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Nanoparticles in Cancer Treatment: Physics Principles and Therapeutic Applications

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Annotation: The use of nanomaterials in cancer therapy is an example of promising enhanced therapeutic ability, particularly in the diagnostic and drug delivery fields. Tumor treatment using magnetic particles in hyperthermia methods was also proposed. All those treatment possibilities, in relation to normal surgical and/or chemotherapeutic approaches, provide distinct advantages like minimal invasiveness, spatial and temporal treatment selection, simultaneous imaging, and selective treatment, i.e., allowing treatment only on the cancer-affected tissue while the healthy tissue remains unchanged. The tissue imaging followed by the therapy can increase the success rate, decrease the possibility of life-treated part malfunction, and represents a major advantage to the use of nanoparticles properly conjugated with the right molecule. Typically, the process that a nanoparticle undergoes inside the human body starts with

intravenous injection, signaling to a specific compound within the blood vessel to link to it and transport it to the targeted location. Here, the nanoparticle-conjugated specific molecule can release drugs or be activated by an external agent or suffer from a distortion of its characteristics. The visualization of whether there is a tumor presence is always necessary. A diagnosis followed by chemotherapy or surgery brings the excellent possibility of eliminating the tumor. [1] [1][2][3]

1.1. Overview of Cancer and Current Treatment Challenges

Cancer is, as yet, a profoundly feared disease. In the past, a diagnosis of cancer usually was a death sentence. However, nowadays, with advances in biotechnology and other sciences, the death rate from cancer has decreased. Generally, our bodies are billion-member cell societies, obeying complicated rules and regulations encoded within the DNA. The word "cancer" is derived from the Greek word for "crab." Whoever named this complex disease chose the name, apparently, because of the crab-like appearance of a tumor invading normal tissues. Cancer is not a single disease entity, but a plethora of interrelated diseases involving the breakdown of the normal set of cellular checks and balances.

Cancer, a disease involving the growth of new forms of life descending from our own cells, generally is divided into categories involving carcinomas, sarcomas, leukemias, lymphomas, and endocrine tumors. Carcinomas are tumors originating in the skin or linings of the stomach, intestines, breast, and lung; these represent 90% of human cancers. Furthermore, the mechanisms of carcinogenesis, tumor invasion, metastasis, and angiogenesis have been elucidated. Early diagnoses of carcinomas also have been made through cancer-specific antigens, enzymes, oncogenes, and other products identified on the cancer cell surface. Consequently, highly specific killing of cancer cells has been achieved pharmacologically. Small molecule inhibitors and monoclonal antibodies against established targets have been introduced to control the spread of established tumors and metastases. An even more exciting period exists in the offing as researchers pursue the unraveling of the cancer mystery. With gene therapy, cancer truly may be cured. This could become possible simply by replacing malfunctioning cancer genes or introducing genes to help our immune systems kill the cancer cells. [4][5][6]

1.2. Role of Nanoparticles in Cancer Therapy

In general, nanoparticles can be categorized as (1) lab-engineered, exogenous in nature: nanoparticles are developed in the lab and introduced into biological systems; these include both inorganic and organic nanoparticles; and (2) naturally occurring, endogenous in nature, such as ferritin or metallic elements in the body or biological tissues. Ceramic nanoparticles, lipid nanoparticles, proteins, liposomes, carbon nanotubes, and quantum dots are used for developing new and innovative healthcare products. Although still in the stages of experimental and clinical testing, nanoparticle-mediated targeted cancer therapies have shown great potential as a new cancer therapeutic modality. Tumors are difficult to treat because tumor cells have the ability to divide indefinitely. If tumor cells are not dividing, chemotherapy is not effective. Nanoparticles can be delivered into tumor cells via non-specific passive targeting or targeted active methods using ligands or cellular receptors. In both cases, minimal damage to normal cells and better

distribution patterns are observed compared to current cancer medications. Cancer treatment is a highly desirable clinical problem that has been tackled by nanotechnology for the last 30 years to produce genetically modified DNA and other inorganic and organic structures that deliver cancer drugs, gene sequences, and other materials to specific diagnostic or therapeutic sites in the human body. Such nanoscale therapeutic agents help produce highly effective and low-toxicity treatments. Currently, nanoparticles are utilized to locally direct a significant quantity of therapeutic agents inside endothelial cells and cancer cells, thereby minimizing nearby tissue toxicity. [7][8][9]

2. Fundamental Physics Principles of Nanoparticles

The extensive clinical use of metal nanoparticles in oncology, particularly gold, unfolded the importance of their fundamental key characteristics and peculiar ionizing and non-ionizing radiation physics effects, which have not been widely recognized by biomedical investigators. This review aims to present fundamental physics principles that signify nanoparticles in terms of potential clinical applications and to determine their particular experimental behavior based on known nanoparticle features, shapes, and sizes, revealing radiosensitizing potential in their two roles in radiotherapy and in protection against ionizing radiation. The original and reviewed radiation and nanoparticle experimental and clinical studies serve the purpose of critical clinical applications analysis and the ultimate goal of alerting clinicians to the possibilities and dangers of nanoparticles, based on fundamental photoelectric and Rayleigh behavior and recent experimental behaviors of nanoparticles and ionizing radiation systems.

