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Nanotechnology Applications in Cancer Therapy: a Physics-Based Approach

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Abstract: The physicochemical properties of nanoscale materials have not yet been incorporated in the development of current software tools for the simulation of biological systems. However, an integrated package at a computational cost adapted to the scale of this technology does not yet exist. We report a suite of software developed for filling this gap. The suite comprises three primary components: (a) a package for building material configurations and for guiding genetic/protein conjugation; (b) a package for optimizing material parameters with a genetic algorithm; (c) a LAMMPS-based package which computes thermal parameters and diffusion profiles of polymer and heat transmission properties for biological tissues. The implemented computational tools open the possibility to establish guidelines for the rational design of Polimer Curved Patch Antennas (PCPAs) as agents of microwave hyperthermia. The complex dielectric properties of the tumor and three designs of PCPAs injected into the tumor are considered. For the addressed frequency band the third

design ensures an improved deep and homogenous temperature distribution.

Keywords: Nanotechnology, Cancer Therapy, Physics-Based Approach, Polymer Curved Patch Antennas, Microwave Hyperthermia, Tumor Targeting, Nanoparticle Drug Delivery, Personalized Cancer Care.

1. Introduction to Nanotechnology and Cancer Therapy

From the ancient days to the current modern times, fighting diseases like cancer has been the concern of medical and scientific communities. Even though treatment methods are well developed, understating advances in technology is very important for the best possible solution to the cancer problem. In recent decades, nanotechnologies have improved the lifestyles and the quality of life of human beings dramatically. Most Abundant of all, nanotechnologies have evolved various nanomaterials that are broadly used in the scientific community and also daily life. These nanomaterials possess various properties that cannot be able to find in regularly used traditional micron-sized materials, e.g., superparamagnetism, enhanced mechanical properties, high thermal stability, etc. In particular, unique properties like this would enhance the final product or durability and would make it more tolerable and unique. Nanoparticles with a smaller size and high aspect ratio have unique properties compared to their bulk solids. In the last few decades, the advancement of numerous advanced nanomaterials has allowed scientists to develop a variety of approaches to the design of nanoparticles (NPs) according to the desired shape and size. In the current condition of the global market, a variety of selective nanomaterials are available for use in various fields by scientists and industries. Nevertheless, describing the usage of such nanomaterials is also crucial in understanding their final product result. [1][2]

Another main aspect of nanoparticles is that not only is the size, but also, its morphology would provide unique properties that different sets of both. Depending on the application, the morphology of the NPs is crucial to the product yield. Thus, various experimental advanced characterization and theoretical investigation are needed to understand and predict the NP morphology, and the subsequent unique properties. Some of the experimental methods for examining both the morphology and, further, the other characteristics are described as relevant. A skilled scientist can examine these potential-based experimental outcomes of the characteristics of the NPs and would modify the process parameters to obtain the desired end result. Both Scanning Electron Microscopy (SEM) and provide detailed information about the particles form, their elemental composition, the level or state of agglomeration, and can also deduce the roughness profile. For example, the undulations on the outer surface of the film or coating material can be identified by obtaining and subsequently examining the SEM micrograph. Based on the roughness parameters, one can create a simple I-function for smoothing or polishing the coated material. Furthermore, the SEM can also use EDS analysis to characterize the NP type and concentration in the common phase. During the coating process, the NPs can take a particular shape due to the applied temperature and optimize the applied voltage. The height and width of this responsible fallen arrangement NP agglomerate can be controlled by statistical modeling. For the uniform and organized arrangement of the NPs only, the uniform NP assembly having the best aerodynamic performance can be fabricated in the single-step process of the high-velocity oxygen transport plasma machine by optimizing the process parameters through this scientific approach [3].

1.1. Overview of Nanotechnology

The development and control of matter at a nanometric scale is called nanotechnology. Nanotechnologies are employed in the fabrication of nanomaterials for a wide spectrum of applications. Some key benefits of nanotechnologies and nanomaterials, realized in the last decade, have been to enhance the quality and durability of humankind's lives. Nanomaterials exhibit superior qualities by virtue of their physical, chemical, and mechanical properties compared to bulk materials of the same composition. One example is the sturdiness of silver nanoparticles against mildew, then enabling the application of nanocomposite coatings for improved duration of medical implants. A more well-known example is nanodrugs, which can become circulative, more resistant, and tolerable compared to traditional materials. There are four commonly posed questions about nanoparticles: what are they made of, what size and shape are they, and what properties thereof. Characterizing nanoparticles, particle size, morphology, and composition are separable and important properties to be evaluated.

A variety of techniques exist to define the dimensions of objects, the simplest of which is an indicator measurement. Knowing that the volume of a sphere scales with the cube of its radius and smaller objects have larger surface volume, particles smaller than about 20 μm have escalated chemical, mechanical, and optical properties; one can infer that even tinier particles, say less than 200 nm, harbor even more escalated properties. A common practice to know the size of nanomaterials is dynamic light scattering, yet there are more precise methods available, like atomic force microscopy and X-ray diffraction. Shape is one characteristic of the morphology, alongside roughness/surface area, density, porosity, and crystal structure—properties influenced by the conditions of particle preparation as well as storage. Shape can be particularly important for the so-called "man-made" crystals: ones that are engineered to perform a specific task based on their geometry. [4][5][6]

