

Nanotechnology in Biomedical Engineering: Advances in Drug Delivery, Diagnostics, and Cancer Therapy in the United States

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Abstract

In the United States, nanotechnology is a major area of current biomedical engineering research, influencing the way diseases are diagnosed, monitored, and treated. In the last 20 years, the U.S. federal funding for nanoscale materials such as liposomes, lipid nanoparticles (LNPs), polymeric nanoparticles, metallic and carbon-based nanostructures, and quantum dots has brought these materials from bench to bedside through the National Nanotechnology Initiative, the National Institutes of Health (NIH), and the National Cancer Institute's Alliance for Nanotechnology in Cancer. The review focuses on recent developments in three related areas: (1) drug delivery systems based on nanoparticles to enhance the solubility and targeting of bioactive molecules, as well as their pharmacokinetics; (2) diagnostics and biosensors based on nanomaterials that allow for the early and point-of-care detection of diseases; and (3) cancer therapy using nanotechnology, including nanocarriers for chemotherapy, nucleic acid therapeutics, and personalized vaccines based on nanoparticles. Special focus is given to the FDA approved nanomedicines, current clinical trials, and remaining regulatory and translational hurdles such as nanotoxicology, manufacturing scalability, and the lack of harmonized regulatory guidance, which still hinder clinical uptake. The review concludes with an outlook on new directions such as AI-assisted design of nanoparticles, multifunctional theranostic platforms, and mRNA-LNP cancer vaccines that are poised to shape the next ten years of nanomedicine in the United States.

INTRODUCTION

The design and manipulation of matter at the 1 - 100 nanometer scale (nanotechnology) has come from a theoretical stage into one of the most promising biomedical engineering technologies. Sustained federal funding since the National Nanotechnology Initiative in 2000 and translation funding mechanisms at the NIH and the National Cancer Institute (NCI) have placed academic medical centers, national laboratories, and biotechnology companies of the USA at the leading edge of nanomedicine research and commercialization [1, 2]. The unique physicochemical properties of nanoscale materials are not found in bulk materials or in small molecule drugs; they include a high surface-area-to-volume ratio, tunable surface chemistry, and the ability to pass biological barriers [1].

The three most advanced applications are drug delivery, molecular diagnostics and cancer therapy. The challenges of low aqueous solubility, high clearance in the bloodstream and off-target toxicity seen with many therapeutic agents have been partly overcome by the use of nanocarriers that can be used to deliver drugs [1], [3]. Nanomaterial-based biosensors are employed in the field of diagnostics, where they use the unique optical, electrical, and catalytic properties of nanostructures for the detection of disease biomarkers present in levels much lower than in typical immunoassays, thus allowing earlier and more accurate diagnostics [11, 12]. Nanomedicine has yielded some of the most salient clinical achievements for oncology, including the first FDA-approved nanodrugs such as liposomal doxorubicin (Doxil) in 1995, and lipid-nanoparticle mRNA platforms which have powered the development of the COVID-19 vaccine, and are now being repurposed to develop personalized cancer vaccines [15, 20].

This review offers a unified synthesis of these three domains with a U.S. focus. Changes in the field of drug delivery with nanoparticles are discussed in Section II. Section III discusses the nanotechnology-based diagnostics and biosensing. Section IV deals with the application of nanomedicine in cancer therapeutics, where FDA approved agents and upcoming immunotherapeutic platforms are discussed. The U.S. Regulatory Environment and Challenges for Clinical Translation are discussed in Section V. Section VI provides directions for future research and Section VII summarizes.

NANOTECHNOLOGY IN DRUG DELIVERY

RATIONALE AND CORE PLATFORMS

The classical pharmacotherapy is often limited by low solubility and/or non-specific biodistribution and/or fast clearance from the blood by renal or hepatic clearance. The limitations can be overcome by nanoscale drug delivery systems (NDDSs) in which therapeutic payloads are encapsulated, adsorbed or conjugated to nanocarriers that are designed to be engineered for controlled release, long circulation times and — increasingly — active targeting to diseased tissue [1, 3]. Clinical and preclinical applications include the use of lipid nanoparticles (liposomes, lipid nanoparticles containing polymer and solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs); dendrimers; inorganic particles (gold, iron oxide, silica); and viral and non-viral nucleic-acid carriers [3, 4].

