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Update on Current and Potential Nanoparticle Cancer Therapies

Jonathan S. Rink[1], **Michael P. Plebanek**[1,2], **Sushant Tripathy**[1,2], and **C. Shad Thaxton**[1,3,4,5,*]

[1]Northwestern University, Feinberg School of Medicine, Department of Urology, Chicago, IL, USA

[2]Driskill Graduate Program in the Life Sciences, Northwestern University, Chicago, IL, USA

[3]Robert H. Lurie Comprehensive Cancer Center of Northwestern University, Northwestern University, Chicago, IL, USA

[4]International Institute for Nanotechnology (IIN), Northwestern University, Evanston, IL, USA

[5]Institute for Bionanotechnology and Medicine (IBNAM), Northwestern University, Chicago, IL, USA

Abstract

Purpose of review—The purpose of this review is to summarize the most recent pre-clinical and clinical advancements in therapeutic nano-oncology.

Recent findings—First generation nanotherapies are well-tolerated in humans and evidence shows that they are efficacious while at the same time reducing the burden of side effects. Most of these therapies are not specifically targeted but take advantage of enhanced passive accumulation within tumors to preferentially deliver chemotherapies that are toxic when systemically administered. Actively targeted nanotherapies are entering the clinical arena and preliminary data are encouraging. Finally, a number of exciting pre-clinical developments in nanotechnology provide clear evidence that nanotherapies will continue to find their way into the clinic and will have a significant impact in oncology.

Summary—A number of intriguing nanoparticle therapies are being tested in pre-clinical and clinical trials. Nanoparticles with increasing molecular sophistication, specific targeting properties, and unique mechanisms-of-action will find their way to the clinic. Certainly, nanoparticle-based therapies will be increasingly represented in drug development pipelines, and will continue to provide efficacious and safe drug options for patients with cancer.

Keywords

Nanoparticle; Targeted Drug Delivery; Chemotherapeutic

Introduction

Cancer is the second leading cause of mortality in the United States, with an estimated 580,000 deaths in 2013 [1]. Thus, there is a significant need for new cancer therapies. Longstanding efforts to develop biological and small molecule cancer therapies continue to

*Corresponding Author: Dr. C. Shad Thaxton, Northwestern University, Department of Urology, 303 E. Chicago, Tarry 16-703, Chicago, IL 60611, cthaxton003@northwestern.edu, Ph: 312-503-1826.

produce new drugs, but at ever-increasing cost and reduced efficiency [2]. New opportunities need to be explored to increase the number of new drugs that make it to the clinic. Nanotechnology, the science of materials with size dimensions between 1–100 nm, is having a significant impact on the treatment of cancer. This review provides a brief overview of the potential and realized benefits of nanoparticle-based therapies and a summary of recent advancements in nanoparticles that are systemically administered to treat cancer. In this context, therapies based upon nanoparticles are FDA approved while more sophisticated next generation designs are being developed and introduced into the clinic. This article also highlights some exciting pre-clinical developments in nanoparticle therapies to illustrate their continued and, likely, increased presence in cancer drug development pipelines.

Features of nanoparticle drugs

Nanoparticle drugs are, typically, between 10 and 100 nm in diameter. The 10 nm lower limit is an outcome of the finding that nanoparticles smaller than 10 nm are filtered by the kidney and excreted in the urine [3]. The vast majority of current nanoparticle therapies for cancer, with some highlighted exceptions, are comprised of therapeutic molecules (e.g. small molecules, nucleic acids, etc.) that self-assemble with lipids or polymers into nanostructures [4–6]. There are many perceived benefits of nanoparticles; however, one critical benefit that has been realized in the clinic is a reduction in the side-effect profile of nanoparticle formulations of notoriously toxic small molecule chemotherapeutics. This is mostly achieved through drug targeting, either passive or active, by nanoparticles. Passive targeting is believed to result from the small size of nanoparticles and the enhanced permeation and retention (EPR) effect. Solid tumors can display increased vascularization and permeability, resulting in greater nanoparticle accumulation in the interstitial tumor space compared with normal, healthy tissue [7]. While the EPR effect has been exploited to target tumor cells pre-clinically, the heterogeneity of solid tumors may limit the effectiveness of EPR-based nanoparticle therapeutics in humans and has been the topic of intense recent investigation [8]. It is becoming clearer that a variety of factors influence the EPR effect and nanoparticle accumulation in tumors such as tumor vasculature, blood pressure, and tumor type (primary vs. metastatic lesion) and location. For active targeting, nanoparticles can be endowed with surface ligands that specifically bind to cancer cells. A prominent clinical example of an active targeting ligand, although not the first or only example, is transferrin (Tf), the 80 kDa glycoprotein responsible for delivering iron to cells. The transferrin receptor (TfR) is highly expressed on the surface of many cancer cells [9], therefore incorporation of Tf in nanoparticle formulations allows for preferential uptake.