1.2. Overview of Cancer Therapy

Cancer is one of the leading causes of mortality worldwide. The goal of cancer therapy is to irreversibly eliminate cancer cells while sparing healthy tissues. The main treatment methods include surgery, radiation therapy, and chemotherapy with various combinations. Despite a tremendous effort put into improving cancer therapy, a great number of drawbacks remain. Surgery can be very effective if cancer is identified early, is localized, and does not spread to other organs. However, surgery can be very complex, the tumor might be inoperable, or the risk of surgical complications is significant. Radiotherapy can help kill cancer cells or reduce tumor growth by affecting human DNA. However, ionizing radiation inevitably affects healthy tissues making the treatment highly toxic. Radiation-induced health problems include fibrosis, myelosuppression, locomotor toxicity, and other types of tissue damage. Though it might be possible to deliver radiation to a tumor more 'precisely', a tumor is a continuously changing and growing system. At the same time, healthy tissues adjacent to a tumor can easily move during radiation exposure, which makes it very difficult to concentrate the dose of a lethal radiation only on a tumor. As for chemotherapy, it is known that a great number of drugs can be used to stop/delay the growth of a tumor with various mechanisms of action. However, drugs can affect the admixture of healthy and cancerous cells by the same mechanism leading to severe side effects and reducing the effectiveness. Chemotherapy drugs might be precluded from cancer cells by specific pumps, or cancer cells might have resistance pathways which decrease drug efficacy. Moreover, cancer can recur after a long period due to acquired resistance. But the main drawback of chemotherapy is the inability to deliver anti-cancer drugs to a specific location. The half-life of drugs in the body is very short, leading to multiple administrations over time. Because of the lack of desired selectivity, most of the administered drugs (about 95%) are removed in 10-40 minutes by kidneys. Given these significant drawbacks of available cancer treatment modalities, the development of innovative localized cancer therapy is on the rise. Nanotechnology is emerging as a promising technology with a physics-based approach that can be used for drug delivery systems that allow for targeting cancer cells . In the last 2 decades

much research is focused on nanoparticles (NPs) due to their uncommon optical, electronic, mechanical, and magnetic properties compared to their bulk counterparts, which make them very useful in medical applications. Their size, shape, surface properties, and high surface-to-volume ratio represent additional beneficial properties. With these versatile properties, the surface of NPs can be modified with various functional groups, including drugs, to design a multitask nanosystem. Such a system can deliver it to the target with a minimal drug dose while having improved biodistribution and longer half-life. Cancer therapy is an active research area for NPs because under a certain size they preferentially enter the cancerous tissue due to a leaky structure of tumor vessels which allows for NPs to be accumulated with the tumor – enhanced permeability and retention effect (EPR effect). Due to the ability to design NPs in a controlled manner, they can arrive at the same time and accumulate in a cancerous tissue. This presents a technological breakthrough in cancer therapy leading to the new direction – Nanomedicine – which is the result of the fusion of two or more disciplines, such as cancer research, physics, chemistry, and biology. It has been possible to treat cancer with hyperthermia using Fe3O4, which is then stimulated by an external oscillating magnetic field (MF) and induces tumor death. This approach demonstrates the highest effectiveness if it is possible to elevate the temperature of the tumor by a certain value (<5°C). One of the possible treatments is also based on the same photothermal effect but with the difference that a laser stimulates the NP accumulation. For this purpose it is possible to use noble metals like Au which have localized surface plasmon resonances (LSPR), making it possible to absorb light at specific wavelengths. Treatments from spaser from Ag Dimer Cluster (DC) avoid overheating the media and present a pulse technique. Fulfillment of that method allowed nearly complete ablation of tumor cells (as much as 90%) without affecting the viability of endothelial cells. On the other hand, there is significant research to design systems that help to localize antitumor drugs at higher concentrations and with a controlled manner to cancer cells. Amplification with NPs is based on the MPL overcoming tissue diffusion limitation. To do this, NPs are accumulated in the cells, and after being exposed to radiation, they produce shock waves and kill cells. Various reports confirm increased apoptosis of drug-resistant cells. DNS was filled with SiO2 NPs, acquired a negative charge, and included p-tetrahydro benzyl nitrocellulose which can reverse charge of the container. For charge reversal it is possible to use external MF adding to therapeutic scheme and improve the results of utilized drugs. Another way to improve the effectiveness of chemotherapeutic drugs could be using them simultaneously with NPs doped with Fe2+. Taking into account the spin orbit force Fe2+ NPs induces different trajectories in DNA of a cell than regular drugs leading to cell self-destruction with synergistic effect improving the effectiveness of cancer chemotherapy. A great number of calculations on NP systems applied in radiation therapy is based on the fact the tumor finds itself under an MF which induce to change phase distribution. This leads to a change in power deposition, increasing efficacy of tumor irradiation, decreasing doses of radiation to normal tissue up to 50%. From the perspective of a clinical point of view, the NP used in the treatment must be biocompatible. To estimate potential NP toxicity in the in vivo model, it is possible to use two approaches: to monitor the treated cell culture for a long time or follow the standard practice, obtain information in blood or induce tissue after treatment with NPs. In the latter, it is crucial to understand the exact mechanism how NPs translocate through the membrane cell into or outward the cell. Bio-distribution of NPs via lungs has also significant aspect due to inhalation of NPs in routine work. Oxidative stress induced by Au NPs could be inhibited by external cavitating MF. Dosage and concentrations of NPs useful in laboratory conditions could not be enough for clinical applications therefore, the effect of NPs without a significant concentration effect should be also estimated. Though many food items include carcinogenic hydrocarbons, their packaging might provide systemic exposure to NPs. Another potential threat could be STING protein activation by TiO2 NPs, producing unwanted proteins and autoimmunity. Cancer immunotherapy is part of the fourth pillar of cancer treatment, which have rapid progress in the last few years. There have been a significant number of works developing NP systems to improve immunotherapy efficacy. These systems range from NPs

improving immune cell uptake, to the improved delivery of to specific cells, to the mavas cell to produce antibodies. NPs including adjuvants have been used to improve cancer vaccine effectiveness. Economic feasibility could also be a significant concern in the matter of creating new formulations, although the enhancement of currently market drugs with NP systems could become a cheaper approach. [7][8][9]

2. Fundamentals of Nanoparticles in Cancer Treatment

Nanotechnology has enabled novel approaches that can complement cancer treatment for improved survival rates. In the field of oncology, these technologies have been work to overcome the limitations of conventional chemotherapy concerning the poor specificity, the low drug solubility, the rapid drug clearance, biodistribution and immune-response limitations, the emergence of multiple-drug resistance, the toxicity and the reduced therapeutic index. The physical principles that drive the behavior of nanoparticles, a variety of concepts are presented and the basics of the theoretical framework underlying these mechanisms are reviewed: electrostatics and Dipole-Dipole Interactions, van der Waals forces, Debye theory, electrical fields, magnetic fields and Langevin's equation, Agitation and Brownian Motion, thermal energy and Boltzmann's distribution, radiation, generation and attenuation [10].

