Published in final edited form as:

Nanomedicine (Lond). 2012 March ; 7(3): 303–305. doi:10.2217/nmm.11.191.

Are high drug loading nanoparticles the next step forward for chemotherapy?

Joseph Della Rocca,

Department of Chemistry, CB#3290, University of North Carolina, Chapel Hill, NC 27599, USA

Demin Liu, and

Department of Chemistry, CB#3290, University of North Carolina, Chapel Hill, NC 27599, USA

Wenbin Lin

Department of Chemistry, CB#3290, University of North Carolina, Chapel Hill, NC 27599, USA
and Lineberger Comprehensive Cancer Center, University of North Carolina, Chapel Hill, NC 27599, USA

Wenbin Lin: wlin@unc.edu

Keywords

cancer; chemotherapy; nanocrystal; nanomedicine; nanoscale coordination polymer

Cancer remains one of the deadliest diseases known to man, causing significant mortality and morbidity and costing hundreds of billions of dollars in healthcare expenses in the USA annually [1]. Despite remarkable advances in our knowledge of the fundamental biology of cancer and the billions spent on drug research and development, there has not been a significant increase in overall patient survival for many types of cancer. A major reason for this is the lack of effective chemotherapeutic options. Over the past 30 years, the rate of new drug approvals has remained relatively constant (20–30 drugs annually) and most new approvals are reformulations, new applications or new combinations of previously approved agents [2]. The treatment options for many cancers have remained nearly unchanged as a result of the lack of new drug approvals. Pharmaceutical development is limited by a number of factors including high R&D costs and regulatory barriers, but the lack of effective drug delivery vectors remains a major bottleneck. Many drug candidates identified through high-throughput screenings do not possess sufficient solubility to be bioavailable [3], and the biologically derived agents (e.g., peptides, proteins and siRNA) are degraded readily by the endogenous enzymes in the circulation. The currently approved agents, mostly small molecules, are limited by their nonspecific biodistribution, leading to dose-limiting side effects. There exists an acute need to identify a method to make small molecule drugs more bioavailable, protect biologics from premature degradation, and increase tumor uptake of the agent while minimizing nonspecific uptake.

© 2012 Future Medicine Ltd

Financial & competing interests disclosure

The authors acknowledge financial support from NIH (U01-CA151455 and U54-CA151652). W Lin is a co-founder of Coordination Therapeutics, Inc. (NC, USA). The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

For reprint orders, please contact: reprints@futuremedicine.com

Nanoparticle-based chemotherapeutics are an emerging class of drug delivery systems that have the potential to revolutionize cancer chemotherapy. Broadly speaking, a nanoparticle-based chemotherapeutic (nanotherapeutic) consists of a therapeutic embedded within, or attached to, a nanoparticle matrix. A variety of different nanocarriers have been developed to deliver a wide range of cancer chemotherapeutics [4]. Nanoparticles possess many advantages over conventional therapeutics such as extended systemic circulation times, increased tumor uptake due to the enhanced permeability and retention effect, and targeted delivery to specific tissues with surface conjugated ligands. Due to their size, nanotherapeutics cannot penetrate normal vasculatures and capillaries, leading to a lower nanoparticle dose to normal tissues such as skin, muscle, lungs, hearts and kidneys compared with small molecules. The clearance of nanotherapeutics is generally through the mononuclear phagocytic system (MPS), resulting in nanotherapeutic accumulation in the Kupffer cells of the liver and the macrophages of the spleen. This unique biodistribution generally results in lower systemic toxicity of nanotherapeutics. In addition, nanoparticles can be engineered to incorporate multiple types of therapeutic or diagnostic agents, allowing for the synergistic therapeutic efficacy and real-time monitoring of therapeutic response. The promise of nanoparticle therapeutics is validated with the clinical success of multiple entities such as Doxil[®] (Janssen Products, LP, PA, USA) and Abraxane[®] (Celgene Corporation, NJ, USA) [5].

The story of nanoparticle therapeutics cannot, however, be considered an unblemished success. Clinically deployed nanotherapeutics have limitations. For example, Doxil has an improved safety profile but not better efficacy compared with doxorubicin [6,7]. Abraxane shows improved efficacy compared with paclitaxel, but it is extremely expensive to manufacture and has not generally replaced paclitaxel clinically [5,8]. Most nanocarriers can only be used to deliver drugs with specific properties (e.g., charge and hydrophobicity) and have a fairly low threshold for drug incorporation, typically a few weight percent of active pharmaceutical ingredients (API). Most nanomedicines are in fact composed mostly of non-API components. The commercialization of nanotherapeutics is also hindered by high production costs and persistent manufacturing issues such as scalability to multikilogram batches and batch-to-batch consistency. The toxicological impact and biological persistence of many nanoparticles remain poorly investigated, posing long-term issues from exposure to these materials [9].

