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Theranostic Nanoparticles: Imaging and Therapy Combined

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Nanoparticles are de ned as structures that are nanometers in size (o en smaller than 100 nm) [1-4]. In contrast to atoms and molecules, nanomaterials have an extensive available surface area per unit of volume and tunable optical, electronic, magnetic and biologic properties, which can be obtained, in some cases, only in nanometer scale. ey can be engineered to have di erent sizes, shapes, chemical compositions, chemical surface characteristics, and hollow, porous or solid structures [5,6]. Nanoparticles can be made of materials of diverse chemical nature, the most common being metals, metal oxides, silicates, polymers, carbon, lipids and biomolecules. Nanoparticles exist in several di erent morphologies such as spheres, cylinders, platelets, tubes, etc. When used in living organisms, the study of these structures is known as nanomedicine. us, nanomedicine can be de ned as the use of nanoparticles for diagnosis, monitoring of physical and pathologic processes, for therapy and for control of biological systems [1].

Over the last years, many studies have been reported in order to describe novel drug delivery systems. In fact, nanotechnology can be used to prepare nanostructures which will present advantages over regular chemotherapeutic agents, especially against cancer. For instance, drug carriers can be tailored to overcome some of the mechanisms conferring drug resistance to multidrug resistant cancer cells [7]. Long-circulating nanocarriers, such as lipossomes, micells, lipid solid nanoparticles, and polymeric nanoparticles can accumulate in several a ected areas where vasculature is somehow abnormal, by the EPR (Enhanced Permeability and Retention) e ect. ese particles, typically, display higher bioavailability and concentration in targeted tissues. Furthermore, reduced side e ects compared with free drug were observed [8]. us far, Doxil and Abraxane are the most successful nanotechnology-based treatments on the world market. Both nanocarriers showed reduction of toxicity allowing for elevated doses [9].

Along with drug delivery researches other studies have been done to develop new tracers for diagnostic applications. Based on advances in molecular imaging, nanoparticles can be used to visualize, characterize and measure biological process at molecular and cellular level. Molecular imaging takes advantage of the traditional diagnostic imaging techniques and introduces molecular imaging probes to measure the expression of indicative molecular markers at di erent stages of diseases [10].

Radiotracer-based imaging either using single-photon emission computed tomography (SPECT) or positron-emission tomography (PET) is particularly suited for targeted *in vivo* molecular imaging. e major advantages of SPECT or PET molecular imaging techniques over other approaches include high sensitivity, the ability to make quantitative measurements, and the absence of a tissue penetration limit [11]. In addition, multimodality imaging (such as, PET/SPECT, MRI, CT, NIRF) can allow detecting the nanoparticle with various imaging techniques, providing more accurate and dependable data than SPECT or PET alone [10].

Currently, many e orts have been made to conciliate both therapy and diagnosis properties in just one particle, leading to advantages over single approaches. e word “theranostics” refers to the simultaneous integration of diagnosis and therapy approaches [12]. erefore, the purpose is to diagnose and treat the diseases at their earliest stage, when the diseases are most likely curable or at least treatable. eranostic nanomedicine shows better characteristics than other theranostics agents since they have advanced capabilities in an all-in-one single platform, which include sustained/controlled release, targeted delivery, and multimodality diagnosis and/or therapies.In works conducted in our labs [13,14], gadolinium-159 radioisotope (negative beta [1001 keV] and gamma [main energy: 363.54 keV] radiation emitter, suitable for theranostic applications) was encapsulated in liposomes functionalized with folic acid with mean size of 100 nm. ese particles were injected in mice aiming to imaging and study the *in vivo* antitumor activity and toxicity on tumor-bearing mice. e results showed that a er 31 days of treatment, animals treated with radioactive formulations had a lower increase in tumor volume and a signi cantly higher percentage of necrosis compared with controls revealed by histomorphometry studies. Furthermore, mice treated with these theranostic formulations exhibited lower weight gain without signi cant hematological or biochemical changes.

