Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Pharmacology

Progress in the delivery of nanoparticle constructs: towards clinical translation

Sinéad M Ryan and David J Brayden

The application of nanoparticle constructs in drug delivery and nanomedicine is anticipated to have a great impact on future public health. Progress in this area is expected to address some of modern medicine's unresolved problems and recent literature contains many articles discussing this topic. We focus here on recent nanomedicine developments mainly in relation to cancer, which have either being approved for the market or clinical trials. We review nanomedicines in clinical use, nanoconstruct delivery systems (both non-targeted and targeted), imaging agents, as well as theranostics.

Addresses
School of Veterinary Medicine and Conway Institute, University College Dublin, Belfield, Dublin 4, Ireland

Corresponding author: Brayden, David J (David.Brayden@ucd.ie)

Current Opinion in Pharmacology 2014, **18**:120–128

This review comes from a themed issue on **New technologies**

Edited by **Gleb B Sukhorukov**

http://dx.doi.org/10.1016/j.coph.2014.09.019

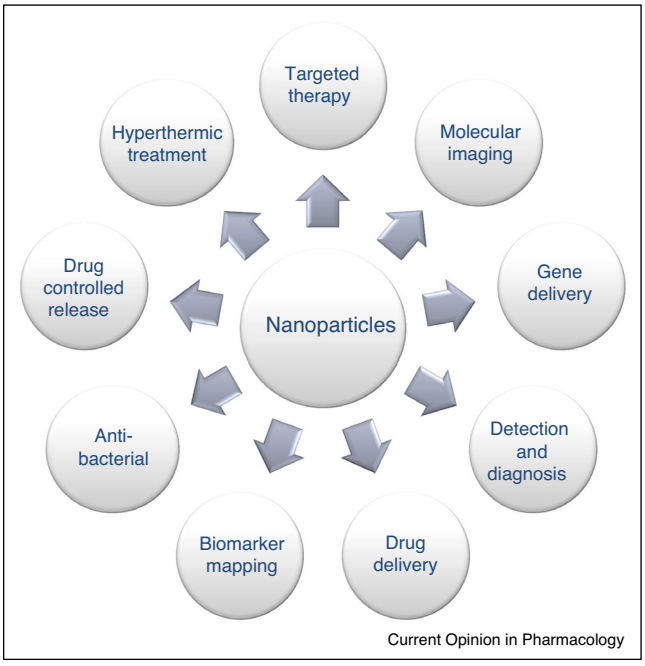
Introduction

There is ambiguity in defining nanoparticle or nanoparticle constructs, which stems from the fact that the associated research is interdisciplinary and has applications in many areas of the nanotechnology industry. One of the most important areas is nanomedicine, the main focus of this review. The European Technology Platform on Nanomedicine (ETPN) defines nanoparticles for medical applications as particles with a size in at least one direction of 1–1000 nm (Nanomedicine, Nanotechnology for Health; URL: (ftp://ftp.cordis.europa.eu/pub/nanotechnology/docs/nanomedicine_bat_en.pdf).
Nanomedicine is anticipated to have a great impact on public health. Many of its uses are illustrated (Figure 1). It uses nanosized tools for the diagnosis, prevention and treatment of diseases and encompasses drug delivery [1], *in vivo* imaging [2] and *in vitro* diagnostics [3–5]. Nanomedicine's role in the pharmaceutical research and development area is increasing primarily in the nanoparticle-based delivery systems for drugs and imaging agents [6•]. This is evident by the upsurge in publications, clinical trials and patents in recent years [7••]. However amidst this enthusiasm, concern has been expressed. There is some skepticism in relation to the numerous publications and patents confidently expressing great ambition for applications, but then few nanomedicines have reached the market to date [8,9]. Although the time line estimated for such approvals may be regarded as ambitious, there are few nanomedicines in clinical trials compared to traditional injectable or non-injectable drug formulations. Although there have been many articles describing the anticipated benefits of nanotechnology, there has been less effort placed on providing a comprehensive picture of its current status and how this will guide the future trajectory. This review aims in part to fill this gap by looking at the current status and highlighting the progress made in clinical aspects of nanoparticle delivery.