The medical application of non-ionizing nanoparticle radiation, referred to as the nanomedicine application of metal nanoparticles, is increasing nowadays with numerous testing systems for individual applications and increasing collective knowledge obtained. The primary applications include selective blood cancer cell killing by applying infrared laser treatment with nanoparticles combined with cancer cell internalization, x-ray tumor treatment positioning while increasing effects on contrast imaging, and cell radiographic analysis, diagnosis, and treatment stimulation, as well as imaging particles ex vivo. Cancer treatment induction stimulation is again achieved using non-invasive heating of the containment of nanoparticle tissues and the release of therapy induction of the degradation. [10][11]

2.1. Quantum Mechanics and Nanoparticles

Quantum mechanics is a fundamental theory in physics that describes nature at the smallest scales. It provides a mathematical description of much of the dual particle-like and wave-like behavior and interactions of energy and matter. It thus provides a partial foundation for the modern understanding of the behavior of atoms, molecules, nuclei, subnuclear particles, and light. Given its expanded scope, as treatment of particle motion, in such waves as sound and seismic waves, in confined wave packets, in relativistic motion, and in tunneling probabilities, it is not unreasonable to argue that quantum mechanics should be given pride of place in any description of the general framework of physics.

However, its mathematical structure, involving the determination of probabilities for distinguishing various classes of events, rather than prediction of definite future states, and its description of a wide variety of such probabilities through mathematical expressions, which provide no real intuitive understanding of quantum behavior, makes analysis of quantum properties somewhat difficult for the average physical scientist to digest. And so, such principles have generally only been covered in four-year physics courses; some engineering and medical students do not receive instruction in quantum mechanics. [12][13][14]

2.2. Optical Properties of Nanoparticles

The color of noble colloidal solutions arises from the surface plasmon oscillations of the nanoparticles—a collective excitation of conduction-band electrons. Latent metal atoms for these particles exist in oxidation states that are thermodynamically stable at most temperatures used for colloidal nanoparticle synthesis. The spherical shape is common for these particles, but the shape anisotropy is also within experimental reach. For dielectric and semiconductor materials, oscillations in the visible and near-infrared regions have been reported. In nanoparticles, the shape and material-dependent absorption spectrum can be well understood using Mie theory for dielectric spheres. Interparticle coupling leads to particularly interesting optical phenomena that have potential applications in vibrant areas of biotechnology and photonics. The most exciting optical property of noble metal nanoparticles is that they display unusually strong scattering and absorption properties at their specific plasmon wavelengths, caused by the nearly free electron gas present in the conduction bands of these metals.

Plasmon shift is another unique property of metal nanoparticles. Shapes and materials of the particles are the primary factors determining plasmon peak positions. Small gold and silver nanoparticles show unique non-linear properties with exceptionally high local optical fields and strong surface-enhanced Raman scattering peaks that are the kernel of surface-enhanced Raman scattering used in various sensing and detecting applications. Other optical properties that have been reported are part of a broader new research field that might have a grand impact in tumor biology. Using many surface immobilization strategies, these nanoparticles can easily be functionalized by selecting appropriate reagents to form stable and biocompatible hybrids. These unique optical properties of noble metal nanoparticles have prompted wide and increasing use in biological applications, which are focused on research that began a little more than a decade ago. [15][16][17]

3. Types of Nanoparticles Used in Cancer Treatment

The thorough classification of NPs is not developed until today. We could find more than several NP types that are used in oncology, but almost all the papers could be combined by the type of materials used for constructing the NPs. The most significant classifications are made for gold NPs, quantum dots, and carbon NPs. Besides the named materials, for cancer diagnosis and therapy, polymeric NPs, especially organic NPs, such as liposomes, and inorganic NP applications are developed, for example, Fe2O3 and Fe3O4 NPs. These NPs could be used for tissue engineering, biomaterial staining, and medical nanosystems. We propose to systematically consider many NP types that could be used for cancer diagnostics and therapy.