As the patient survives several years after diagnosis, the rate of second primary tumors increased. These cancers can be connected to the first chemotherapy treatment. Related to this issue, nanoparticle-based drugs for cancer therapy are in the research focus as they have the potential to accumulate predominantly in tumor tissue by a passive or active targeting strategy or by a stronger retention due to the EPR effect, ensuring lesse side effects on surrounding healthy tissue. Many cancerous lesions are not further reachable by surgical methods, either because of their location, spread or size. Moreover, for patients with advanced-stage cancer, surgery is not an option anymore. In these cases, current standard therapy implies applying chemotherapeutic drugs or ionizing radiation. Progress in cancer understanding and in time-resolution imaging has described how current treatment procedures fall short. This has increased the interest in developing new approaches for the treatment of cancer by means of nanoparticles [11].

2.1. Properties of Nanoparticles

A quite significant amount of experimentation has been developed regarding the application of nanoparticles in cancer therapy, including the study of magnetic or plasmonic nanoparticles. However, most of these studies were done within the spheres of chemistry, biochemistry, or biology, and their physical effects on cells are not marginal, despite other effects such as chemical. In this regard, the present contribution is an analytic investigation in which physiological effects of varying temperature are taken into account. Throughout the discussion, units of length and time are presented in the metric system, the former is taken in terms of micrometers and the latter in terms of seconds. It is simply intended to demonstrate that the interactions of nanoparticles and cells can very well be explained by using physics exclusively, without resorting to biology. Any and all results could be widely developed, contrasting different cases employing parameter such as time and space of the action of heat, type of nanoparticles, size or shape of the latter, or physiological particularities of a specific organism [12]. Furthermore, this analysis ought to inspire further experimental work.

2.2. Targeting Strategies

First of all, it is necessary to distinguish between 'Tumor Targeting' (TT) and 'Tumor-Cell Targeting' (TCT), and exploit sensing to support these analyses. TT involves nanoparticles (NPs) that passively accumulate at the tumor site, usually taking advantage of the Enhanced Permeability and Retention (EPR) phenomenon. The effective TT motif is prepared with the corresponding 'Tumor-Addressed' antigen. TCT mode ready for per se preclinical performances involves NPs purposefully selected to target the cancer cells themselves. Then a series of TCT motifs specific to the desired kind of CS are conjugated to the NP. Under these circumstances,

the proper CS stage I should be used, which is where sensing comes into place. The link between the mNPs and the targeting motifs must be appropriately selected to prevent a loss in their targeted efficacy [13]. Focusing on metal-based nanoparticles, upcoming protocol details the necessary guidelines to perform a TT or TCT, taking full advantage of sensing techniques (dominant type of CS, optimal dimensions, etc.), and further analyzing the NP targeting efficacy. As for TCT, the easy-to-follow protocol provided could substantialize conclusions that could be of high interest for formulating the most appropriate targeting strategies in terms of CS and/or CS stage for the development of CS-based NP cancer theranostics.

3. Physics Principles in Nanoparticle Design

A well-established primarily physics-based framework was used to survey an extensive body of work for the effects of specific nanoparticle design parameters on overall NP performance in cancer applications. Physically motivated mechanisms were reviewed based on the literature in an effort to motivate the noted trends. In the age of FDA-approved NPs for tumor treatment, improved understanding of tumor-NP angiokinetics can guide design the next generation of tumor-oriented carriers [14]. Pre-treatment and time-shift protocols are considered with patient concerns in mind, and are predicted to drastically enhance NPs delivery to tumor cells even in the presence of ubiquitous systemic circulation conditions.

3.1. Quantum Mechanics in Nanoparticle Behavior

Nanotechnology is an interdisciplinary area attracting interest from chemists, physicists, bioengineers, material scientists, and physicians. This proposition is also true in the treatment of cancer diseases. The Enhanced Permeability and Retention (EPR) effect describes the accumulation phenomenon of macromolecular drugs or nanodrugs in tumors with an uncharacteristically high vascular density. The EPR effect causes the delivery of nanomedicines to the tumor site and increases their selectivity to malignant cells. The accumulation of nanodrugs in pathological neoplastic sites is a foundation of anticancer action. The functionalizations of nanodrug vehicles with a receptor for specific ligands, e.g., with biorecognizable moieties conjugated to the nanodrug surface, are needed for the active accumulation in cancer tissues. However, localization of the nanodrug vehicle in cancer cells is complicated by various phenomena, like immune response and opsonization that lead to the clearance of systemic circulation nanovehicles, a mononuclear phagocyte system that allows the nonspecific uptake of nanovehicles by the liver, or the tight intercellular connections/proteins of the cell as in the blood-brain barrier [15].

