Review

CellPress

Cancer nanomedicine: from targeted delivery to combination therapy

Xiaoyang Xu[1,2,3], William Ho[1], Xueqing Zhang[1], Nicolas Bertrand[1,2], and Omid Farokhzad[1]

[1] Laboratory of Nanomedicine and Biomaterials, Brigham and Women's Hospital, Harvard Medical School, Boston, MA 02115, USA
[2] The David H. Koch Institute for Integrative Cancer Research, Massachusetts Institute of Technology, Cambridge, MA 02139, USA
[3] Department of Chemical, Biological and Pharmaceutical Engineering, New Jersey Institute of Technology, Newark, NJ 07102, USA

The advent of nanomedicine marks an unparalleled opportunity to advance the treatment of various diseases, including cancer. The unique properties of nanoparticles (NPs), such as large surface-to-volume ratio, small size, the ability to encapsulate various drugs, and tunable surface chemistry, give them many advantages over their bulk counterparts. This includes multivalent surface modification with targeting ligands, efficient navigation of the complex *in vivo* environment, increased intracellular trafficking, and sustained release of drug payload. These advantages make NPs a mode of treatment potentially superior to conventional cancer therapies. This review highlights the most recent developments in cancer treatment using NPs as drug delivery vehicles, including promising opportunities in targeted and combination therapy.

Nanomedicine in cancer therapy

Nanomedicine (see Glossary) is the design and development of therapeutics and diagnostic tools distinguished by the nanoscopic scale of its delivery vehicles and diagnostic agents [1]. The nanomedical field is rapidly gaining recognition through developing ways of administering treatment, particularly anticancer therapy, with unprecedented safety and efficiency. Researchers have improved on the current standards in drug delivery relating to biodistribution, intracellular uptake, and dosing efficacy by utilizing NPs to encapsulate therapeutic agents and target sites of disease [2]. The successful application of processes to improve the delivery of biomedical entities through functional NPs is a revolutionary approach to disease treatment. Several liposome- and polymer-based therapeutic NPs have been approved by the FDA for clinical use [1]. This review discusses the NPs under investigation with an emphasis on systems that have reached clinical trials (Table 1).

NPs are minute particles, typically less than 200 nm in diameter. Their nanoscopic size facilitates intracellular uptake. NPs have the ability to encapsulate therapeutic agents and release them in a controlled manner to specifically target diseased cells. NP encapsulation also improves the solubility of unmodified drug compounds [3]. Additional advantages of NPs have brought widespread attention to the field of nanomedicine, including their large ratio of volume to surface area, modifiable external shell, biodegradability, and low cytotoxicity [4]. Furthermore, nanomedicine brings us dramatically closer to realizing the full promise of personalized medicine [5].

Engineered therapeutic NPs offer numerous clinical advantages. Surface modification with polyethylene glycol (PEG) protects NPs from clearance from the blood by the mononuclear phagocytic system (MPS), markedly increasing both circulation times and drug uptake by target cells [2,6]. Functionalization of the NP surface with multivalent targeting moieties not only improves drug efficacy but simultaneously reduces the dose, providing a novel method to optimize drug pharmacokinetics [6]. NPs spatially localize through passive/active targeting and are capable of delivering drugs through epi/endothelial barriers [3]. Below we present some examples of engineered NPs and their features

Glossary

Active targeting: the targeted homing of NPs to sites of disease by modifying the surface of the particle with ligands specific to biomarkers overrepresented in target cells.
Amphiphilic: possessing both hydrophilic and hydrophobic parts.
Combinatorial nanodelivery: the delivery of more than a single therapeutic agent in one particle, often in an optimized ratio for synergistic effect. Multiple cancer pathways may be targeted with one particle.
Liposome: a spherical vesicle comprising a lipid bilayer.
Microfluidics: a technology used to quickly fabricate uniform NPs by manipulating minute amounts of liquid via channels on the micrometer scale.
Mononuclear phagocyte system (MPS): the MPS, also called the reticuloendothelial system, comprises the phagocytes located in reticular connective tissue present in the liver, lymph nodes, and spleen that are responsible for the eventual clearance of most NPs.
Nanomedicine: the design and development of therapeutic agents and diagnostic tools distinguished by the nanoscopic scale of its delivery vehicles and diagnostic agents.
Nanoparticle (NP): particles, usually comprising lipid or polymer, typically less than 200 nm in diameter.
Passive targeting/enhanced permeability and retention (EPR) effect: refers to the observation that the permeable vasculature and disordered basement membrane of tumor tissue leads to preferential accumulation of entities of 10–500 nm in size.
Poly(D,L-lactide-co-glycolide) (PLGA): a commonly used polymer for the construction of NPs, usually selected for its controlled release capabilities.
Polyethylene glycol (PEG): a polymer used to modify the NP surface, resulting in the prevention of nonspecific binding to blood components. These 'stealth' particles are better able to evade clearance by cells of the MPS.
RNAi: a pathway in eukaryotic cells where short pieces of RNA are able to induce the breakdown of complementary mRNAs.
Zwitterionic polymer: a polymer that is capable of exhibiting both positive and negative charges and has been shown to resist nonspecific protein adsorption.

Corresponding authors: Xu, X. (xiaoyang@njit.edu);
Farokhzad, O. (ofarokhzad@zeus.bwh.harvard.edu).
Keywords: nanomedicine; targeted delivery; combination therapy; cancer.