Also, nanoparticles are tailorable such that they can be synthesized to bind and stabilize difficult-to-formulate hypdrophobic drugs or ones that require enhanced stabilization, such as nucleic acid-based therapies [e.g. short interfering RNAs (siRNA)]. With regard to nucleic acids, nanoparticles are playing a pivotal role in bringing this exciting class of therapeutic molecules to clinical reality due to the ability of nanoparticles to carry nucleic acids, stabilize them against nuclease degradation, and target their delivery to appropriate cell types. Tailorability not only allows one to incorporate diverse drugs, but also provides

an opportunity for multi-functionality in the form of targeting, multiple drug loading, or the addition of molecules that provide image contrast.

In short, nanoparticles can be functionalized with diverse molecular payloads and can preferentially deliver therapies to malignant cells while minimizing exposure to healthy tissue.

Passively targeted nanoparticles/small molecules

Several nanoparticle-based drugs have moved into the clinic [10]. Two well-known passively targeted nanoparticle therapies are Doxil and Abraxane. Doxil is a liposomal drug containing doxorubicin and Abraxane is a formulation of paclitaxel and albumin. The nanoparticles help improve the solubility of the chemotherapeutics, allowing them to remain in circulation longer, while ameliorating some of the adverse side-effects of the free drugs. While Doxil has been approved for treatment of ovarian cancer, recent clinical trials have been focused on combinational therapies, with efficacy seen when Doxil is combined with panitumumab to treat platinum-resistant epithelial ovarian cancer [11]; with rituximab, cyclophosphamide, vincristine and prednisone in AIDS-related lymphoma [12]; and with cisplatin in malignant pleural mesothelioma [13]. Abraxane, currently used to treat metastatic breast cancer [14] and ovarian cancer [15], is finding clinical success against pancreatic cancer [16], non-small cell lung carcinoma [17] and drug resistant metastatic cervical cancer [18].

Further, a recently developed self-assembled polymeric nanoparticle containing the topoisomerase I inhibitor camptothecin, called CRLX101 (formerly IT-101), has shown efficacy in phase I/IIa clinical trials in a variety of solid tumor malignancies, including non-small cell lung cancers [19]. Camptothecin is most efficacious when applied continuously to the tumor cells; however, prolonged exposure is associated with severe bone marrow suppression and hemorrhagic cystitis. Incorporation of camptothecin into polymeric nanoparticles improved delivery to solid tumor cells and was well tolerated in patients, with stable disease reported in 64% of patients [19].

Actively targeted nanoparticles/small molecules

Prostate specific membrane antigen (PSMA) is presented exclusively on prostate cancer cells and tumor-associated endothelial cells [20]. A short PSMA-targeting peptide, which binds to the extracellular domain of PSMA, was incorporated into a polymer-based nanoparticle encapsulating docetaxel (BIND-014). In pre-clinical data, BIND-014 demonstrated prolonged circulation, with controlled release of docetaxel and minimal liver accumulation in mice and non-human primates [21**]. In mice bearing human prostate tumor xenografts, treatment with BIND-014 led to an increased accumulation of docetaxel in the tumors and decreased tumor weights compared to free docetaxel [21**]. Preliminary results from a phase I trial demonstrated shrinkage of tonsillar lesions in a patient with advanced tonsillar cancer and of multiple lung metastases in a patient with metastatic cholangiocarcinoma [21**]. BIND-014 is an actively targeted nanodrug that has reached clinical trials, and illustrates the significant opportunity of targeted nanotherapies.

Nanoparticles and nucleic acid delivery

Nucleic acids, such as siRNAs, have long been studied as cancer therapies based upon their tremendous versatility and target specificity [22]. However, delivery of sufficient quantities of siRNAs to achieve target gene knockdown as a therapy for cancer is a major challenge. Nanoparticles have the potential to deliver therapeutic doses of nucleic acids to tumor cells. Critical to the design of these nanoparticles is the need for nucleic acids to avoid endosomal sequestration in order for them to reach the cytoplasm of targeted cancer cells where the mRNA target resides.