Nanodrugs may demonstrate unexpected properties due to quantum size effects, a consequence of small particle sizes, in the range of 1-15 nm [16]. Based on the particle size of nanodrugs, the quantum confinement of electron movement forms the basis for understanding the potential of quantum designs composed of the semiconductors of transition metals. Unlike the traditional field of pharmacology, in which the therapeutic indices of drugs intend for their accurate delivery to the sites of action, much recent research has shown that transition metal NPs in the size of quantum dots can move from their site of administration, cross bioinert morphological structures including the blood-brain barrier and blood-air barrier, and reach deeply into the CNS and pulmonary parenchyma, leading to fears that they may cause novel types of toxicity.

3.2. Electromagnetic Interactions

Nanomedicine or nanotechnology for healthcare uses small materials already present in the body i.e., in the form of Calcium Phosphate in the bones but raises concern when inhaled or ingested in nanoparticulate form. In the nineteenth century already it has been well known that particulate material are more toxic than bulk material and also seen that long inhaled fibers in rats and hamsters provoke diseases that are not generated with bulk material. The European Group for the Evaluation of the Carcinogenicity of Chemicals in Food, Consumer Products and the Environment issued a policy statement expressing concern about the potential of nanomaterials

to cause cancer due to their high reactivity of ROS of ultra fine materials ([17]). However with nanoparticles the ROS generation is greatly increased while with microparticles an increase in the ROS generation was not observed being primarily of mechanical etiology, and hence restricted to airborne particles.

Since 2001 nanotechnologies are experiencing an amazing development in the field of biology and medicine allowing an important contemporaneous evolution in the cancer care domain. Indeed, cancer is still a major cause of mortality in developed countries. However chemotherapy cures only a fraction of cancers, most of them being resistant to usual treatments and inducing harsh side effects. Such a gathering of difficulties inspires hope for the realization of significant progress thanks to the development of these new technologies. In another hand, physics' concepts in nanotechnology are really different from biology's ones. Indeed biological systems are mainly described by rates of reactions or probabilities to have effect whereas physical one can be described by equations involving force, mass, energy and geometry. Thus physics may point out some specific limitations in drug discovery strategies. It is the reason why this article will focus more on physical than biological aspects of drug delivery in nanomedicine.

4. Nanoparticle Synthesis Techniques

4. Overall There are several nanoparticle synthesis techniques: (a) Physical, e.g. milling, laser ablation, evaporation-condensation, (b) Chemical, e.g., metallic, micelles, sol-gel, hydrothermal, microemulsions, (c) Biological/Environmental, e.g., bio-coating, green synthesis, spider silk, biomineralization, virus-templated growth, (d) Bulk combination, e.g. blowing powders, sintering, add nanoparticles to the bulk material, (e) Combustion, e.g., sol-gel combined with combustion, flame spray pyrolysis.

There are many techniques including milling, laser ablation, evaporation-condensation, elements in these groups. For the second question, yes, all other means of making nanoparticles involves altering their chemical properties or putting a desired coating. This includes using metallic, micelles, sol-gel, hydrothermal, microemulsions techniques, modifying the size or working environment to meet specific results: increase drug stability, improve biodistribution, and evade immune recognition. However, physical methods are unable to completely control any one set of particle characteristics during synthesis.

A new understanding of many time oriented natural systems is possible that one can almost predict the future when faced with examples of certain systems. Growth and decay processes of natural systems are generally more predictable than chaotic behavior. Though the development of systems is often chaotic, it may be predicted with exactness. The addition of one capability will return the system to its prior chaos. Instead, complex temporal behavior can be assigned in only a limited number of conditions in natural systems. [18][19][20]

4.1. Top-Down vs. Bottom-Up Approaches

Presently, all types of researches are undergoing, developing new techniques for simpler, more practical ways of fighting cancer. In this respect, nanotechnologies, nanomaterials, have gained importance, proving to increase quality and durability of human lives positively. Advanced treatment methods supported by physical applications propose more attractive results. There are reports in the literature, which nanomaterials possess specific properties like physical, chemical, magnetic etc., [3]. These properties provide improvements, such as, pro-longing drug circulation, resistance, tolerability, enhancement etc., more effectively than traditional materials used. They also become feasible for various other applications besides their improvements on drugs. A number of characterizations are employed in the examination of nanoparticles (NPs) such as scanning electron microscopy, X-ray diffraction, Fourier-transform infrared, energy-dispersive spectroscopy, and thermogravimetric analysis. There are also selective nanomaterials, which are convenient for various fields since they possess properties, which suit their necessities. Morphology is the most elementary property of NP since it governs other properties as well.

There are bi-, tri-dimensional features such as size, shape, anisotropy etc. While size is a dimension, which is easy to control, the shape constitutes a property, which is quite challenging to be controlled. Various techniques supplement morphological observations. Out of these techniques scanning electron microscopy and transmission electron microscopy are the most commonly used for morphological studies. These techniques provide the necessary knowledge about NP shapes, mono-poly elemental composition, agglomeration, roughness etc.; forces of NP-X29As:30-31 the homogeneity dispersion of NPs are vital in applications, which require diversely shaped NPs such as cosmetic products, fabrication. Astoundingly, this property enables magnified biomedical studies. There are also significant interests, which extend to other physical properties, e.g. melting point increment, transmission deficiency due to quantum effect, photo-acoustic radiations, adsorption of radiation gases, which are diffused by NPs. There are nanoparticles in the metallic forms, which provide a possibility for radiation gases such as hydrogen, helium. Applications of these gases have been proposed such as food storage, pollution detectors; moreover, driving fields are developed in medical uses like storing thermal energy.