There are several materials that are regularly used in oncology for NP synthesis and NPs functionalization. The first nanoparticle type is by far the most popular type of nanosystems for cancer diagnostics, therapy, and monitoring the therapeutic NP distribution during animal and patient experiments. Gold NPs are one of the most ancient types of NPs, dating back to Ancient Egypt, and it is not surprising that Au NPs are so popular in present-day nanotech and biotech routines. Although Au NPs are the most commonly used NPs, there are many materials that could be used as theranostic NPs in oncology, and we propose to consider all these materials. Advanced nanoparticles could be used as molecular carriers that direct the anticancer drug to the same cells. The important class of such NPs, potent anticancer substances, is now fabricated and successfully used for targeted treatment of different cancers. Thus, the Handbook of Nanophysics could be useful not only for students but also for senior research officers in oncology clinics, institutions, and laboratories. [18][19][20]

3.1. Metallic Nanoparticles

Among different nanoparticles, metallic ones are surely the first that triggered enormous clinical

and research interest. The reasons for these niches are the simplicity of synthesizing them, combined with their unique physical, optical, and electronic properties. Moreover, noble metal nanomaterials are generally innocuous and can be surface modified by means of functional groups in order to easily interact with bio-substrates or vectors. Given these basic properties, the possible therapeutic applications are many-fold in both diagnostics and therapy. When discussing possible cancer therapy, gold nanoparticles are certainly the most used and interesting, with utilization dating back to the 1980s, first discovered for the purpose of enhancing tumor cellular destruction in combination with radiation. It is known that cancerous cells are more sensitive to ionizing radiation compared to normal body cells, but sometimes patient therapy had to be interrupted due to observed side effects on body tissues.

In order to reduce damage to healthy tissue and enhance radiation damage to tumor cells, the main concept of several cellular oncotherapies is to increase the radiation amount inside the tumor while minimizing the radiation effect in the surrounding tissues. Scientists took advantage of the ability to synthesize gold nanoparticles having a size within the 1–100 nm range, easy to disperse in aqueous media and easy to functionalize. Such materials, once attached to specific targeting vectors, accumulate passively in the neoplastic tissue, acting as radiation absorbers. The idea is that the incident electromagnetic radiation would be strongly scattered by the irradiated nanoparticle electrons, resulting in the generation of short-range, high-energy electrons, which should significantly damage the surrounding cells. [21][22][23]

3.2. Polymeric Nanoparticles

Polymeric nanosystems have been gaining increasing attention in cancer treatment research, mainly as drug delivery systems in order to minimize the adverse side effects of antitumor compounds. The formulating strategy corresponds to polymeric blends, prepared through spontaneous emulsification or solvent evaporation, entrapping antitumor compounds such as alkylating agents, anomic agents, antimetabolites, and/or alkaloid derivatives. The enhancing anticancer activity is due to a passive targeting mechanism; the antitumor compound leads to a significant process to the tumor sites.

The dynamic therapy with drug-loaded nanoparticles is a yet accepted application. The drug release is achieved after exposure alongside tumor tissues followed by the release of the active compound to the tumor site. Polymeric nanoparticles have shown both internalization kinetics and diverse cellular distribution ranges. Folate, a well-known tumor-targeting ligand for cancer cells overexpressing the folate receptor, has been used as a targeting ligand to facilitate the internalization of the drug-loaded nanoparticles. Polymers are mainly synthetic, with side chains, adjustable hydrophobicity, and can be quickly mass-produced in both large and small scales. Small hydrophobic characteristics, biodegradability, and the addition of bio-affinity groups mainly make polymers compelling tools for cancer treatment. In a perspective of translational cancer research, heterogeneities in the levels of expression and the stability of the disease, leading to the individual therapy development, may be a requirement for the utilization of polymeric nanoparticles, but the next years may not only bring forward many other exciting conclusions. [24][25]

4. Synthesis and Characterization Techniques

4.1. Synthesis Polymer impregnation and dialysis have become popular techniques for nanoparticle formation. Specific to nanoparticle–polymer blends, this technique impregnates polymer with nanoparticles and is characterized by a two-step process. In the first step, nanoparticles are dispersed in a solvent and then blended with a polymer. A film is prepared from the blend. In the second step, the prepared film is soaked in a polymer-compatible solvent to leach out the impregnated nanoparticles, and drying results in the formation of nanoparticle-embedded

polymer nanocomposite films. It was widely concluded that the increase in polymer chain mobility, the drop in surface energy, and the decrease in crystallinity of polymers modulate the unprecedented properties of mechanically reinforced elasticity. This technique has been widely utilized to develop nanoparticle-bombarded polymer composites, particularly for polymer thin films. The other well-known methods of nanoparticle formation are a combination of chemical and physical techniques including disproportionation, ion exchange, sol–gel process, high-energy milling, vacuum deposition, and chloride exchange. An overview and in-depth discussion of the techniques can be found in the reviews.