The nanostructure CALAA-01, consisting of a cyclodextran polymer, an siRNA targeted against the M2 subunit of ribonucleotide reductase (RRM2) and Tf, serves as an excellent example of a TfR-targeted nanoparticle for delivering siRNA. CALAA-01 has imidazole residues, a sink for protons in acidified endolysosomes, which can lead to endosomal disruption and siRNA release into the cytoplasm of target cells [23]. In a groundbreaking clinical trial, systemic administration of CALAA-01 to patients with solid tumors led to accumulation of CALAA-01 in tumor tissues, delivery of functional siRNA, and knockdown of RRM2 at both the mRNA and protein level [24**]. This is the first published report of RNAi occurring in humans and strongly supports the concept of siRNA-based cancer therapeutics. Additionally, CALAA-01 is a relatively complex nanoparticle formulation and demonstrates how such entities can be successfully moved to the clinic [25].

Lipid nanoparticles have displayed efficacy at delivering siRNAs in pre-clinical cancer models. Data show that modifying siRNAs with cholesterol, or other lipophilic moieties, results in their adsorption and stabilization by naturally occurring blood components that bind cholesterol, namely, lipoproteins and albumin [26*]. Based on these data, siRNA-containing lipid nanoparticles have been formulated for targeting cells that express lipoprotein receptors. Upon injection, siRNA-lipid nanoparticles are opsonized by apolipoprotein E facilitating their uptake into the liver through the LDL-receptor (LDLR), making them well-suited for targeting liver cancers and metastases [26]. A lipid nanoparticle formulation containing siRNAs against vascular endothelial growth factor and kinesin spindle protein, termed ALN-VSP, has recently undergone a phase I clinical trial [27**]. ALN-VSP was well tolerated by patients, whom had at least one measureable tumor in the liver, and treatment resulted in the knockdown of target genes in the liver tissue.

Without a doubt, many new passive and actively targeted nanostructures that carry nucleic acid-based therapies are on the horizon and will make their way into the clinic.

Beyond lipid and polymer-based nanoparticles

Lipid and polymer-based nano- and microparticles have run the gauntlet of development, approval, and clinical use faster than other nanoparticles, such as those based upon noble metals or other scaffolding nanomaterials. However, these nanoparticles are also making their way into the clinic. One recent clinical example is the use of gold nanoparticles (AuNP) to deliver the vascular disrupting agent (VDA) tumor necrosis factor-alpha (TNF-α). Currently, VDAs are hampered by dose-limiting side effects such as systemic hypotension and cardiotoxicity. Conjugation of TNF-α to AuNPs (NP-TNF) improves

tolerance in a mouse model by passively targeting the therapy to tumors and effectively disrupting tumor vasculature, enabling synergistic thermal therapies to decrease tumor volume [28*]. Conjugation of polyethylene glycol to the AuNPs allowed them to avoid clearance by the reticuloendothelial system [29]. Phase I clinical trial data demonstrated that systemic NP-TNF administration results in a TNF-α concentration that is three times as high as when TNF-α is given alone with no maximal tolerable dose achieved, suggesting that nanoparticle formulation of TNF-α significantly mitigated the adverse effects of systemic administration [29]. This study demonstrates that AuNPs are making their way into the clinic as a component of a systemically administered therapy that may provide a new and effective therapeutic opportunity for patients with cancer.

Pre-clinical nanoparticle-based therapeutics

Novel delivery

While most nanoparticle therapies are aimed at systemic administration, overcoming physical barriers to drug delivery, such as the blood brain barrier (BBB) and the stratum corneum of the skin can provide critical new opportunities for cancer therapy. Some recent examples demonstrate that nanoparticles may provide ways to overcome these barriers. For instance, to improve delivery of nanoparticles to the brain, AuNPs were surface-functionalized with Tf, which aided in shuttling the particles across the BBB via receptor mediated transcytosis [30*]. Also, in a pre-clinical model, AuNPs surface-functionalized with siRNAs, termed spherical nucleic acid nanoparticle conjugates (SNA-NCs), were able to fully penetrate mouse and human epidermal layers without additional agents needed to disrupt the stratum corneum, and with no observed toxicity [31**]. These SNA-NCs delivered functional siRNAs against EGFR, resulting in decreased EGFR expression and epidermal thickness in a mouse model [31**]. These examples demonstrate that nanoparticles will play an ever-increasing role in the delivery of therapeutics, in some cases, overcoming significant barriers that have traditionally been quite difficult to circumvent.