The most clinically advanced class is lipid-based nanoparticles. Spherical vesicles known as liposomes, which were first described in the 1960s, can carry both hydrophilic and hydrophobic drugs, with the hydrophilic drugs remaining in the

interior of the vesicle and the hydrophobic drugs attached to the surface [4]. These also have the ability to accumulate more at sites of disease due to the enhanced permeability and retention (EPR) effect, which also makes them useful for carrying these drugs, and reduces the systemic toxicity of the drugs. Lipid nanoparticles are the platform that has gained traction in the delivery of nucleic-acid therapeutics, most notably for the mRNA-1273 and lipid nanoparticle (LNP) delivered BNT162b2 COVID-19 vaccines developed and deployed at scale in the United States, and the earlier FDA approval of patisiran (Onpattro), the first LNP-delivered siRNA therapeutic for hereditary transthyretin amyloidosis [20].

OVERCOMING BIOAVAILABILITY LIMITATIONS

Poor water solubility is a major issue for a significant proportion of new molecular entities under development for the U.S. drug market. They have been demonstrated to have significant enhancements in dissolution rate, absorption and bioavailability, and to allow for more precise regulation of drug release rate, through nanoscale formulation strategies such as nanocrystals, nanoemulsions, nanogels, and lipid-based carriers [3]. These strategies are especially relevant in the context of academic and industry drug-development pipelines in the United States where, compared to de novo drug discovery, reformulation of existing active pharmaceutical ingredients (APIs) through the use of nanotechnology provides a comparatively less risky avenue for improved therapeutic products [3].

TARGETED AND STIMULI-RESPONSIVE DELIVERY

Another important area of biomedical nanotechnology research in the United States has been the development of actively targeted nanocarriers that take advantage of receptor overexpression, tumor associated antigens or microenvironmental cues (such as pH, redox potential, enzymatic activity) to trigger the localized release of therapeutic agents [1, 4]. By functionalizing their surfaces with antibodies, aptamers, peptides or small molecule ligands that bind to cell surface receptors, nanoparticles can specifically bind and enter cells without harming normal tissue. Within the field of nanocarriers, stimuli-responsive (smart) ones which can release their payload selectively in the acidic or hypoxic tumor microenvironment are a particularly active field of investigation, and offer the potential of further enhancing the therapeutic index of the cytotoxic agent being delivered [4].

DERMAL, TRANSDERMAL, AND MUCOSAL DELIVERY

The topical and transdermal delivery systems based on nanocarriers such as SLNs, NLCs and nanoemulsions, have also made significant progress in terms of better skin penetration and sustained release and less irritation than traditional topical drug delivery systems. These systems are being investigated for a variety of applications including antimicrobial and anti-inflammatory treatment, and targeted cancer therapy, a wider application of nanocarrier systems than that of systemic administration [3].

NANOTECHNOLOGY IN DIAGNOSTICS

NANOMATERIAL-BASED BIOSENSORS

Early and accurate disease detection is a key element to improving clinical outcomes and nanomaterial based biosensors are a key technology to realizing the sensitivity and specificity necessary for early detection of biomarkers [11] [12]. A number

of biosensing platforms are based on metal nanoparticles (mainly gold and silver), quantum dots, carbon nanotubes, graphene derivatives and magnetic nanoparticles, all of which are employed as signal transduction and signal amplification components [5, 6, 9].

The major advantage of gold nanoparticles is their tunable localized surface plasmon resonance, a high surface-to-volume ratio and the ability to be easily bioconjugated; these properties make them the most widely used nanomaterials for colorimetric, electrochemical, and SERS-based assays for a wide variety of analytes [5]. Carbon-based nanomaterials, such as carbon nanotubes and graphene, have outstanding electrical conductivity and biocompatibility, allowing the development of transistor-based and electrochemical biosensors that can detect nucleic acids and proteins associated with cancer, at femtomolar to attomolar concentrations [12].