4.2. Chemical Vapor Deposition

Chemical vapour deposition (CVD), or one of its variants, such as photo-initiated chemical vapour deposition (PICVD), is an equally viable particle functionalization technology [21]. The role of temperature is different in the different variants of CVD. In thermally-activated CVD, the monomers are made to react and deposit as a film on the substrate through increasing their temperature. PICVD, expanded and flash-activated CVD operate differently by initiating monomers at high energies. While these CVD methods depend on the energy of photons, electrons, holes, and ions to decompose the monomers and deposit a film, they have the potential of doing so with a wider range of monomers as compared to the thermally-activated CVD. Concern for the environment, as well as the great demand for prints in color or black-and-white on an industrial scale, motivated researchers to come up with cheaper ways to produce inks. As such, inks for processes such as photocopying, offset printing, flexography, and so on, that are dependant on the quality of pigments with certain characteristics were developed. With the advent of the CVD of polymer, diamond, silicon carbide, and microcrystalline silicon, an intense effort has been made in adapting it to the modification of nanoparticle surfaces. Sixteen years after the first patent was granted on the passivation of porous silicon surfaces by PICVD, many researchers are still trying to adapt it to modify nanoparticle surfaces. This technology enables the functionalization of nanoparticles with virtually any organic compound. [22][23][24]

4.3. Sol-Gel Synthesis

After synthesis of the monodispersed NPs using a suitable method, the next step would be to coat the NPs with a protective cover. The protection is essential to stop agglomeration of the NPs due to both the Van der Waals forces and the forces between contacting species, such as the ballistic and frictional forces present when the NPs are injected. Similar to the dose calculations made in conventional treatment planning algorithms, magnetically induced dose distributions can be generated through a simple modeling approach. The thermal energy generated by the NPs can be modeled through fundamental physics using appropriate thermodynamic laws to relate the heating pattern of the NPs to the energy received at a given tissue site. Ultimately, the goal of these methods is to improve the understanding of the basic principles governing the biophysics of NPs, to quantify the biological response of cells and tissues to NPs, and to facilitate the design of implementation of new experimental approaches to further investigate these aspects, ideally leading to the development of new therapeutic technologies in nanomedicine. Two types of NPs are of interest for the treatment: metallic NPs and superparamagnetic iron oxide (SPIONs) NPs. Optimal NPs are used when heating the NPs can eliminate cancerous cells while keeping healthy cells undamaged in the surrounding tissue [3].

5. Characterization Methods for Nanoparticles

Nanoparticles (NPs) are being pervasively researched for application in cancer therapy. Measurement of drug-loaded NP size, shape, distribution, and molar mass became important elements for the validation of their quality. Characterization methods, by which one can probe the properties of NP-containing solutions, are necessary in the industry and laboratory environment to validate NP-based drug quality. Capabilities, pros, cons and solutions for a vibrating sample magnetometer, Fourier-transform infrared spectroscopy and dynamic light scattering for NP research were presented as examples of such a framework.ourcemetry is defined for a single peak, the widths of the multi-modal NP populations would be averaged and not indicative of the smallest NP population. Conversely, analyzing multiple peaks results in peak widths that increase with cumulative intensity [25]. Certain Correlations particle sizesdls is sensitive to gradient statein the recent estimation of the lsa uncertainty has been expanded to size-distribution independent dynamics. Nevertheless, taking best of the state of the art DLS hardware, detectability of modal sizes is constrained by a range of volumetric fill factors. The modeling provides a predictive process that may be used at the point of synthetic design or post-synthetically to assist in parametrization. Certain Correlations between particle size, molar mass, concentration and shape properties and the derived sizing modality and its operationalizability are shown to be necessary.

5.1. Scanning Electron Microscopy

Scanning electron microscopy (SEM) is currently used not only for studying the structures and morphology of biological samples, including biomedical and biotechnological research, but also for developing and observing artificial nanostructures. Scanning electron microscope (SEM) technology, coupled with analytical techniques such as energy dispersive X-ray spectroscopy (EDS) to perform elemental mapping, is widely exploited. This technology is appreciated for its possibility to obtain a highly magnified image of a biological, biomimic, or nanobiotechnological sample and its three-dimensional perspective of images, thus overcoming the other two classical prerequisites of light and transmission electron microscopy (TEM). Cancer is one of the principal causes of morbidity and mortality worldwide. Still nowadays, radiotherapy and chemotherapy are frequently used to treat solid tumors, but the severe side effects associated with these treatments are a strong stimulus for investigating alternate strategies. In the field of nanotechnologies, the possibility to synthesize particles of a few nanometers in size has opened up the exciting opportunity to create a novel generation of nanodevices, the synergistic combination of the physicochemical properties of the material and the unique characteristics of the nano-size enabling completely innovative applications. Consequently, during the past decade, a wealth of papers has studied the effects of NP administration on cancer cells, and especially NPs potentially suitable for being used as carriers of different active principles have been assayed [26].

5.2. Transmission Electron Microscopy

To a physicist interested in the applications of nanotechnology to cancer therapy, what are the most exciting recent developments? Experimental results are described that use the techniques of the physicist to answer the questions of the biochemist. The methods of making dynamic measurements of the properties of polymerization in vivo showed a heterogeneous reaction proceeding by a different mechanism from free-radical polymerization in vitro. Ideas for a biophysicist looking for problems in the nanopharmacy of cancer. How the transporting of particles within the body is best tackled, especially whether to treat the system macroscopically or to take detailed account of each particle. How theories of the radiobiology of nanoparticle effects could be tested by combining in vitro experiments with computer modelling of the dose distribution produced in the cell nuclei?