4.1. Top-Down vs. Bottom-Up Synthesis

There are two major approaches to nanoparticle synthesis: the 'top-down' method and the 'bottom-up' method that refer to different scales at which they are produced. The top-down method involves the reduction of larger precursors synthesized through common chemical and physical processing such as laser ablation, electron beam lithography, and the chemical oxidation or reduction of bulk metal, as well as ion implantation and reactive ion beam sputtering. However, the nanoparticle size distribution is broad, and the more negatively charged nanoparticles are generally smaller. By contrast, the bottom-up method allows for the self-organized formation of particles from atom to molecule to cluster in a condensing fluid and has been widely used to synthesize nanoparticles due to the potential formation of monodispersed nanoparticles with uniform parameters and definable structures, controllable compositions, and tunable surface modifications.

In addition, control of particle size and morphology through these methods varies from easy to difficult, and there are also variations of these two major methods. For instance, the microemulsion and sol-gel techniques have aspects of both top-down and bottom-up synthesis routes. The thermal decomposition of organometallics is also regarded as a bottom-up method. The micelle template method is classified as bottom-up but is a special synthesis method compared to others. Among these methods, reduction methods are practical and straightforward methods that result in well-defined particles and narrow particle size distributions. Organic solvents are preferred to water because the magnetic susceptibility of water is paramagnetic, meaning it produces spurious magnetic field gradients. The reduction method includes the slow decomposition and reduction in solution synthesis of inorganic salts at high temperatures. [26][27][28]

4.2. Characterization Methods

Nanosystems are at the forefront of technological and biological sciences, attracting considerable attention in chemistry, biology, physics, and medicine. These systems are playing an important role in the generation of great advances at the interface between basic research and clinical practice, and their implications and potential are fascinating, especially in the area of anticancer therapy. The application of nanomaterials to cancer diagnosis and therapy is an emerging field that is making tremendous strides. Nanoparticles and nanomaterials have stable physical properties, structural stability, and tailorable surface functionalities, which are necessary for the accumulation of a large payload of controlled-release functional agents and desired targeting groups, the activation of tumor microenvironments to decrease healthy cell damage, and efficient transition through various biological barriers.

In the biomedical context, it is important to comprehensively understand the interactions of nanomaterials with cells, tissues, and the entire organism: only a detailed understanding of the cell-material interaction can help to elucidate complex nanoparticle-biosystem interactions to help promote the rational design and translation to the field of medicine. These systems can also include ferromagnetic dendrimers and micelles and non-ferromagnetic systems such as liposomes or viral-based systems. The major areas where these nanomaterials are developing are chemotherapy, drug

and gene delivery, imaging, and hyperthermia therapy roles. Consequently, the design and characterization of the function that occurs when nanocarrier formulations are obtained are very important concerns. Here, our aim is to review the methods used for characterizing these nanocarriers in in vitro and in vivo systems.

5. Targeting Strategies for Enhanced Cancer Therapy

Nanoparticle targeting is important to minimize drug use and off-target side effects and was originally a small molecule chemical design optimizing the selective interaction with a tumor-associated receptor. The revolutionary potential of nanotechnology comes from the ability to selectively deliver drugs to diseased tissues using subcellular assemblies of matter significantly smaller than the cancer cell. Physical targeting strategies using nanoparticle physical properties, such as particle size and shape, once again broaden the entire nanoparticle toolkit. A critical consideration of targeting is the immediate delivery of nanoparticles to cancer cells that allows us to take full advantage of a cell's constantly changing chemical or mechanical properties.

The diseased tissue size, permeability of the diseased vasculature near the target tissue, and targeting/transferrin receptor expression near the target tissue are critical physiological properties that can guide the design of a cancer-fighting nanoparticle. At the physical size scale, nanoparticles ranging from 50 to 200 nm can gain access to diseased tissue through vasculature damage surrounding the cancer mass or differential barrier size pores. By tuning particle size, we can successfully take occluding junctional barriers around a cancer mass or selectively penetrate cell-cell junctions in inflamed tissues to reach the targeted tissue. The supply of oxygen favors tumor tissue but not patients. Large 100-800 nm particles are found in the inflamed margins of a tumor with little promise for an inflammation-seeking drug nanoparticle.