Targeted Drug Delivery

Pre-clinical research has focused on delivering an assortment of current chemotherapeutic drugs to cancer cells using a targeted nanoparticle platform. In addition to doxorubicin and paclitaxel, nanoparticle-based delivery of gemcitabine [32], docetaxel [33*], and cisplatin and irinotecan [34] have demonstrated promising results in the preclinical setting, ameliorating associated adverse effects and enhancing drug efficacy. A myriad of targeting moieties have been investigated for their ability to direct nanoparticles to tumor sites, including the HER2 monoclonal antibody Herceptin [35,36*], folate [37], and aptamers [33,38,39]. Additional work has focused on enhancing the penetration, retention, and release of therapeutic cargo of nanoparticle-based therapeutics in cancer cells by taking advantage of the relatively low pH and increased protease expression in the tumor microenvironment. For instance, matrix metalloproteinase 2 sensitive molecules [40], pH-sensitive linkers [41], and ester linkages [42] have been utilized to improve uptake and drug delivery to tumor cells.

Nucleic Acid Delivery

Pre-clinical investigations have utilized polymeric [43*–45] and DNA-based [46] nanoparticles to deliver siRNAs to tumor cells. Additionally, lipoproteins have been investigated as delivery vehicles for siRNAs modified with lipophilic moieties. Looking beyond the LDLR, HDLs have been shown to bind and stabilize native [47] and lipophilic nucleic acids [26] and are emerging as potent nucleic acid delivery vehicles due to their targeting of scavenger receptor type B-1 (SR-B1) expressed by cancer cells. Numerous tumor cell types express SR-B1 [48,49]. Surface-functionalization of 5nm AuNPs with apolipoprotein-A1 (ApoA1) and phospholipids resulted in HDL nanoparticles (HDL-NP) with similar size, shape and surface chemistry to natural, mature, spherical HDLs [50,51*, 52**,53**]. Cholesterylated nucleic acids adsorbed to HDL-NPs were shown to be resistant to nuclease degradation [52**]. Treatment of prostate cancer cells with these conjugates resulted in decreased target gene expression with data suggesting that the HDL-like delivery vehicle provided a means to avoid endolysosomal sequestration of therapeutic nucleic acids [52**]. Further, incorporation of siRNAs into reconstituted HDL (rHDL), consisting of ApoA1 and phospholipids around a core of siRNA and a templating polymer, yielded rHDL nanoparticles capable of delivering siRNA to silence target genes *in vivo* [47]. Finally, lipid nanoparticles containing siRNA targeted against the androgen receptor achieved knockdown in human prostate cancer cells both *in vitro* and in tumor xenografts [54*].

Novel biomimetic nanoparticle cancer therapies

While most nanoparticle research has been aimed at using nanostructures as drug delivery vehicles, new lines of investigation are being directed towards using nanoparticles with inherent biological function as cancer therapy. Biomimetic, synthetic HDL-NPs, like their natural counterparts, have been shown to tightly bind cholesterol [51*] and efflux cholesterol from target cells [51*]. HDL-NPs are synthesized using an AuNP template that occupies the real-estate reserved for esterified cholesterol in natural HDLs. As such, HDL-NPs bind to the high affinity receptor for natural mature spherical HDLs, SR-B1, and differentially modulate cholesterol flux [53**]. In diffuse large B cell lymphoma cells, this results in the induction of apoptosis *in vitro* and inhibits the growth of tumor xenografts [53**]. In this context, biomimetic HDL-NPs may represent a paradigm shift in how nanostructures can be used to generate new cancer therapies with novel mechanisms-of-action.

In addition to lipoproteins, exosomes are 30–100 nm nanovesicles produced by all cells and responsible for the intercellular trafficking of biological material like nucleic acids and proteins [55]. Researchers have begun to engineer exosomes for the targeted delivery of therapy, including siRNA, to cancer [56*]. For instance, mouse dendritic cells were engineered to produce exosomes with a brain targeting protein fused to LAMP2b, an essential component of exosomes. The engineered exosomes were loaded with siRNAs targeting beta-secretase 1 using electroporation and then systemically administered to animals. Treatment resulted in knockdown of beta-secretase 1 expression in the brain. In another study, exosomes derived from bone marrow stromal cells were engineered to contain miR-146b. Treatment of rats with primary brain tumors resulted in significantly

reduced growth of glioma cells [57]. These results expand on the idea of studying endogenous nanostructures to aid in the design of new therapeutics for cancer.