Electron microscopy is at present the only technique able to image objects down to the nanometer size range. Although the apparent resolution of an electron microscope image is on

the nanometer scale, it represents the arrangements of clusters of a great many atoms and electron microscope images give a contrast that provides information on atomic number and crystallography as well as morphology. However, the wide application of ultrastructural analyses in cell biology has recently permitted the import of these well established techniques in this new field of research into innovative nanoconstructs. The abundance of recent applications of electron microscopy in the study of the interaction of nanoparticles and biological systems in the drug delivery arena is the clearest evidence of the great potential of electron microscopy in the field of nanomedicine. [27][28][29]

6. Drug Delivery Systems Using Nanoparticles

Nanoparticles hold tremendous potential as an effective drug delivery system. Many nanoparticles, including liposomes, dendrimers, and nanoemulsions, have been used as vehicles for drug delivery. Nanoparticles have been used for drug delivery in various routes of administration, and the use of nanoparticles as drug delivery devices contributes to enhanced formulation development for new and existing drugs. Many nanoparticles represent a promising class of drug-delivery devices because they can be used in a controlled and targeted manner. Nanosuspensions are colloidal dispersions of solid drug particles in an aqueous or non-aqueous vehicle. Nanosuspensions for drug delivery have proven useful for both intravenous and non-intravenous routes, and can improve the solubility and bioavailability of poorly soluble drugs. Research on PTX/CS nanosuspensions is focused on their potential application in drug delivery. Cancer is one of the most common diseases that usually affects older people, however, there are different types of cancer that can affect people of any age. In recent years, nanobiotechnology has become a growing field of research. Currently, there is a great interest in the application of nanobiotechnology as a means to develop new drug delivery systems and tools for use in research, diagnosis, and therapy. In therapeutics, nanobiotechnology is used to deliver drugs, genes, and other biomolecules.

Research in nanobiotechnology differs because drug delivery systems are used for medications that work by modulating the patient's response to the disease; they must, therefore, be taken continually and can cause severe side effects. As a result, research in nanobiotechnology transitions into the exploration of the ability of bioactive compounds to prevent diseases, which are generally well tolerated by the body. In recent years, the pharmaceutical industry has been focused on developing new types of encapsulated drugs, known as nanocapsules. A nanocapsule is a core-shell type drug delivery system in which the drug is confined to a cavity that is surrounded by a polymeric membrane. Along with nanosuspensions and nanocapsules, there have been continuing efforts to improve or create new forms of nanoparticles that have an appreciable porosity and a high specific surface area. The common denominator for these materials has been the emphasis on their use as drug delivery devices. The application of these particles as drug delivery devices contributes to the enhanced absorption of bioactive agents with low bioavailability, enhanced formulation development for new and existing drugs, and allows for the delivery of these agents to various parts of the body, including those previously inaccessible [30].

6.1. Passive vs. Active Targeting

Targeted delivery of drugs is important for the safety and efficiency of cancer treatment. A common approach to increase the specificity of drug delivery is to encapsulate them into nanoparticles that preferentially accumulate in tumor tissues [31]. At this stage, the vast majority of cancer nanomedicines have a size between 10 and 100 nm, meaning they are predominantly cleared by the hepatobiliary system and to a lesser extent by spleen macrophages. On the other hand, detailed investigation of a variety of cancer models utilizing a range of nanoparticle types has revealed that many tumor types accumulate nanoparticles significantly more than healthy tissues, regardless of particles size. It was concluded that there are likely to be alternate, yet currently unidentified, clearance pathways for nanoparticles in cancer.

Most nanomedicines are currently in development accumulate in the liver and spleen following systemic injection, which can result in biological responses and off-target effects [32]. Multiple strategies have been explored to try and promote the effective delivery of nanomedicines to target cells and reduce off-target accumulation, including altered nanoparticle surface properties or the use of endogenous blood proteins as a means to improve colloidal stability and bioavailability. However, once systemically administered, these nanomedicines remain in the circulation for prolonged periods, resulting in passive interactions with non-targeted tissues that lead to low specificity and low bioavailability in the target organ.

6.2. Release Mechanisms

Current cancer therapeutics have many limitations driven from the high doses and broad range of exposure needed for efficacy, and applications of new nanotechnologies can provide improved solutions. A multifaceted current-limitation solution is presented, combining first quantitatively predictive in silico models for newly engineered gold nanoparticles, driven by basic first principles of physics, experimentation, and state-of-the-art medical imaging and treatment planning techniques [33]. The general strategy will be demonstrated with a silver nanoparticle model. If successful, the strategy will be broadly applicable to any nanomedical development, providing a novel paradigm in cancer therapy development, synergetic across multiple treatment development fields. While the synthesis and development of Nanoparticles (NPs) and their deposition within a tumor mass is of utmost importance for cancer treatments, delivery is the ultimate endpoint for a potential therapeutic agent. A physics-based methodology approach will be utilized by way of the ROSI program, the DEPOSAMI model, and the multi-modal image-guidance incorporating NP visualization and treatment planning algorithms.

In orthotopic disease models utilizing the biopolymer PRINT hydrogel system, 55 nm x 60 nm NPs preferentially deposited in both the primary site and lung metastasis of HER-2+ breast cancer. Plans with adequate coverage index deemed as at least 98% of an established threshold dose being prescribed to at least 99% of the primary tumor planning target volume - thereby ensuring total deposition forced by the binding mechanism behavior of the NP-cell microenvironment properties. Normalization to the modeled curcumin diffusivity provided well-optimized parameters across all studied behaviors and on average.