5.1. Passive Targeting

Nanoparticles reach the tumor tissue due to the EPR effect (enhanced permeation and retention effect). A tumor is characterized by increased permeation of macromolecules from the blood flow into the tissue. This is caused by disrupted or leaky blood vessels that are mainly formed by randomly and chaotically oriented endothelial cells with large fenestrations between them. As a result, the tumor vessels are highly permeable to circulating macromolecules. The lymphatic drainage of a tumor is also anatomically affected, so lymphatic clearance is partially suppressed. Macromolecules, including large nanoparticles, are retained in the tumor tissue longer than in normal tissues; meanwhile, normal tissues do not exceed the size of the endothelial fenestrations. The size of the fenestrations and the level of porousness of the epithelial cells depend on the type, location, and stage of the tumor, as well as on surgical treatment or radiotherapy. Overall, the size of the sonocontrast agent conjugated with a molecular cytotoxic agent should also be optimized. The size and structural parameters of nanoparticle conjugates used for tumor therapy can also depend on various factors, such as the experimental therapeutic goals or nanoparticle characteristics. The critical size range of nanoparticles following systemic administration for passive targeting is estimated to be between 10 nm and 200 nm. However, the specific limits can depend on the animal model and the architecture of the tumor. Tumors from 200 to 800 mm^3 in volume have a narrow distribution with an average pore size of 380-780 nm and a peak in vascular porosity at 183-488 nm. [29][30]

5.2. Active Targeting

Active targeting with some type of molecule, for example an antibody, that binds specifically to a cell-surface receptor protein is intended to increase the concentration that can be achieved inside a tumor of a treatment to which that molecule cannot specifically direct the particle. There are two principal challenges to such targeting. First, the target must be specifically overexpressed on the

cell type of interest, and second, the affinity of the targeting molecule to its receptor should be high. The first obstacle is the most problematic. The therapeutic agent must be extracted from the nanoparticle by diffusion to some receptor far from the binding site. This requires two things to be true: the agent must be in rapid equilibrium with the receptor, and the equilibrium constant must not be unfavorable. Even if the binding constant is favorable, an agent being presented to a number of different tissues that do not avidly absorb the molecule will reduce the tendency for extraction by any given tissue.

One reason to choose a targeting molecule with only moderate affinity is that the tighter the binding, the longer the particle will take to clear. Binding affinity is certainly important, as the antibody-coated nanoparticles in many studies accumulate in normal organs as well as in the tumor; yet the variety of results reported indicates that it may not be the dominant factor. Even with high-stability binding, nanoparticle exchange between tissues and blood would not occur rapidly if there were no potential tissue-specific kinetic sites with the ability to bind a large molecule like an antibody. In nanomedicine, with demonstrated efficacy, there are virtually no cases except for nanoparticles covalently linked to aptamers where appreciable binding of nanoparticles mediated by targeting molecules has been reported anywhere except in the liver.

6. Biological Interactions of Nanoparticles

The cellular uptake of nanoparticles is one of the central topics in their medical applications. In the case of living cells, the internalization mechanisms depend on nanoparticle composition, size, shape, stability, and surface charge, which define the manner of particle-cell interactions. The cellular uptake of nanoparticles can be divided into the uptake of a single nanoobject by free cells and the engulfment of nanoparticle-loaded target cells by plasmodia. These processes can be more complicated if the cells are exposed to a combination of different nanoparticles or their mixtures. In particular, the possible cellular responses to the interactions with nanoparticles include variations in biochemical processes, genome instability, or environmental behaviors. The nanosized intruders can lead to different damages, including changes in morphology and viability, and impairment of gene expression, which make them promising candidates for anticancer therapy. Ionizing radiation, high-intensity chemotherapeutic drugs, or toxic particles can cause DNA damage, activating safeguard molecular machineries and ultimately leading to or accelerating cell death.

6.1. Intracellular Uptake Mechanisms

Nanoparticles enter cells mainly through processes that are considered to be forms of endocytosis. There are two types of endocytosis mechanisms: phagocytosis and pinocytosis. Both are very inefficient, with a typical molecule transfer ratio of well below 5%, with the higher transfer ratios observed in synthetic particles. Pinocytosis is a nonspecific, passive flow of bulk fluid containing solutes into the cytoplasm. Cells acquire nutrients through macropinocytosis, which is a type of pinocytosis that results in macropinocytic vesicles capable of engulfing a large volume of extracellular fluid. Pinocytosed contents are delivered to lysosomes for degradation and release. Pinocytic uptake in both normal and cancer cells is generally fast, with most of the floatable drug taken up within a few hours. However, micropinocytosis has only limited selectivity because all extracellular particles are engulfed. Larger particles are only taken up by cancer cells engaged in more intense macropinocytosis. Larger positively charged colloids are more effectively engulfed compared to negatively charged particles and neutral lipid dispersions. Many types of nanoparticles are taken up fairly efficiently by cells, although few enter the nucleus. These intercellular targeting systems usually require invagination of either the endosome or plasma membrane. Invagination of the nuclear membrane occurs more effectively with nuclear

components.