Conclusions

Nanotechnology is having a significant impact in medicine. Nanoparticle anticancer agents have been used in the clinic for some time and there are clear advantages of nanoparticles with regard to reducing the side-effects of drug cargo, enhanced tumor targeting, and, in some cases, therapeutic efficacy. Newer nanoparticles with increased active tumor cell targeting properties are making their way into clinical trials. In addition, an increased number of nanoparticle sub-types are gaining approval and being tested in humans. Thus, the armamentarium of approved nanoparticle drugs will certainly increase as regulatory agencies and clinicians become more familiar with their safety profiles and efficacy. The pre-clinical literature is replete with examples of nanostructures that improve upon the properties of previous ones with regard to drug cargo, targeting, and reduced toxicity. Particular recent examples hint at the use of biomimetic, inherently functional nanostructures to derive therapeutic effects in cancer. Certainly, the need for new cancer therapies is significant and nanoparticle-based ones will find an ever-increasing presence in the clinic, hopefully, to the benefit of cancer patients across the spectrum of disease activity.

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References

1. American Cancer Society. Press Release. 2013. Cancer facts & figures 2013.
2. Mestre-Ferrandiz, J.; Sussex, J.; Towse, A. The r & d cost of a new medicine. London: Office of Health Economics; 2012.
3. Davis ME, Chen ZG, Shin DM. Nanoparticle therapeutics: An emerging treatment modality for cancer. Nature reviews Drug discovery. 2008; 7(9):771–782.
4. Heath JR, Davis ME. Nanotechnology and cancer. Annu Rev Med. 2008; 59:251–265. [PubMed: 17937588]
5. Heidel JD, Davis ME. Clinical developments in nanotechnology for cancer therapy. Pharm Res. 2011; 28 (2):187–199. [PubMed: 20549313]
6. Schutz CA, Juillerat-Jeanneret L, Mueller H, et al. Therapeutic nanoparticles in clinics and under clinical evaluation. Nanomedicine (Lond). 2013; 8(3):449–467. [PubMed: 23477336]
7. Tanaka T, Shiramoto S, Miyashita M, et al. Tumor targeting based on the effect of enhanced permeability and retention (epr) and the mechanism of receptor-mediated endocytosis (rme). International journal of pharmaceutics. 2004; 277(1–2):39–61. [PubMed: 15158968]
8. Prabhakar U, Maeda H, Jain RK, et al. Challenges and key considerations of the enhanced permeability and retention effect for nanomedicine drug delivery in oncology. Cancer Res. 2013; 73(8):2412–2417. [PubMed: 23423979]
9. Steegmann-Olmedillas JL. The role of iron in tumour cell proliferation. Clin Transl Oncol. 2011; 13 (2):71–76. [PubMed: 21324793]
10. Wang RB, Billone PS, Mullett WM. Nanomedicine in action: An overview of cancer nanomedicine on the market and in clinical trials. J Nanomater. 2013