7. Nanotechnology-Based Imaging Techniques

Recent advances in nanotechnology have resulted in great progress of synthetic techniques, which become increasingly established in the design of many nanomaterials . Many of these nanomaterials, because of their unique features, have been explored for applications in bioimaging, tumor diagnosis, and therapy, with largely expanded opportunities. During the past years various types of nanomaterials have been used in medical imaging to selectively guide the use of family and cell biology studies and to learn about the biology of cancer cells. These nanomaterials have bright fluorescence, wide absorption cross sections, or strong magnetic moments. Because of their small size, the time it takes these nanomaterials to use is longer, and they enter delta tissues, including tumors. As the tumor graduates, patients can be given "contrast" nanoparticles as a form of diagnosis. This has several advantages. First, cancer is diagnosed earlier, leading to better treatment and cure. Second, the smaller tumor will take less time to heal and be cheaper to treat, making it easier for patients to pay the bills. Lastly, it will reduce the suffering caused by cancer. The general method is that nanoparticles attach themselves to cancer cells and vibrate when stimulated by radio waves. They then emit light of a particular wavelength, indicating that they attach to cancer cells and the presence of cancer. In this context, there is emerging promise of next-generation nanotechnology that is expected to offer a significant impact on imaging techniques, which have great potential to improve cancer diagnosis and prognosis. A simple glance through the current scientific literature evidences the great effort being made in using nanotechnology as a relevant tool for clinical purposes, ranging from imaging and diagnosis to targeted therapy. On one hand, the design of new nanoconstructs

is being developed towards their integration within contrast agents in conventional imaging modalities. On the other hand, as substantial progress was made in targeted nanoconstructs, there is a synergistic advance in the possibilities offered to functionalize these systems with specific ligands, hereby fostering their use in molecular imaging. With resolution characteristics in the nanometric scale, is already an essential complement in oncological imaging to surgery or conventional imaging methods. Up to now, most of the developed techniques aim at visualizing the tumor tissue; a relevant setback consists in the difficult assessment of the tumor margins, which are expectedly the most important boundary of the tissue to be surgically removed. At this point it seems that optimization fully requires the use of novel technologies and materials. [34][35][36]

7.1. Magnetic Resonance Imaging (MRI)

Magnetic resonance imaging (MRI) provides deep imaging of soft tissues, allowing molecular and structural abnormalities to be detected. Since the milieu of these abnormalities has an altered magnetic Relaxation Time (T1, T2 etc), MRI is an ideal diagnostic tool to detect such changes. The earliest MRI experiments were performed in the 1930s on bulk water samples, but attempts to adapt MR techniques for the detection of human cancers started in the 1950s. However, as it did not prove to be immediately successful, X-ray based approaches dominated throughout the second half of last century. In the early 1980s MRI was successfully introduced into the clinic, and since then its use in clinical oncology has grown exponentially [37].

In recent years, with the advance of dedicated high field standard MRI scanners, high field dedicated whole-body human MR systems with advanced RF probes, and optimized data acquisition sequences, MRI has been established as an accurate and sensitive imaging method. Nowadays, MRI is the standard method to examine soft tissues and organs. Despite not being a widely available imaging system, MRI is used to help with the diagnosis of serious or unusual medical conditions. MRI can also help investigate medical conditions that may develop post-infection and is likely to cause severe health condition in patients. In such situations, UVR or other type of referral is needed. Moreover, the GPs would be less familiar with the MRI system and they might be able to participate in the decision-making and planning of the scan. MRI has also the potential as a highly useful diagnostic tool for diseases where multiple organ systems are affected. For example, both the liver and the brain are affected by Wilson's disease, or the brain, one or more skull nerves and the cerebellum are affected by neurofibromatosis of type 2. The MRI scans show the typical changes associated with the condition. Nevertheless, MRI can also show other changes not readily detectable by other method. MRI has commonly been used for the observation of brain development and is an important tool for the diagnosis of various brain related diseases. Magnetic nanoparticles (MNPs) are modular, versatile, and responsive materials that may substantially extend the capabilities of MRI. Being a part of tunable, specifically targeted and bio-sensorized nanoscale systems, MNPs can provide the surveillance of numerous molecular processes in living organisms extending far beyond the horizon of contemporary imaging methods.

7.2. Fluorescence Imaging

Fluorescence imaging is a key non-invasive methodology. The general approach is to use a range of fluorescent molecules linked to gold nanoparticles. The idea is that different cancer cells express different biomarkers, which can be targeted by the correctly functionalized nanoparticles. In order to validate this model alone, the simplest case in which two cancer cell lines and two fluorescent molecules are used such that each cell line selectively takes up one of the fluorescent molecules is explored. To achieve this, the ratio of the two cell lines is monitored by calculating a number of different statistical measures of the images, e.g. components of the images themselves, image-simple ratios, image-simple differences, variance of the image intensity, and size of the tumours.

The method, however, requires quantitative comparison of the images with a given metric, i.e.

the measures mentioned above. This is easily realized with any predetermined metric, but ideally the images themselves should be assessed in a straightforward manner, without requiring any further training. A possible way to overcome this limitation is to average over a number of different measures. In such a situation a comparison is performed between a known cell ratio for each biomarker and the value of one of the statistical measures for this ratio in the fluorescence image at a given time.

8. Clinical Applications of Nanotechnology in Cancer Therapy

9. Conclusions and Future Direction There is great enthusiasm and promise for the application of nanomedicine in cancer therapy. Many preclinical studies have shown that nanoparticles can be used as efficient drug delivery vehicles, radiosensitizers, and contrast agents in cancer treatment. Translation of these exciting findings to clinical applications will benefit significantly from the application of a physics-based approach. Improved design of nanoparticles that takes into consideration the dynamics of the particle transport in physiological systems will enhance the effective delivery of anti-cancer drugs to solid tumors, which was a major obstacle in the past. At the same time, nanoparticles used as imaging contrast agents should maximize the anti-tumorigenic effects. Such dual-use of nanoparticles will make possible better monitoring and control of the performed therapy. Broad sets of in silico, in vitro and in vivo tools, already in use or under development, enable the performance of a reliable, cost-effective and humane numerical and physical experimentation, and thus holds great promise for the growth and application of nanomedicine in oncology. All these new tools, approaches and developments should facilitate interdisciplinary communication between the life and physical sciences and contribute to the rise of a new generation of experts in cancer nanotechnology.