High drug loading nanoparticles are a potential strategy for circumventing many of the issues that plague nanotherapeutics. Since most nanocarriers have low drug loadings, a large amount of nanoparticle is needed to deliver a clinically relevant dose of a therapeutic, leading to the use of a large amount of excipients, which may cause undesirable side effects and drive up the cost of a nanotherapeutic. Increasing the drug loading in a nanotherapeutic has several benefits. First, for a nanotherapeutic that can avoid immediate recognition and clearance by the MPS system, its circulation time is independent of the total nanoparticle dose [10,11]. As a high-loading nanotherapeutic can deliver more API per tumor localization event, it is more efficient in delivering the API. The total nanotherapeutic dose needed to deliver a given amount of API can thus be significantly reduced with a high drug loading nanoparticle. Second, as a higher drug loading nanoparticle requires fewer non-API components, it not only lowers potential adverse effects of excipient agents, but also has a potential to reduce the manufacturing cost of the nanotherapeutic. These benefits become even more pronounced for well-tolerated anticancer drugs (e.g., gemcitabine) or nanotherapeutics that have much higher maximum tolerated doses than their small molecule APIs.

The highest drug loading nanoparticles are drug nanocrystals, which can contain up to 100% API. Nanocrystals are commonly used for the oral delivery of highly hydrophobic drugs,

where the nanocrystal formulation can slow the dissolution rate and increase the bioavailability of the drug [12,13]. Nanocrystals have only been more recently investigated as a means for systemic drug delivery. Unfunctionalized nanocrystals are rapidly taken up by MPS organs, but they can still have efficacy from the slow release of the API from the MPS. Moreover, nano crystals can be surface functionalized to increase the circulation time and still retain a very high drug loading. Nanocrystal formulations have been used to rescue abandoned drugs by altering the biodistribution and alleviating the toxicity issues surrounding the use of cosolvents (e.g., Cremophor® with paclitaxel) [8,12]. For example, Liu and coworkers formulated paclitaxel nanocrystals with up to 20 wt% paclitaxel [8]. These nanocrystals showed lower toxicity and higher efficacy and oral bioavailability than paclitaxel formulated with Cremophor. Merisko-Liversidge and coworkers reformulated two abandoned anticancer drugs, camptothecin and pipsulfan, into nanocrystals for systemic delivery. These formulations demonstrated improved efficacy compared with their small-molecule counterparts, which were never successfully formulated for intravenous injection [14]. However, nanocrystals can only be used with poorly soluble anticancer drugs, as water soluble drugs would rapidly dissolve under physiological conditions. For most small molecule drugs, it would be difficult to balance the drug release rate and the particle morphology to reduce MPS recognition and uptake with nanocrystal formulations.

We have developed nanoscale coordination polymers (NCPs; also known as nanoscale metal–organic frameworks) as drug delivery vehicles [15]. NCPs are composed of polydentate bridging ligands connected by metal ions or clusters, and are capable of encapsulating a variety of chemotherapeutics at exceptionally high loadings (up to 79 wt%) [16]; however, most NCPs are unstable under physiological conditions and must be surface coated to prevent rapid drug release. We have developed two different surface coating strategies to slow the drug release: a silica shell [17,18] and a lipid bilayer [16]. NCPs have shown impressive efficacy *in vitro*, often improving the efficacy of the free drug, but have not yet been evaluated in animal models. Systematic *in vivo* studies must be performed to validate the therapeutic potential of NCP formulations. We recently developed the polysilsesquioxane (PSQ) nanoparticle, a more stable version of NCP, to deliver high loadings of platinum-based chemotherapeutics [19]. The platin prodrug is covalently bound to the robust siloxane network of PSQ, carrying up to 47 wt% active agent. The PSQ nanoparticles have minimal drug release under normal physiological conditions, but rapidly release the drug in the tumor microenvironment as a result of the intrinsic redox property of the platinum prodrug. Preliminary *in vivo* studies showed that the PSQ nanoparticles possessed significant activity against a pancreatic cancer xenograft, while oxaliplatin showed no activity. Extensive preclinical evaluations of the PSQ platform are ongoing.

Nanoparticle drug delivery offers a clinically validated method to improve patient outcome in cancer chemotherapy by improving efficacy and reducing side effects. It also allows for the clinical translation of otherwise discarded drugs. However, current nanoparticle platforms are not without limitations, notably low drug loading capabilities, use of potentially toxic non-API agents, high production costs and formulation issues. New nanotherapeutics with much higher drug loadings could be a step forward for cancer therapy, but they have not undergone the same systematic study as their more established counterparts. More preclinical and clinical studies are urgently needed to validate the therapeutic potential of high drug loading nanoparticles.