Other interesting approach aims to develop multimodal nanotheranostics systems that use co-encapsulation of multiple di erent diagnostic modalities and therapeutic in targeting nanomedicine platforms. As an example of studies published in recent years, we highlight the combination of a therapeutic e ect of a traditional chemotherapeutic drug (i.e. paclitaxel, doxorubicin) and an excitable probes agent for imaging (i.e quantum dots, gold or metals) [15]. In this sense, a work, conducted by Bae et al. [16], quantum dots and paclitaxel were incorporated in solid lipid nanoparticles functionalized with siRNA aiming anticancer theranostics. e prepared solid lipid nanoparticles/siRNA complexes was e ciently delivered both paclitaxel and Bcl-2 targeting siRNA into human lung carcinoma cells and exhibited synergistic anticancer activities triggered by apoptotic mechanisms. Furthermore, the intense uorescence of quantum dots within solid lipid nanoparticles enabled *in situ* visualization and intracellular translocation of solid lipid nanoparticles in cancer cells. Another example of multimodality nanotheranostic system was created by Chen et al. [17]. Nanoparticles were prepared with Doxorrubicin (DOX) conjugated to gold nanoparticles through Au-S bond by using a peptide Cys-Pro-Leu-Gly-Leu-Ala-Gly-Gly (CPLGLAGG),

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which is speci cally cleaved by the protease. Studies conducted in tumor-bearing mice showed that a er injection of the functionalized gold nanoparticles, the over-expressed protease in tumor tissue and intracellular glutathione conducted to a fast release of DOX from the functionalized gold nanoparticles, leading to enhanced e cacy on tumor growth inhibition and uorescent imaging simultaneously.

Saho et al. [18] introduced the concept of synergy of photothermally-activated physical and biological e ects in nanoparticle-drug conjugates for theranostic objectives. e authors utilized tumor necrosis factor-alpha coated gold nanospheres (Au-TNF) heated by laser pulses. *In vivo* studies demonstrated higher therapeutic e cacy in mice, over action of laser at wavelength of 690 nm with Au–TNF conjugates. In addition, according to the authors, the photothermal activation of low toxicity Au-TNF conjugates, which are in phase II trials in humans, with a laser approved for medical applications, opens new possibilities for the development of platforms for clinically relevant nanodrugs with synergistic antitumor theranostic action.

A multifunctional pH-sensitive polymeric nanoparticle system for simultaneous tumor magnetic resonance imaging (MRI) and therapy was developed by Liu et al. [19]. e nanoparticles were self-assembled using the multi-block polymer poly(lactic acid)-poly(ethylene glycol)-poly(L-lysine)-diethylenetriamine penta acetic acid and the pH-sensitive material poly(L-histidine)-poly(ethylene glycol)-biotin. e anti-hepatocellular carcinoma (HCC) drug sorafenib was incorporated inside the nanoparticles. Gd-DTPA complexes were distributed on the nanoparticle surface and vascular endothelial growth factor receptor (VEGFR) antibodies were linked to the surface biotin groups of nanoparticles to form the target pH-sensitive theranostic nanoparticles (TPTN). In *in vivo* anti-tumor studies, TPTN showed signi cantly higher antitumor e ect in H22 tumor (VEGFR overexpressed cell line) bearing mice compared to free sorafenib and a positive contrast agent, with higher resolution and longer imaging time (more than 90 min) in the MRI diagnosis of tumor-bearing mice compared to Magnevist , indicated that TPTN was a promising theranostic carrier which could be a platform for the development of novel multifunctional theranostic agents.

In conclusion, it is clear that nanotheranostic probes possess several advantages when compared with other traditional single approaches. ese new nanoplatforms may be used as diagnostic probes and therapeutic agents, resulting in an exquisite strategy to treat and monitor the stage of the disease using a single particle. Although much remains to be done to e ectively detect the real gains brought by theranostic nanoparticles, such as issues regarding nanotoxicity, we strongly believe that those particles will have great impact in the eld of nanomedicine.

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