11. Steffensen KD, Waldstrom M, Pallisgard N, et al. Panitumumab and pegylated liposomal doxorubicin in platinum-resistant epithelial ovarian cancer with kras wild-type: The palido study, a phase ii nonrandomized multicenter study. Int J Gynecol Cancer. 2013; 23(1):73–80. [PubMed: 23211422]
12. Levine AM, Noy A, Lee JY, et al. Pegylated liposomal doxorubicin, rituximab, cyclophosphamide, vincristine, and prednisone in aids-related lymphoma: Aids malignancy consortium study 047. J Clin Oncol. 2013; 31(1):58–64. [PubMed: 23169503]
13. Arrieta O, Medina LA, Estrada-Lobato E, et al. First-line chemotherapy with liposomal doxorubicin plus cisplatin for patients with advanced malignant pleural mesothelioma: Phase ii trial. Br J Cancer. 2012; 106(6):1027–1032. [PubMed: 22353806]
14. Gradishar WJ, Tjulandin S, Davidson N, et al. Phase iii trial of nanoparticle albumin-bound paclitaxel compared with polyethylated castor oil-based paclitaxel in women with breast cancer. J Clin Oncol. 2005; 23(31):7794–7803. [PubMed: 16172456]
15. Coleman RL, Brady WE, McMeekin DS, et al. A phase ii evaluation of nanoparticle, albumin-bound (nab) paclitaxel in the treatment of recurrent or persistent platinum-resistant ovarian, fallopian tube, or primary peritoneal cancer: A gynecologic oncology group study. Gynecol Oncol. 2011; 122(1):111–115. [PubMed: 21497382]
16. Hosein PJ, de Lima Lopes G Jr, Pastorini VH, et al. A phase ii trial of nab-paclitaxel as second-line therapy in patients with advanced pancreatic cancer. Am J Clin Oncol. 2013; 36(2):151–156. [PubMed: 22307213]
17. Socinski MA, Bondarenko I, Karaseva NA, et al. Weekly nab-paclitaxel in combination with carboplatin versus solvent-based paclitaxel plus carboplatin as first-line therapy in patients with advanced non-small-cell lung cancer: Final results of a phase iii trial. J Clin Oncol. 2012; 30(17): 2055–2062. [PubMed: 22547591]
18. Alberts DS, Blessing JA, Landrum LM, et al. Phase ii trial of nab-paclitaxel in the treatment of recurrent or persistent advanced cervix cancer: A gynecologic oncology group study. Gynecol Oncol. 2012; 127(3):451–455. [PubMed: 22986144]
19*. Weiss GJ, Chao J, Neidhart JD, et al. First-in-human phase 1/2a trial of crlx101, a cyclodextrin-containing polymer-camptothecin nanopharmaceutical in patients with advanced solid tumor malignancies. Invest New Drugs. 2013 A phase I/IIa trial utilizing camptothecin containing polymeric nanoparticles to treat advanced solid tumor cancers.
20. Rajasekaran AK, Anilkumar G, Christiansen JJ. Is prostate-specific membrane antigen a multifunctional protein? American journal of physiology Cell physiology. 2005; 288(5):C975–981. [PubMed: 15840561]
21**. Hrkach J, Von Hoff D, Mukkaram Ali M, et al. Preclinical development and clinical translation of a psma-targeted docetaxel nanoparticle with a differentiated pharmacological profile. Sci Transl Med. 2012; 4(128):128ra139. First reported use of prostate specific membrane antigen-targeted nanoparticles to deliver docetaxel to cancer cells in a clinical setting. Preliminary results of DTXL-TNP treatment suggest the nanoparticles were efficacious.
22. Aagaard L, Rossi JJ. Rnai therapeutics: Principles, prospects and challenges. Adv Drug Deliv Rev. 2007; 59 (2–3):75–86. [PubMed: 17449137]
23. Davis ME. The first targeted delivery of sirna in humans via a self-assembling, cyclodextrin polymer-based nanoparticle: From concept to clinic. Mol Pharm. 2009; 6(3):659–668. [PubMed: 19267452]
24*. Davis ME, Zuckerman JE, Choi CH, et al. Evidence of rnai in humans from systemically administered sirna via targeted nanoparticles. Nature. 2010; 464(7291):1067–1070. Demonstrated administration of siRNA-containing CALAA-01 to humans and confirmed RNAi in human tumor tissue. [PubMed: 20305636]
25. Eifler AC, Thaxton CS. Nanoparticle therapeutics: Fda approval, clinical trials, regulatory pathways, and case study. Methods Mol Biol. 2011; 726:325–338. [PubMed: 21424459]
26. Wolfrum C, Shi S, Jayaprakash KN, et al. Mechanisms and optimization of in vivo delivery of lipophilic sirnas. Nat Biotechnol. 2007; 25(10):1149–1157. [PubMed: 17873866]
27**. Tabernero J, Shapiro GI, LoRusso PM, et al. First-in-humans trial of an rna interference therapeutic targeting vegf and ksp in cancer patients with liver involvement. Cancer discovery.

2013; 3(4):406–417. First report of RNA interference in humans, using siRNA targeted against VEGF and KSP. These results demonstrate the feasibility of siRNA-based therapeutics in humans, using a nanoparticle platform to deliver sufficient quantities of nucleic acids to decrease target expression at both the mRNA and protein level. [PubMed: 23358650]

28*. Shenoi MM, Iltis I, Choi J, et al. Nanoparticle delivered vascular disrupting agents (vdas): Use of tnf-alpha conjugated gold nanoparticles for multimodal cancer therapy. Mol Pharm. 2013 Gold nanoparticle delivery of TNF-α disrupts tumor vasculature, enabling imaging and decreasing tumor growth.