CANCER BIOMARKER DETECTION

There are numerous cancer biomarkers for which a nanomaterial-based biosensor has been developed, such as prostate-specific antigen (PSA), carcinoembryonic antigen (CEA), CA-125, HER-2, circulating tumor DNA (ctDNA) and various microRNA species [11]. The ability to detect multiple biomarkers in cells and tissue with high sensitivity has been achieved using fluorescence-based nanoparticle probes, which are antibody and/or aptamer functionalized [8]. Immunochemical biosensors using nanoparticle labels have also shown significant improvement in analytical sensitivity over traditional ELISA-based assays, and have significantly shortened the time and sample volume required for the assays [9].

One such example is the detection of ctDNA by coating magnetic nanoparticles with gold, allowing the detection of biomarkers at attomolar concentrations (10^{-8} to 10^{-20} molecules per liter of blood) that is orders of magnitude lower than what is possible through traditional clinical blood markers, showing the promise of nanotechnology in providing truly early cancer detection from liquid biopsy samples [10]. These can be extended to multiplexed panels of protein and nucleic-acid-based biomarkers for breast, liver, and bladder cancers by optical biosensing platforms such as SERS-based immunoassays and plasmonic nanopore sequencing approaches [11].

POINT-OF-CARE AND MULTIPLEXED DIAGNOSTICS

One of the long-term translation targets in U.S. biomedical engineering has been to miniaturize assays that utilize nanomaterials into portable, point-of-care (POC) devices. POC biosensors enabled by nanoparticles and microfluidic architectures enable access to diagnostic services beyond centralized clinical laboratories for the detection of biomarkers relevant to cancer, cardiovascular disease, and diabetes, in a rapid and low-cost manner [10] [14]. Recent new multi-analyte biosensor platforms also enable simultaneous detection of multiple protein and nucleic-acid biomarkers from the same sample, thereby creating a combinatorial biomarker signature that increases the diagnostic accuracy, instead of relying on a single analyte threshold. [13] In particular, magnetic nanoparticle-based POC platforms are becoming popular because they can be read using low power, simple equipment, and devices that are ideally suited for decentralized or resource limited testing environments [14].

NANOTECHNOLOGY IN CANCER THERAPY

CLINICALLY APPROVED NANOMEDICINES

Nanomedicine continues to have the greatest clinical impact in the United States in the field of oncology. Many nanoparticle-based chemotherapeutic agents are now in clinical practice, mostly in the form of lipid-based carriers that take advantage of the EPR effect for passive targeting to the tumor [4]; PEGylated liposomal doxorubicin (Doxil) was the first nanomedicine approved for clinical use in 1995 for metastatic ovarian cancer. Based on data from the American Cancer Society [11], cancer remains one of the major causes of morbidity and mortality in the United States and continues to be a clinical need for better delivery systems that increase the therapeutic window and decrease systemic toxicity from cytotoxic chemotherapy.

LIPID NANOPARTICLES AND NUCLEIC-ACID CANCER THERAPEUTICS

LNP-mRNA platforms' success during the COVID-19 pandemic spurred the speedy advancement of LNP technology into oncology. The development of delivery systems to co-deliver small-molecule chemotherapeutics alongside nucleic acids or immune modulators that will yield synergistic anti-tumor effects and overcome challenges of targeting specificity, immune clearance and scalable manufacturing is now underway based on LNP formulations. One of the most promising new applications of this technology in the U.S. oncology pipeline is the personalized neoantigen-based mRNA-LNP cancer vaccine, which are developed from an individual patient's tumor mutation profile; early-phase combination trials (e.g., personalized mRNA cancer vaccine plus checkpoint-inhibitor immunotherapy in high-risk melanoma) have shown that these vaccines lead to improved recurrence-free survival compared to checkpoint-inhibitor immunotherapy alone.

NANOPARTICLE-ENABLED CANCER IMMUNOTHERAPY

In addition, lipid-based and polymeric nanoparticles are being employed to address the pharmacokinetic and solubility challenges that plague many cancer immunotherapeutics such as cytokines, immune checkpoint inhibitors and antigen/adjuvant combinations of cancer vaccines [4]. Nanoparticle platforms can expand the therapeutic window of immunotherapies and may facilitate the simultaneous delivery of two or more agents per particle, which could decrease side effects of the systemic administration of immunotherapies.

TUMOR MICROENVIRONMENT TARGETING

There has been an increasing number of studies focused on the tumor microenvironment, such as targeting tumor associated macrophages (TAMs) which are a key component of tumor immune evasion and progression, directly. In addition to direct targeting of tumor cells, there is an emerging trend of cancer nanomedicine towards manipulation of the tumor immune ecosystem by functionalized nanoparticles designed to reprogram/mutate tumor associated macrophages (TAMs) [4].