1471-4914/
 http://dx.doi.org/10.1016/j.molmed.2015.01.001

Table 1. Nanomedicines in clinical development

	Targeting ligand	Therapeutic agent encapsulated	Indication	Clinical status
Liposomes				
ALN-TTR02 (NCT01559077)	Passive	siRNA	TTR amyloidosis	Phase II
CALAA-01 (NCT00689065)	Tf	siRNA	Solid tumors	Phase I
CPX-351 (NCT00822094)	Passive	Cytarabine and daunorubicin	Acute myeloid leukemia	Phase III
MBP-426 (NCT00964080)	Tf	Oxaliplatin	Gastroesophageal adenocarcinoma	Phase II
SGT53-01 (NCT00470613)	Antibody fragment	p53 gene	Solid tumors	Phase I
TKM-PLK1 (NCT01262235)	Passive	siRNA	Solid tumors	Phase II
Polymeric NPs				
BIND-014 (NCT01300533)	Small molecule	Docetaxel	Solid tumors	Phase II
Atu027 (NCT01808638)	Protein kinase N3	siRNA	Solid tumors	Phase II
CRLX-101 (NCT01380769)/ (NCT00333502)/(NCT02010567)	Passive	CPT	Non-small cell lung cancer/rectal cancer/renal cell carcinoma	Phase II

that have been designed to address existing challenges in drug delivery, with a specific focus on cancer therapy.

NPs increase drug solubility, mitigate cytotoxicity, and improve drug pharmacokinetic profiles, as exemplified by nanomedicines such as Doxil® and Genexol-PM®. The past decade has witnessed numerous new biotechnological approaches to the treatment of cancer. For example, the 2006 Nobel Prize in Physiology or Medicine brought renewed focus on gene silencing, and the therapeutic opportunities offered by precise regulation of gene expression have fostered the interest of medical stakeholders in siRNA and miRNA technologies [7]. Nevertheless, delivering nucleic acids into cells is challenging to say the least: nucleic acids are vulnerable to nucleases ubiquitous in the blood and their dense negative charges hinder cell internalization. Furthermore, the nonspecific interferon response triggered by the presence of foreign nucleic acids in the cytoplasm is a major impediment to clinical translation [7–9]. To avoid these drawbacks, the ideal siRNA delivery system should efficiently encapsulate the negatively charged siRNA molecule, prevent degradation by endogenous enzymes, and facilitate cellular uptake and intracellular release.

Technologies already in clinical trials addressing the delivery of RNAi therapeutic agents are presented in the following sections. The last section highlights examples of current trends and novel applications of nanomedicine in the field of combination therapy.

Methods of NP preparation

Their nanoscale size means that NPs require a very specialized formulation method. The most common methods employ self-assembly processes to amphiphilic lipid, polymer, or polymer–drug conjugates. Such processes include nanoprecipitation, oil-in-water (O/W) single emulsion, and water-in-oil-in-water (W/O/W) double emulsification [10–12]. The most recent development in the synthesis of NPs involves the discipline of microfluidics, which is capable of manipulating nanoscale volumes in microscale fluidic channels [13]. Microfluidic reactors offer precise control and manipulation of the fluids used to create NPs. Microscale channels offer the advantage of a very large surface-to-volume ratio and controllable mixing time, which promotes higher NP yield and uniform size [14,15]. Through multi-inlet mixing at different ratios and hydrodynamic flow focusing, the NPs self-assemble through diffusive mass transfer at the interface of miscible liquids (Figure 1) [12]. Other significant advantages of microfluidics include the reproduciblility of device fabrication and rapid, consistent NP synthesis with narrow size distributions [14]. Microfluidic devices are tunable and can use 3D hydrodynamic focusing to create NPs of different sizes and targeting ligand densities with multiple polymers, which can in turn produce diverse NP libraries (Figure 1) [16,17]. In addition, microfluidics provides a means of rapidly and continuously forming consistent nano- and microstructures while simultaneously encapsulating drugs, which is not readily feasible with conventional approaches [18,19]. However, to take full advantage of the benefits of microfluidic nanoformulation, the challenges associated with the high costs of glass/silicon fabrication and large-scale production for clinical use remain to be addressed [14].

'Stealth' modification of NPs

Modification with PEG is currently the gold standard for NP coating [10,20,21]. PEG surface functionalization has been shown to dramatically reduce protein adsorption, particularly of apolipoprotein J and complement protein C3, through hydrophilicity and steric repulsion effects, with the effect of extending circulation time in blood [22–24]. This has allowed 'stealth' NP carriers to persist in the bloodstream long enough to reach or recognize their therapeutic site of action [25]. Examples of stealth nanocarriers include PEGylated liposomal doxorubicin (Doxil®) and the polylactic acid (PLA)–PEG micelle form of paclitaxel (Genexol-PM®). Since the first PEGylated nanomedicine, Doxil®, was approved in 1995, many of the current FDA-approved NPs and NPs in clinical trials have begun to carry the PEG modification. In addition to PEGylation, new biomaterials and delivery strategies have been developed to prolong the circulation time of NPs [26–29]. For example, zwitterionic polymer-based NPs are resistant to nonspecific protein adsorption due to electrostatically induced hydration [30,31]. Modification of the zwitterionic polymer with a pH-switchable moiety allows the NP