Nanomedicine translation and commercialization

The ultimate goal of the research and development of a nanomedicine is its successful translation from bench to bedside. However, there are significant obstacles and challenges in bringing nanomedicine products to the market, which are discussed in detail elsewhere [6•,10–12]. The following are significant challenges: (1) scalability; (2) reproducibility from batch to batch with respect physicochemical characteristics; (3) lack of knowledge regarding the interaction between nanosystems and living tissue *in vivo* (e.g. behavior as colloids in blood and interstitial fluid, receptor targeting of ligand-conjugated particles and toxicity); (4) nanotherapeutic optimization for maximum therapeutic potential; (5) the pharmaceutical industry's reluctance to invest in nanotechnology; (6) relative unpredictability of the European Medicines Agency and Food Drug Administration (FDA) with respect to regulatory and safety guidelines pertaining to nanomedicines. Potential health benefits of nanomedicine products can only be realized only if such products can be made reproducibly and are commercially viable and are differentiated from current products in respect of improved efficacy, safety and pharmacokinetics. Etheridge *et al.* [7••] provides an interesting study of the number and type of nanomedicine products approved for commercial use. Seven fall under the FDA classification for biologicals, 38 for devices, and 32 for small molecules. There are many nanoparticle technologies under development, many of them still in the preclinical testing stage. Examples for cancer treatment are provided in Table 1a and other diseases in Table 1b. Of the

Figure 1



Applications of nanoparticles in health care.

7666 articles on 'nanomedicine' reported in Pubmed (May 2014), more than half were published only since 2012, emphasizing that research efforts in this area have grown exponentially in recent years.

Diseases expected to benefit most from nanotechnology are osteoarthritis [13], diabetes, heart disease, HIV and currently many types of cancer [14]. Reasons for is the latter are that many cancer treatments are under development, cancer is the worldwide leading cause of death [15] and life-threatening late stage cancers warrant the investigation with pioneering treatments using emerging technologies such as nanotechnology. Etheridge *et al.*, confirms that forty-seven percent of the nanomedicine constructs were intended for acutely life-threatening advanced cancers. The majority of the cancer treatment applications identified in this study were aimed at increasing the efficacy of therapeutic delivery by improving pharmacokinetics and reducing side-effects of the already-approved active pharmaceutical ingredient.

Clinically approved non-targeted nanoparticles in nanomedicines

Some of the important nanoparticle platforms currently used are liposomes, polymeric conjugates, nanoshells, metallic nanoparticles, polymeric micelles, protein, cyclodextrins, and nucleic acid-based nanoparticles [16]. Many of the nanoparticle therapeutics available for clinical use are liposome-based. Some of the main non-targeted nanoparticles clinically approved as nanomedicines are shown in Table 2 and discussed below. The first nanomedicine approved by the FDA was Doxil® for the treatment of Karposi's sarcoma in 1995. It was approved in Europe in 1997 with the brand name Caelyx®. Doxil® contains the active drug doxorubicin encapsulated within PEGylated liposomes [17] which improved greatly the pharmacokinetics and biodistribution of the drug, resulting in an extended circulation half-life. This improved the accumulation of doxorubicin in tumor tissue. Despite this liposomal delivery system being clinically validated for Karposi's sarcoma, it did not provide the same stability, controlled release or drug accumulation at the target tumor tissue for the treatment of multiple myeloma, metastatic breast cancer and ovarian cancer.

DepoCyt® was approved in 1999 for local intrathecal treatment of lymphomatous meningitis. It is a non-PEGylated liposomal nanocarrier which provides a sustained release of the active drug cytarabine. It has currently entered Phase III trials for leukemia and Phase I/II clinical trials for glioblastoma (US clinical trials database; URL:http://clinicaltrials.Gov/ct2/show/nct01802333).

Abraxane® (FDA approval, 2005), is a nanoparticle composed of paclitaxel attached to the serum protein albumin, also known as nab-paclitaxel (nanoparticle-albumin bound). Albumin helps to make paclitaxel more soluble and is able to bind the drug in circulation [18]. Cremophor® EL is a non-ionic surfactant used as a delivery vehicle for the solubilization of hydrophobic drugs including paclitaxel. In comparison with the standard treatment of paclitaxel formulated using Cremophor® EL, treatment of Abraxane® in patients with metastatic breast cancer, showed a higher tumor response rate along with longer times to tumor progression and reduced hypersensitivity from avoiding Cremophor®. Cremophor® EL is limited to improving the therapeutic index of hydrophobic anti-cancer agents. A reduction in acute toxicity in patients was reported in clinical trials using Abraxane® [19]. Lower toxicity allows higher doses and infusion rates of paclitaxel to be administered compared to paclitaxel alone, with the added advantage of no premedication requirements to reduce acute side effects. Gemzar® (gemcitabine) is the chemotherapeutic used most often to treat pancreatic cancer. Patients with metastatic pancreatic cancer were treated with a combination of Gemzar® and Abraxane® in an randomized phase III trial. Patients who received both drugs lived a little longer than patients treated with gemcitabine alone [20]. In a press release in Jan 2014 (Abraxane® Plus gemcitabine Receives European Marketing Authorization for First-Line Treatment of Patients with Metastatic Pancreatic Cancer URL: http://ir.celgene.com/releasedetail.cfm?releaseid=821049), the combination of Abraxane® and gemcitabine for first line treatment of patients with