29. Libutti SK, Paciotti GF, Byrnes AA, et al. Phase i and pharmacokinetic studies of cyt-6091, a novel pegylated colloidal gold-rhtnf nanomedicine. Clin Cancer Res. 2010; 16(24):6139–6149. [PubMed: 20876255]

30*. Wiley DT, Webster P, Gale A, et al. Transcytosis and brain uptake of transferrin-containing nanoparticles by tuning avidity to transferrin receptor. Proc Natl Acad Sci U S A. 2013 Conjugation of nanoparticles with transferrin allows them to traverse the blood brain barrier.

31**. Zheng D, Giljohann DA, Chen DL, et al. Topical delivery of sirna-based spherical nucleic acid nanoparticle conjugates for gene regulation. Proc Natl Acad Sci U S A. 2012; 109(30):11975–11980. SNA-NCs penetrated the epidermal barrier, delivering functional siRNA to the cells below. This is the first publication describing a nanoparticle technology that can penetrate the epidermal barrier. [PubMed: 22773805]

32. Lee GY, Qian WP, Wang L, et al. Theranostic nanoparticles with controlled release of gemcitabine for targeted therapy and mri of pancreatic cancer. Acs Nano. 2013; 7(3):2078–2089. [PubMed: 23402593]

33. Xiao Z, Levy-Nissenbaum E, Alexis F, et al. Engineering of targeted nanoparticles for cancer therapy using internalizing aptamers isolated by cell-uptake selection. ACS Nano. 2012; 6(1):696–704. [PubMed: 22214176]

34. Valencia PM, Pridgen EM, Perea B, et al. Synergistic cytotoxicity of irinotecan and cisplatin in dual-drug targeted polymeric nanoparticles. Nanomedicine (Lond). 2013; 8(5):687–698. [PubMed: 23075285]

35. Han H, Davis ME. Targeted nanoparticles assembled via complexation of boronic-acid-containing targeting moieties to diol-containing polymers. Bioconjugate chemistry. 2013; 24(4):669–677. [PubMed: 23461746]

36. Zhang K, Hao L, Hurst SJ, et al. Antibody-linked spherical nucleic acids for cellular targeting. Journal of the American Chemical Society. 2012; 134(40):16488–16491. [PubMed: 23020598]

37. Dohmen C, Edinger D, Frohlich T, et al. Nanosized multifunctional polyplexes for receptor-mediated sirna delivery. ACS Nano. 2012; 6(6):5198–5208. [PubMed: 22646997]

38. Zhao N, You J, Zeng Z, et al. An ultra ph-sensitive and aptamer-equipped nanoscale drug-delivery system for selective killing of tumor cells. Small. 2013

39. Zhu G, Zheng J, Song E, et al. Self-assembled, aptamer-tethered DNA nanotrains for targeted transport of molecular drugs in cancer theranostics. Proc Natl Acad Sci U S A. 2013; 110(20): 7998–8003. [PubMed: 23630258]

40. Huang S, Shao K, Liu Y, et al. Tumor-targeting and microenvironment-responsive smart nanoparticles for combination therapy of antiangiogenesis and apoptosis. ACS Nano. 2013; 7(3): 2860–2871. [PubMed: 23451830]

41. Nam J, La WG, Hwang S, et al. Ph-responsive assembly of gold nanoparticles and “spatiotemporally concerted” drug release for synergistic cancer therapy. Acs Nano. 2013; 7(4): 3388–3402. [PubMed: 23530622]

42. Zhang HF, Wang JQ, Mao WW, et al. Novel sn38 conjugate-forming nanoparticles as anticancer prodrug: In vitro and in vivo studies. Journal of Controlled Release. 2013; 166(2):147–158. [PubMed: 23266448]

43. Dunn SS, Tian S, Blake S, et al. Reductively responsive sirna-conjugated hydrogel nanoparticles for gene silencing. Journal of the American Chemical Society. 2012; 134(17):7423–7430. [PubMed: 22475061]

44. Hasan W, Chu K, Gullapalli A, et al. Delivery of multiple sirnas using lipid-coated plga nanoparticles for treatment of prostate cancer. Nano letters. 2012; 12(1):287–292. [PubMed: 22165988]

45. Ren Y, Cheung HW, von Maltzhan G, et al. Targeted tumor-penetrating sirna nanocomplexes for credentialing the ovarian cancer oncogene id4. Science Translational Medicine. 2012; 4:147.