References

1. The American Cancer Society Factbook. American Cancer Society; GA, USA: 2011. Cancer Facts and Figures 2011.

2. Bawa R. Patents and nanomedicine. *Nanomedicine (Lond)*. 2007; 2(3):351–374. [PubMed: 17716180]
3. Lipinski CA, Lombardo F, Dominy BW, Feeney PJ. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Adv Drug Delivery Rev*. 1997; 23(1–3):3–25.
4. Peer D, Karp JM, Hong S, Farokhzad OC, Margalit R, Langer R. Nanocarriers as an emerging platform for cancer therapy. *Nat Nanotechnol*. 2007; 2(12):751–760. [PubMed: 18654426]
5. Wang AZ, Langer R, Farokhzad OC. Nanoparticle delivery of anticancer drugs. *Annu Rev Med*. 2012; 63:185–198. [PubMed: 21888516]
6. Judson I, Radford JA, Harris M, et al. Randomised Phase II trial of pegylated liposomal doxorubicin (DOXIL/CAELYX) versus doxorubicin in the treatment of advanced or metastatic soft tissue sarcoma: a study by the EORTC soft tissue and bone sarcoma group. *Eur J Cancer*. 2001; 37(7): 870–877. [PubMed: 11313175]
7. O'Brien MER, Wigler N, Inbar M, et al. Reduced cardiotoxicity and comparable efficacy in a Phase III trial of pegylated liposomal doxorubicin HCL (CAELYX™/Doxil^R) versus conventional doxorubicin for first-line treatment of metastatic breast cancer. *Anal Oncol*. 2004; 15(3):440–449.
8. Liu F, Park J-Y, Zhang Y, et al. Targeted cancer therapy with novel high drug-loading nanocrystals. *J Pharm Sci*. 2010; 99(8):3542–3551. [PubMed: 20564383]
9. Dobrovolskaia MA, Germolec DR, Weaver JL. Evaluation of nanoparticle immunotoxicity. *Nat Nanotechnol*. 2009; 4(7):411–414. [PubMed: 19581891]
10. Akiyama Y, Mori T, Katayama Y, Niidome T. The effects of PEG grafting level and injection dose on gold nanorod biodistribution in tumor bearing mice. *J Control Release*. 2009; 139(1):81–84. [PubMed: 19538994]
11. Panagi Z, Beletsi A, Evangelatos G, Livanou E, Ithakissios DS, Avgoustakis K. Effect of dose and the biodistribution and pharmacokinetics of PLGA and PLGA-mPEG nanoparticles. *Int J Pharm*. 2001; 221(1–2):143–152. [PubMed: 11397575]
12. Muller RH, Gohla S, Keck CM. State of the art of nanocrystals-special features, production, nanotoxicology aspects and intracellular delivery. *Eur J Pharm Biopharm*. 2011; 78(1):1–9. [PubMed: 21266197]
13. Rabinow BE. Nanosuspensions in drug delivery. *Nat Rev Drug Discovery*. 2004; 3(9):785–796.
14. Merisko-Liversidge E, Sarpotdar P, Bruno J, et al. Formulation and antitumor activity evaluation of nanocrystalline suspensions of poorly soluble anticancer drugs. *Pharm Res*. 1996; 13(2):272–278. [PubMed: 8932448]
15. Della Rocca J, Liu D, Lin W. Nanoscale metal–organic frameworks for biomedical imaging and drug delivery. *Acc Chem Res*. 2011; 44(10):957–968. [PubMed: 21648429]
16. Huxford RC, Dekrafft KE, Boyle WS, Liu D, Lin W. Lipid-coated nanoscale coordination polymers for targeted delivery of antifolates to cancer cells. *Chem Sci*. 2012; 3:198–204.
17. Rieter WJ, Pott KM, Taylor KML, Lin W. Nanoscale coordination polymers for platinum-based anticancer drug delivery. *J Am Chem Soc*. 2008; 130(35):11584–11585. [PubMed: 18686947]
18. Taylor-Pashow KML, Della Rocca J, Xie Z, Tran S, Lin W. Post-synthetic modifications of iron-carboxylate nanoscale metal-organic frameworks for imaging and drug delivery. *J Am Chem Soc*. 2009; 131(40):14261–14263. [PubMed: 19807179]
19. Della Rocca J, Huxford RC, Comstock-Duggan E, Lin W. Polysilsesquioxane nanoparticles for targeted platin-based cancer chemotherapy by triggered release. *Angew Chem Int Ed*. 2011; 50(44):10330–10334.