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Biomedical Nanotechnology for Molecular Imaging, Diagnostics, and Targeted Therapy

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Biomedical nanotechnology is a cross-disciplinary area of research in science, engineering and medicine with broad applications for molecular imaging, molecular diagnosis, and targeted therapy. The basic rationale is that nanometer-sized particles such as semiconductor quantum dots and iron oxide nanocrystals have optical, magnetic or structural properties that are not available from either molecules or bulk solids. When linked with biotargeting ligands such as monoclonal antibodies, peptides or small molecules, these nanoparticles can be used to target diseased cells and organs (such as malignant tumors and cardiovascular plaques) with high affinity and specificity. In the "mesoscopic" size range of 5-100 nm diameter, nanoparticles also have large surface areas and functional groups for conjugating to multiple diagnostic (e.g., optical, radioisotopic, or magnetic) and therapeutic (e.g., anticancer) agents.

I. INTRODUCTION

Recent advances have led to multifunctional nanoparticle probes for molecular and cellular imaging, nanoparticle drugs for targeted therapy, and integrated nanodevices for early disease detection and screening [1-3]. These developments have opened exciting opportunities for personalized medicine in which disease detection, diagnosis, and therapy are tailored to each individual's molecular profile, and also for predictive medicine in which genetic/molecular information is used to predict disease development, progression, and clinical outcome. For medical applications, nanotechnology is often linked with biomolecular signatures or biomarkers that are correlated with a biological behavior or a clinical outcome. These markers are commonly defined as mutant genes, RNA, proteins, lipids, carbohydrates, small metabolite molecules, and altered expression of them. For individualized therapy, biomarkers enable the characterization of patient populations and quantification of the extent to which new drugs reach their intended targets. One example is the drug trastuzumab, a monoclonal antibody designed to target amplified and over-expressed the HER2 tyrosine kinase receptor found in only ~30% of breast cancers.

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II. QUANTUM DOT NANOTYPING

Semiconductor quantum dots (QDs) are tiny light-emitting particles on the nanometer scale and are under intense development as a new class of fluorescent probes for molecular imaging and medical diagnostics [4]. In comparison with organic dyes and fluorescent proteins, quantum dots have unique optical and electronic properties such as size-tunable light emission, superior signal brightness, resistance to photobleaching, and simultaneous excitation of multiple fluorescence colors. These properties are most promising for improving the sensitivity and the multiplexing capabilities of molecular histopathology and disease diagnosis. Recent research has led to highly bright and stable QD probes that are well suited for profiling genetic and protein biomarkers in intact cells and clinical tissue specimens. In contrast to in-vivo imaging applications where the potential toxicity of quantum dots is a major concern, immunohistological studies are performed on in-vitro or ex-vivo clinical patient samples. The use of multicolor QD probes in immunohistochemistry (IHC) is one of the most important and clinically relevant applications in the near term [5].

III. IN-VIVO TUMOR IMAGING.

Traditional *in vivo* imaging probes or contrast agents include radioactive small molecules in positron emission tomography (PET) and single photo emission computed tomography (SPECT), gadolinium compounds in magnetic resonance imaging (MRI), and isotope-tagged antibodies. In comparison, bioconjugated QDs and targeted nanoparticles provide a number of unique features and capabilities that could significantly improve the sensitivity and specificity of disease imaging and diagnosis. First, the size-dependent optical and electronic properties of QDs can be tuned continuously by changing the particle size. This "size effect" permits the use of a broad range of nanoparticles for simultaneous detection of multiple cancer biomarkers. Second, nanoparticles have more surface area to accommodate a large number or different types of functional groups that can be linked with multiple diagnostic (e.g., radioisotopic or magnetic) and therapeutic (e.g., anticancer) agents. This opens the opportunity to design multifunctional "smart" nanoparticles for multi-modality imaging as well as for integrated imaging and therapy. Third, extensive research has shown that nanoparticles in the size range of 10-100 nm are accumulated preferentially at tumor sites

through an effect called enhanced permeability and retention [3].

IV. Nanoparticle Drugs

The use of nanoparticles for drug delivery and targeting is one of the most exciting and clinically important areas in nanotechnology [2,3]. Nanotechnology is used to improve the efficacy and toxicity profiles of chemotherapeutic agents because these agents can be encapsulated, covalently attached, or adsorbed onto nanoparticles. It is also being used to overcome drug solubility problems, because more than 40% of active substances being identified through combinatorial screening programs are poorly soluble in water. Conventional and most current formulations of such drugs are frequently plagued with problems such as poor and inconsistent bioavailability. For example, paclitaxel (Taxol™) is one of the most widely used anti-cancer drugs in the clinic. It is a microtubule-stabilizing agent that promotes tubulin polymerization, disrupting cell division and leading to cell death. It displays neoplastic activity against primary epithelial ovarian carcinoma, breast, colon, and lung cancers. Because it is poorly soluble in aqueous solution, the formulation available currently is Chremophor EL (polyethoxylated castor oil) and ethanol.

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