6.2. Toxicity and Biocompatibility

Intracellular and extracellular biocompatibility of nanoparticles is an important issue in biomedical applications because signaling to the biological system can influence the behavior of cells and the immune response. One of the most harmful factors in quantifying the biocompatibility of both metal and low-dimensional nanoparticle systems is the release of inorganic ions and related toxic effects. Low-dimensional and nanosized particles are easily dissolved, and released metal ions show toxic effects that can be distinct from the toxic effects of the solid form of the corresponding particle. Which part of the particles plays a key role, and to what extent the toxicity of the type of nanoparticulate particle should be anticipated, are very important issues that must be quantified according to the safety and health criteria related to occupational, medical, and other settings in which nanoparticulates are manufactured or used. In order to predict or understand the interactions that occur at both the atomic or molecular level and between nanoparticle–biomolecules and nanoparticle–proteins, scientists have studied or used experimental approaches on various methodologies in the field of nanotechnology. When nanoparticles are applied as medicine, their particle size can play a key role in determining their circulation time in the body as well as their distribution, metabolism, and elimination, and can ultimately impact their bioavailability, therapeutic efficacy, and the possible occurrence of side effects. Future research should be utilized to better understand the severe challenges and questions in the context of nanoparticle toxicity and biocompatibility, the potential use of nanoparticulates in medicine and biology, and the behavior of nanoparticles in order to support commercialization while devising regulatory frameworks.

7. Clinical Translation and Regulatory Considerations

At present, very few nanoparticle cancer therapies have entered the clinical stage. The rapid growth in nanotechnology and nanomedicine has great potential to revolutionize patient care, but emerging products will need to meet safety and effectiveness standards before they can be approved for use and marketed to patients. This chapter discusses the statutory authority for medical devices intended for human use, the regulatory environment, and the approval process for new therapies, using the example of metal nanoparticles as anticancer therapeutic agents.

The medical device provisions of the Federal Food, Drug, and Cosmetic Act are primarily implemented through the premarket notification process to which all medical devices must undergo either before or after they are commercially distributed. The Center for Devices and Radiological Health is the responsible unit at the U.S. Food and Drug Administration for the review of devices intended for human use. In general, medical devices are those intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease, intended to affect the structure or any function of the body, which do not achieve their primary intended purposes through chemical action and which are not dependent on being metabolized.

7.1. Challenges in Clinical Translation

Because several imaging methods that are used for preclinical studies are the same as those in the clinic, there are natural opportunities for clinical translation. As several SPION-based negative contrast-enhancing agents are clinically established for MRI, SPION-based bimodal agents have also been studied in clinical environments, including those conjugated with antibodies against various cancer cell types. Especially because of the biodegradability and reuse of iron in the body, SPIONs are leading the way in this area. In the case of radiation-based cancer treatment, there are also natural pathways for clinical translation for AuNPs and FeNPs. In the first case, AuNPs preferentially accumulate in, for example, head-and-neck tumors and improve the effectiveness of radiation treatment by thousands of times if the beam energy is tuned for the characteristic X-ray

energy of gold.

In the second case, FeNPs increasingly accumulate in tumors after successive injections and damage both in the presence and in the absence of radiation treatment, inducing cell death by quenching cancer metabolism. Also, the heat from FeNP relaxation has therapeutic effects more broadly and safely by acting as a catalyst for various bioenergetic cellular reactions. Both are natural pathways for clinical translation of therapeutic NPs. Yet, the same challenges described here still need to be faced: NP heterogeneity, access to tumor models, long-term distribution studies, control of publication bias, feature-based publication of results, and statistical learning. Therefore, navigating this obstacle is extremely important in driving potential therapeutic NPs to the clinic and reducing patient financial risk.

7.2. Regulatory Guidelines

The testing of novel therapies in clinical trials has to follow a dangerous progression not previously experienced with conventional therapies or even with new but marginal modifications. However, if the toxicity is very low, safety data can start being obtained from the clinical trials. Biotechnology is a developing science-based technology of the 21st century, mainly through the molecular cloning and genetic manipulation of cells so that they can be recycled. Its origin is recent, and despite its huge potential, biotechnology does not yet reach sufficiently developed profiles. Regulatory agencies ensure a dynamic and evolving regulatory framework, defined collectively by experts from different countries and regulatory agencies, or are developed solely by those agencies.