REGULATORY LANDSCAPE AND CLINICAL TRANSLATION IN THE UNITED STATES

Although significant scientific advances have been made, the clinical translation of nanomedicines in the United States remains limited by a number of interrelated challenges. Nanotoxicology is still not fully understood: size, shape, surface chemistry and dose of nanoparticles critically determine the interactions with biological systems and the toxicity, and there

are not yet standardized in vitro and in vivo assessment methods for nanotoxicity [16]. Second, regulatory frameworks (such as FDA) have traditionally reviewed nanoparticulate products through standardized pharmaceutical or biologic regulatory pathways that do not adequately consider the nanoscale-specific physicochemical properties, which can lead to regulatory decisions on a case-by-case basis and extended timelines to approval [17]. Third, the manufacturing variability from batch to batch and scaling up the synthesis of nanoparticles from the laboratory to mass production remain challenges for many nanomedicines that have advanced to the clinical trial stages and are likely to reach the market [18].

To address these, the National Cancer Institute's Alliance for Nanotechnology in Cancer and other NIH-funded translational programs have provided support for common methods of characterizing nanoparticles, preclinical safety testing, and infrastructure for early-stage clinical trials. However, patient and disease heterogeneity, such as between individuals in the EPR effect and in the tumor biology, has led to few nanomedicines being used as first-line treatments, and clinical efficacy is frequently restricted to certain subpopulations of patients [16]. To overcome these translational hurdles, the regulatory science, uniform characterization protocols, and formulation design based on understanding a drug's mechanism of action must be better aligned among U.S. academics, industry and regulators [17] and [18].

CHALLENGES AND FUTURE DIRECTIONS

Several converging trends are likely to shape the next phase of nanotechnology-enabled biomedical engineering in the United States:

- **AI-guided nanoparticle design.** Machine learning approaches are increasingly being applied to predict nanoparticle biodistribution, optimize lipid and polymer formulations, and accelerate the design-build-test cycle for new nanocarriers, potentially shortening preclinical development timelines.
- **Theranostic platforms.** Multifunctional nanoparticles that combine diagnostic imaging and therapeutic delivery within a single construct are gaining attention as a means of enabling real-time treatment monitoring and adaptive dosing, particularly in oncology.
- **mRNA-LNP cancer vaccines.** Building directly on the manufacturing and regulatory infrastructure established for COVID-19 mRNA vaccines, personalized and off-the-shelf mRNA-LNP cancer vaccine candidates are advancing through U.S. clinical trials, representing one of the most clinically mature next-generation applications of nanomedicine [4].
- **Standardized nanotoxicology and regulatory science.** Continued development of harmonized characterization standards and regulatory guidance — potentially informed by international coordination — will be essential to reducing uncertainty for manufacturers and accelerating safe clinical translation [17].
- **Point-of-care nanodiagnostics.** Continued miniaturization and integration of nanomaterial-based biosensors with microfluidics and smartphone-based readout systems is expected to expand decentralized, early-detection diagnostic capability across U.S. healthcare settings, including underserved and rural communities [10], [13].

CONCLUSION

Nanotechnology has revolutionized biomedical engineering in the United States and ushered in clinically proven breakthroughs in drug delivery, diagnosis, and cancer therapeutics. Nanotechnology has been used to enhance the solubility and targeting, as well as the pharmacokinetic properties of small molecule and nucleic acid therapeutics, and nanomaterial-based biosensors have aided the advancement of the sensitivity and precision of detecting biomarkers, which allows earlier diagnosis and more precise diagnosis. In oncology, nanomedicine has led to a growing pipeline of FDA approved therapeutics and is at the forefront of next generation platforms like personalized mRNA-LNP cancer vaccines. However, there remain ongoing issues in nanotoxicology, manufacturing scale-up and regulatory harmonisation that are holding back clinical progress. To realize the transformative potential of nanotechnology in U.S. biomedical practice over the next decade, sustained investment in regulatory science, in standardized characterization methods, and in interdisciplinary collaboration between the engineering and the clinical and regulatory communities will be critical.

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