46. Lee H, Lytton-Jean AK, Chen Y, et al. Molecularly self-assembled nucleic acid nanoparticles for targeted in vivo sirna delivery. Nat Nanotechnol. 2012; 7(6):389–393. [PubMed: 22659608]

47. Shahzad MMK, Mangala LS, Han HD, et al. Targeted delivery of small interfering rna using reconstituted high-density lipoprotein nanoparticles. Neoplasia. 2011; 13(4):309–U142. [PubMed: 21472135]

48. Leon CG, Locke JA, Adomat HH, et al. Alterations in cholesterol regulation contribute to the production of intratumoral androgens during progression to castration-resistant prostate cancer in a mouse xenograft model. Prostate. 2010; 70(4):390–400. [PubMed: 19866465]

49. Pussinen PJ, Lindner H, Glatter O, et al. Lipoprotein-associated alpha-tocopheryl-succinate inhibits cell growth and induces apoptosis in human mcf-7 and hbl-100 breast cancer cells. Bba-Mol Cell Biol L. 2000; 1485(2–3):129–144.

50. Damiano MG, Mutharasan RK, Tripathy S, et al. Templated high density lipoprotein nanoparticles as potential therapies and for molecular delivery. Adv Drug Deliv Rev. 2013; 65(5):649–662. [PubMed: 22921597]

51. Luthi AJ, Zhang H, Kim D, et al. Tailoring of biomimetic high-density lipoprotein nanostructures changes cholesterol binding and efflux. ACS Nano. 2012; 6(1):276–285. [PubMed: 22117189]

52**. McMahon KM, Mutharasan RK, Tripathy S, et al. Biomimetic high density lipoprotein nanoparticles for nucleic acid delivery. Nano letters. 2011; 11(3):1208–1214. Delivery of nucleic acids by biomimetic high density lipoprotein nanoparticles (HDL NPs) synthesized using a gold nanoparticle template knocks down target genes in prostate cancer cells and data suggest avoidance of endosomal sequestration. [PubMed: 21319839]

53**. Yang S, Damiano MG, Zhang H, et al. Biomimetic, synthetic hdl nanostructures for lymphoma. Proc Natl Acad Sci U S A. 2013; 110(7):2511–2516. Biomimetic, synthetic HDL-NPs are shown to modulate cholesterol metabolism in targeted diffuse large B cell lymphoma cells and effectively induced apoptosis *in vitro* and reduced tumor growth in an in vivo xenograft model. The HDL-NP mechanism of action is dependent upon its inherent biological function and does not carry a drug cargo. [PubMed: 23345442]

54*. Lee JB, Zhang K, Tam YY, et al. Lipid nanoparticle sirna systems for silencing the androgen receptor in human prostate cancer in vivo. Int J Cancer. 2012; 131(5):E781–790. *In vivo* demonstration of the ability of lipid nanoparticles to deliver functional therapeutic siRNAs to tumor cells. [PubMed: 22095615]

55. Valadi H, Ekstrom K, Bossios A, et al. Exosome-mediated transfer of mrnas and micrornas is a novel mechanism of genetic exchange between cells. Nat Cell Biol. 2007; 9(6):654–U672. [PubMed: 17486113]

56. Alvarez-Erviti L, Seow Y, Yin H, et al. Delivery of sirna to the mouse brain by systemic injection of targeted exosomes. Nat Biotechnol. 2011; 29(4):341–345. [PubMed: 21423189]

57. Katakowski M, Buller B, Zheng X, et al. Exosomes from marrow stromal cells expressing mir-146b inhibit glioma growth. Cancer letters. 2013; 335(1):201–204. [PubMed: 23419525]

Key Points

- Clinical trials have demonstrated that nanoparticle-based therapies are effective treatments for a variety of cancers, and can reduce the side-effect profiles of chemotherapeutics.
- Nanoparticles are being used to deliver increasingly sophisticated cargoes including small molecules, nucleic acids, peptides, proteins, and combinations of these molecules to cancer cells *in vitro* and *in vivo*.
- Biomimetic nanostructures may represent a paradigm shift in nanotherapeutics due to their inherent biocompatablity, novel functions, and targeting abilities.