readily destroyed, this drug is sometimes prematurely released

Liposomal nanoparticles
- Spherical particles created by using lipid bilayers
- Allows hydrophilic drugs to be encapsulated by dissolving drug in liquid
- Releases drug by fusing with cell membrane (since lipid bilayer is similar)

Polymeric nanoparticles
- Customized polymers that can vary in molecular weight, biodegradability, and hydrophobicity
- Limitations include shape constrictions and wide size distribution

Dendrimeric nanoparticles
- Spherical macromolecules with many branches originating from a central point
- Created layer by layer

Hydrogels
- Cross-linked water soluble polymers
- Retain fluid in large quantities

Reference

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Regarding imaging techniques, nanoparticles and materials have improved the monitoring of nano-scale cell components. For example, the use of quantum dots, semiconductor crystals modified to appear luminescent on imaging devices, have enabled the visualization of genes, nucleic acids, proteins, and cell processes in real time (8). Radiolabeled nanoparticles have been used to quantify tumor volume, visualize macrophage activity, demonstrate atherosclerotic plaque burden, and quantify metabolic activity at the cellular level.[9] So called "nanoreporters", nanoparticles injected alongside a specific drug, can report on drug accumulation in the tissue, allowing for the monitoring of the efficacy of pharmacokinetics and, as an extension, predicted therapeutic outcome in real time (9).

Drug delivery is another robust and promising aspect of the field of nanomedicine. In the past 20 years, there has been a massive increase in the amount of research and clinical trials aimed at developing nanoparticle delivery mechanisms to enhance drug delivery. One way in which nanomedicine can improve drug delivery is by overcoming existing drug efflux mechanisms in cancer, for example. Drugs bound to nanoparticles can be deployed in order to circumvent drug efflux pumps, to silence transcription of drug resistance proteins, and to inactivate plasma membrane proteins used for intercellular transport (10). Nanotechnology drug delivery platforms have also been shown to reduce the toxicity of bound pharmacological compounds and to increase the selectivity of their destination, thereby reducing off-target effects and increasing therapeutic effectiveness (11).

Nanomedicine also holds special promise in the area of personalized medicine, particularly as it relates to drug delivery. Drug delivery platforms can be optimized to carry a certain type of cargo and to target specific cell types, which makes them amenable to fine modulation to account for diversity within a population. The advances in genomic sequencing have made it possible to

identify personal mutations present in cancerous cells that can then be targeted using tailored therapy. There exists a wide realm of small interfering RNA (siRNA), DNA, micro RNA (miRNA), and lipid-based nanoparticles that are actively being trialed for potential therapeutic activity against many forms of malignancy (11). In some cases, future oncological therapy may involve delivery of a personalized anti-oncogenic payload via nanoparticles to cellular targets that have been selectively chosen, thereby increasing the efficacy of cancer cell destruction while reducing the massive "collateral damage" that is typical of traditional chemotherapy.

Scientists have pushed beyond visualization and response to cellular processes and into the domain of cellular DNA re-programming via gene therapy using nanomedicine. For example, researchers at Johns Hopkins University have demonstrated that biodegradable nanoparticles can be used to deliver specific fragments of DNA for incorporation into the DNA of malignant brain cancer cells, ultimately leading to the death of the cancerous cells while sparing non-malignant "bystander" cells (12). This study shows that nanoparticles can be used as vectors to ferry specific fragments of DNA into targeted cells with the goal of altering their character. This development heralds much promise and simultaneously awakens the ethical dilemma of where to set boundaries in procedures that intend to alter human DNA.

The developments in modern medicine that are ushered in by the continued advances in the multi-disciplinary field of nanomedicine hold much promise. However, the era of nanomedicine, which brings with it increasing precision and ability to manipulate even the most mundane of cellular processes, will inevitably bring with it a host of moral and ethical questions and quandaries. How much manipulation is too much? What cellular processes should remain untouched? Moreover, the attraction of new, personalized, and advanced treatments must be tested against the established "boring" treatments of the past to ensure that they actually provide quantifiable advantage beyond mere "curbside appeal" and the promise of increased billings.

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