Regulatory agencies established the quality, development processes, and a program to assist micro-enterprises in obtaining approval for generic proteins. The Rapid Alert Workshop Network investigates counterfeit drug cases. This integrated plan has been developed to ensure the safety and authenticity of new biotech drugs. Regulatory agencies have also established a unit to provide advice and scientific support in accordance with international harmonization. This establishment, following multiple other programs, intends to facilitate and streamline the process of marketing psychotropic treatment for children and adolescents. These regulatory guidelines provide special protection and ethical considerations for specific groups in society for specific deficiencies in the use of these technologies. [31][32]

8. Current and Future Applications of Nanoparticles in Cancer Treatment

We showed significant progress in the clinical applications of NPs in cancer treatment by understanding the basic NP-biology interactions, which then led to the development of various NPs. The most widely studied, investigated, and utilized NPs in cancer drug delivery are based on the principles of EPR and electrophoresis. The clinical effectiveness of NPs has been widely reported for TBAs, resulting in treatment times that are reduced by one-half to one-third of those in free drugs. Recent progress in the development of photoactive NPs, which exhibit strong absorption in near-infrared regions, provides a light-driven strategy that generates on-the-spot cytotoxic species that only destroy the NP cells. When appropriately utilized, this light-activated NP therapy causes minimal systemic toxicity of the whole body and eventually presents a cure for the targeted lesions. In addition to drug delivery applications, researchers have expanded NP functionalities in cancer therapy, such as hypothermia deployment, multimodal imaging, radiation sensitization, radiofrequency velocity, cancer grading, immunotherapy delivery, high-magnetic field control, photothermal chemotherapy, and reduction of tumor-associated fat by nanoparticles. Due to the versatility of NPs, controlled production techniques, excellent biocompatibility, high selectivity, and less toxic NPs, cancer targeting is expected to reduce patient side effects and improve survival through physicochemical modulation and clinical application, leading to more

efficient intervention strategies. [30][33]

8.1. Drug Delivery Systems

Microencapsulation technologies using biodegradable polymers applied for the delivery of conventional drugs can leak, plug capillary tubes, and delay the chronic delivery response. Nanoparticles are considered to hold promise for targeted delivery of these drugs to their desired site of action, reducing side effects and enhancing the therapeutic benefit. Physiological specificity may be enhanced by a number of mechanisms, the most popular of which may involve the use of macromolecular ligands or antibodies coupled to the nanoparticle surface to effectuate increased binding to various target tissues. A number of advantages, however, may be realized by a non-specific nanoparticle, including prolonged circulation in the blood, extravasation and access to tumor tissues through poor lymphatic clearance, and an enhanced partition coefficient into the cell. Small solid particles less than 5 μm in diameter have been shown to selectively localize in animal tumor tissues as a result of the leaky nature of the endothelial cell structure, especially in comparison to the tight junctions found in cells lining the blood-brain barrier.

In order to increase the specificity and alleviate the limitations associated with the use of these potent anticancer drugs, processes have been developed to fabricate non-specific and specific biodegradable nanoparticles of a size less than 5 μm utilizing various ceramic materials such as albumin, chitosan, polyalkylcyanoacrylates, and polymers such as poly(lactic-co-glycolic). These carriers allow the encapsulation of lipophilic drugs into their hydrophobic core or on their surface with a variety of pharmacokinetic profiles. It has been demonstrated both in vitro and in vivo that the release kinetics and location of the drugs can be tailored by adjusting specific particle size and composition controls and processes. Such controlled release of chemotherapy drugs from biodegradable nanoparticles may enhance the antitumor efficacy of the chemotherapeutic agent by maintaining effective drug concentrations in cancerous tissues for a prolonged period of time. A projected enhancement in therapeutic index is manifested by reduced side effects and, hence, larger quantities of drugs that may be administered, substantial therapeutic gain expected from the improved superior treatment outcome. Such drug carriers could have immense potential to emerge as potent players in the pharmaceutical world. [34][35][36]