8.1. Current Nanomedicines on the Market

Recent advances in nanotechnology have created the appearance of new hope for the detection, prevention, and treatment of cancer. Nanomedicine uses nanoparticles for several applications [38]. The treatment of cancer with nanomedicine can be divided into two categories according to the size of the nanoparticles used: “nanopharmacological” treatment when drug-delivery systems with sizes between 10-100 nm are used, and “nano-oncological” treatment when sizes above 100 nm are used. These categories are not very rigid. Indeed, micro and macro objects (above 100 nm) can also be functionalized into a treatment with nanopharmacological purposes.

In the first option, designed entities transport conventional anticancer drugs. The nanoparticles passively accumulate in the tumor tissue exploiting the enhanced permeation and retention (EPR) effect of the leaky tumor vasculature. This enables a better efficacy of the treatment due to the higher and controlled concentration of the cytotoxic drug in the tumor. Different nano-sized drug-delivery systems have been developed for this application and, at present, several of them are under clinical trials or have been approved and are available on the market. The main nanoparticles used in nanopharmacological treatments for cancer are based on proteins, polymers, lipids, and liposomes [11]. In the second treatment, designated nanoparticles transport therapeutic nanoparticles and distribute them in the required areas. Due to their sizes, they are frequently functionalized with a magnetic nanoparticles core, such as iron oxide nanoparticles, which act as a heat source in an alternative magnetic field or as a contrast agent in imaging.

8.2. Challenges and Future Directions

Although fundamental cancer research has made strides in understanding molecular mechanisms within cancerous cells, a comprehensive theory is still lacking. The majority of current cancer treatments mainly involve surgical procedures, radiation therapy (RT), and chemotherapy [39]. Because of their radical-cure claims, 5-year overall survival rates (OSRs) are currently most frequently used to evaluate their therapeutic efficacy. However, existing treatments have limitations, and consequently, treatments increasingly focus on interdisciplinary and multimodal techniques. Surgical methods appear to have perfected safe principles; nevertheless, in an effort

to prevent recurrence and distant formations, drugs as adjuvants are typically used in the perioperative period. RT, often in combination with surgery and/or drugs, can induce more kinds of DNA damage than chemotherapy; hence, it is typically used in non-operable cases or to minimize side damage to healthy tissues. However, prominent cells' repair mechanisms usually repopulate the fundamental work within hours. This has led radiophysics to exploit different technological directions, utilizing nanotechnological processes and combing them with hyperthermal and academic annihilation by positive pions.

Similar to RT's fundamental principles, which identify the physical parameters of ionizing radiation (IR) on the micro and mesoscale, a relevant approach for nanoparticles (NPCs) is also possible. Existing FDA approved nanomedicines are polymers and polylipids, used to coat cytostatics or encapsulate other drugs. Researchers are working on designing an advanced drug delivery platform based on hybrid nanostructures composed of several materials, often with organic and inorganic core particles coated with different covering layers. Such precise solutions based on nanoparticles offer the possibility of delivering chemotherapeutics to cancer cells, providing guidance for more selective and minimally aggressive surgical enucleation and increasing the effectiveness of RT. For these techniques, the future lies in the development of physics-based multifunctional therapy.

9. Regulatory and Ethical Considerations in Nanomedicine

In the context of medicine of the future, "Bionic Man" emphasizes a new class of healthcare systems that will provide potentially a large opportunity for advances in patients. One of the most important features of these healthcare systems will be the innovative concept of a new generation of treatment methods and healthcare processes, emphasizing the holistic approach aiming to bonding the emerging highly diverse spectrum of advanced technologies with the medical service outcomes. This idea becomes obvious when we jointly consider the potential outcomes of biology, biophysics, nanotechnology, robotics, IT, and medical sciences. Nowadays, this multidisciplinary area of science becomes familiar with the name of the bionics. A phantasmagorical five synergistically interacting areas [systems] are feverishly breeding some new comers which bring aesthetic and satisfaction in people's performance of physical tasks, opening new horizons for global economic growth and security.

The ethical and regulatory considerations about different safety-critical areas and the societal and business risk are divided into quantitative and qualitative methodologies. A model-based structure enables consideration of risk to nanomedicine under regulation or under investigation and the re-establishment of regulation to reduce risk is applied under abnormal operations, maintenance, and R&D activities. Technology that could provide an additional therapeutic fitness and with a much smaller size are called as nanobots. Such nanobots could also be used in cancer treatment on a regular basis by entering the bloodstream to seeking out and killing cancerous cells to avert metastasis, and also monitoring the tumor after the surgery. And they always duplicate themselves while the treatment proceeds. This vision is a little more like traditional miniaturized robots, but no metal gears, sensors and wires; everything is made of diamondoid nanomachinery.

10. Conclusion

To sum up, the book provides a lot of useful information about what cancer is and how nanoparticles can be effectively used with a physics-based approach. Human beings try to find alternative and convenient ways to fight cancer. Nanotechnologies and nanomaterials come into use because they are found to improve the quality and durability of human lives. Various properties of nanomaterials are mentioned. Among them, physical, chemical, and magnetic properties of nanomaterials are highlighted. The physical, chemical, and magnetic properties of nanomaterials enhance prolonged circulation of drugs and drug resistance through those materials, potentially better than those from conventional materials. Nanoparticles have been selectively designed so that their properties are suitable for a wide range of disciplines. Shape,

size, and size distribution of nanoparticles have received attention in this regard since they affect many properties of nanoparticles, such as chemical, mechanical, electrical, thermal, and optical properties.

A variety of techniques can be employed to characterize the properties of nanoparticles. Various technologies have arisen for the synthesis of nanoparticles so that there are selective nanomaterials to suit different requirements. In this regard, particular properties of nanoparticles, which are compared and related to other conventional substances or material forms, are considered. The selected property data presented for a variety of particles, sizes, and particle sizes are based on mathematical equations as well as on advanced modeling and simulation techniques.

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