8.2. Theranostic Nanoparticles

Because a similar type of cancer therapy, known as photodynamic therapy, uses molecular components serving both for detection and direct action on cancer cells, namely by local activation of a photosensitizer substance, the novel type of multifunctional nanoparticles facilitating the simultaneous detection of cancer cells and damaging them by one of the above-mentioned interactions, are termed diagnostic-therapeutic agents, or as recent literature prefers to say theranostic agents. It seems that photonic methods provide ultimate endoscopic, diffuse type, or superficial tumor detection techniques, very attractive for further development, as lasers and photodetectors are now a common place in modern medicine. Unfortunately, though over 100 continuous-wave excitable complexes are proposed for use as sensitizers for photodynamic therapy, the application of PDT in cancer treatment includes only several most spread photosensitizers. In particular, TPP and its derivatives are used for mitochondrial fluorescence imaging and laser photodynamic therapy of cancer tumors. [37][38][39]

9. Conclusion and Future Perspectives

In this report, we have reviewed, in essence, only a small segment of the immense recent progress in the application of nanoparticles to the treatment of cancer. The unique properties of nanoparticles offer remarkable potential for applications ranging from more effective delivery of known therapeutic agents to nanoscale thermotherapy. As will certainly be recognized, we barely

have scratched the surface of the application of nanoparticles to cancer detection and diagnosis. In considering uses of nanoparticles, we must remain cognizant of the fact that, very often, a lot of simple, straightforward answers will be employed. Moreover, we have attempted to emphasize as much as possible the relevant nanophysics of the systems we have considered, for such an approach should help provide an understanding of the principles behind the new applications of nanoparticles. The immediate prospects seem likely to favor the development of more effective nanodelivery vehicles for organic small molecule drugs and small nucleic acid constructs rather than the advent of entirely new drug entities. However, nanoscale effects are diverse and certainly very intricate; quite possibly unique chemical and biological properties will emerge for quite different nanoparticulate entities that will enable equally new and diverse therapeutic activities. It is an exciting time.

9.1. Key Findings and Contributions

Nanoparticle-based therapies in medicine, such as drug delivery, gene delivery, and hyperthermia, are receiving active research attention. These application areas extend to disease detection and imaging. In the current research, we study the mechanical aspects of the delivery of physiotherapeutic agents, both in the context of tumor reduction through robust heating via magnetization relations in drug-coated nanoparticles and to establish ideas that can boost therapies with immune system modulators using mechanical cell deformation. We advance theory, simulation methods, and technological design foundations for both aspects, culminating in a design for selective nanoparticle–cell assembly and guidance to the field in light of complex relationships between tumor reduction, heat delivery, hyperthermia treatment time, and immune aid in nanoparticle therapy cooperative development.

Nanoparticle-based tumor treatment is a promising direction supported by strong advances in nanoparticle design, fabrication, and application. It is known that tumor reduction in the framework of magnetic hyperthermia is aided by the immune system. Here, we are asking the question of whether it is possible to physically manipulate nanoparticles in a way that makes the immune system aid nanoparticle-related therapies more effectively and with fewer side effects. We are interested in the role of mechanical cell deformation by cold nanoparticles and consider two principal mechanical effects: slowed transendothelial cell migration of CD8+ T lymphocytes and increased regulatory T lymphocyte differentiation. The ideas advanced facilitate two selective strategies: functional targeting of CD8+ and regulatory T lymphocytes, respectively.

9.2. Emerging Trends and Future Research Directions

Nanoparticle research encapsulates a variety of interdisciplinary fields, including physics, chemistry, medicine, pharmaceutical science, and environmental science, and has undergone rapid growth in recent years. Despite significant advances, a number of research questions and technical challenges are still to be resolved. For the clinical application of multiple nanosystems to be possible, efforts need to be made regarding the following questions. As seen from the use of nanophosphors for fluorescent imaging, the biocompatibility and functionality of inorganic nanoparticles are still important issues to be addressed. Additionally, the medical application of inorganic particles is restricted due to their potentially toxic impact.

The easily defined high-throughput screening by DNA-encoded nanoparticles of the proteome and signaling processes may lead to a new era of pharmaceutical science. Ultrastructural mapping for stringent examinations of cytoplasmic macromolecules, cell metabolites, signal transduction, and drug activity can be obtained efficiently by scanning within cells. The use of nanostructures as transducers in water, urine, and mixture analysis showed the feasibility of using DNA systems to assemble peptides. Co-organization of multiple peptides relatively near their natural locations in

vivo can be implemented thus far by the DNA nanostructure. Precision in the co-alignment of proteins, nucleic acids, and chemical stimulants capable of forming a functional cellular machine may guide advances in both therapeutic strategies and mammalian biology. Such advantages, combined with reduced costs, promote DNA-directed materials as potential solutions for nanoparticle utilization in diagnostics, medicinal discovery, and the management of improved targeted agents specifically designed for rational medicine.

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