**Progress in the delivery of nanoparticle constructs:  towards clinical translation.**

Sinéad M. Ryan1 and David J. Brayden1.

**Address:** 1School of Veterinary Medicine and Conway Institute, University College Dublin, Belfield, Dublin 4, Ireland.

**Email:** Sinead.Ryan@ucd.ie

**Tel:** +353 1 7166215

**Email:** David.Brayden@ucd.ie

**Tel:** +353 1 7166013

**Corresponding author:** David J. Brayden

**Keywords**

Nanomedicine, cancer, theranostics, clinical and targeted nanoparticles.

**Highlights**

●Most approved nanomedicines are non-targeted anti-cancer therapeutics

●Injectable targeted nanoparticles may improve drug pharmacokinetics, reduce toxicity, and facilitate localized delivery

● Magnetic and superparamagnetic iron oxide nanoparticles show promise in theranostics.

● Labelling stem cells with SPIONS has potential for treatment of human diseases.

●Translation of nanodrug delivery systems requires a multi-disciplinary approach from bioengineers, formulators, and biologists.

**Abstract**

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, nano-contruct delivery systems (both non-targeted and targeted), imaging agents, as well as theranostics.

**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]. While 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 commercialisation**

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* (eg, behaviour 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 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 7,666 articles on “nanomedicine” reported in Pubmed (May 2014), more than half were published only since 2012, emphasising 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. Researchers in Arizona also discovered that the addition of Abraxane® to a standard chemotherapy treatment helped people with advanced pancreatic cancer live a little longer [17]. 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 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 metastatic pancreatic cancer received European marketing authorization.

Samyang Corporation (Seoul, Korea) developed Genexol-PM for the treatment of breast cancer and non-small cell lung cancer in 2007, which was approved [21]. Genexol-PM is a Cremophor EL-free micellar paclitaxel formulation consisting of the block co-polymers PEG (non-immunogenic) and a biodegradable core of poly(D,L-lactic acid) for the solubilisation of hydrophobic drugs. It is currently in phase IIa clinical trials in the US for the treatment of advanced pancreatic cancer [22] and phase I in Korea for ovarian cancer. Sorrento Therapeutics secured Cynviloq™ in 2013 with IGDRASOL, Inc., with exclusive US and European Union distribution rights to Cynviloq™ from Samyang Biopharmaceuticals Corporation. Despite clinical progress of non-targeted nanoparticles, the way forward is the clinical translation of targeting the nanoparticles to diseased tissue with a sustained controlled release of the active drug.

**Clinical development of targeted nanoparticles**

Paul Ehrlich, known as the “father of chemotherapy”, suggested the concept of a “magic bullet”, i.e “a drug that selectively attaches to diseased cells but is not toxic to healthy cells”, a great deal of interest has been focused in this direction, particularly regarding cancer treatment [23]. Several strategies such as passive or active drug targeting and ligand mediated targeting technologies are being explored to reach a putative biological target, [23]. Nanoparticles constitute an important medium for the targeted delivery of therapeutics. Targeting of nanoparticles to a specific cell type is traditionally achieved through the modification of the nanoparticle surface with peptides, aptamers, or other targeting moieties that specifically recognize a cell-surface receptor, leading to internalization. A list of the most active targeting moieties of nanoparticles currently used is listed (Figure 2). In theory, targeting increases efficacy with reduced side effects and systemic drug exposures. Nanoparticles can be designed to incorporate targeting moieties. This enhances drug delivery to the target sites, reduces off-target organ toxicities, and facilitates the cellular uptake of the active drug. The effective delivery of antitumor therapeutics is a high priority, as well as the identification of potential candidates for targeting. This topic has been extensively covered in a recent review by Bertrand et.al, [24]. The development of targeted nanoparticles may contribute to the therapeutic efficacy of anti-cancer drugs and cancer gene therapies compared with non-targeted systems. Although targeted nanoparticles offer numerous advantages, their complex nature presents challenges in reproducibility and concerns of toxicity. Preferably, nanoparticle formulations should be stable and inert towards blood components including opsonins while in circulation. The carrier should protect the drug(s) from systemic degradation while promoting controlled release of the targeted nanoparticle close to the target cells, only at which point does targeting become relevant. A thorough understanding of the biological behavior of nanoparticle systems in a clinical setting is also important. Translation of novel nanodrug delivery systems from the bench to the bedside will require a collective approach [25]. The following section focuses on recent research efforts citing relevant examples of advanced nanodrug delivery in development for cancer therapy.

CALAA-01 was the first targeted polymeric nano-formulation to reach clinical development for siRNA delivery in 2008 [26]. This system consists of TfR (targeting ligand for binding to transferrin receptors transferrin), associated withcyclodextrin-based PEGylated nanoparticles containing anti-R2 siRNA, that is capable of reducing expression of the M2 subunit of ribonucleotide reductase. The safety of CALAA-01 was evaluated in a Phase I trial by intravenous administration to adults with solid tumors refractory to standard of care therapies [27].. There were no dose limiting toxicity issues reported and the most common side effects were fatigue, constipation, nausea and fever or chills.

Antibody-coated immunoliposomes attach more selectively to antigens expressed on the target cells and they are internalized more efficiently. An anti-epidermal growth factor (EGF) receptor immunoliposome (antibody-linked nanoparticle) loaded with doxorubicin (ie, C225-ILS-DOX) entered Phase I investigation for the treatment of solid tumors. Fab fragments of the chimeric monoclonal antibody cetuximab (C225, Erbitux®) were covalently conjugated to the liposome membrane to target nanoparticles against tumor cells overexpressing EGFR (US clinical trials database; URL: [http://clinicaltrials.Gov/ct2/show/nct01702129:](http://clinicaltrials.Gov/ct2/show/nct01702129%3A)). This study was completed, but no results have been issued so far.

A new targeted nanoparticle formulation, BIND-014 is composed of a biodegradable and hydrophobic PLA polymeric core and a hydrophilic PEG corona decorated with small- molecule targeting ligands, a prostate-specific membrane antigen (PSMA) directed dipeptide and Taxotere® (docetaxel) as the encapsulated anticancer drug. PSMA is an attractive target in patients with advanced prostate cancer. This has been developed by a team led by Langer and Farokhzad at the Massachusetts Institute of Technology and BIND Therapeutics. It is the most extensive clinically- investigated actively targeted polymeric nanoparticle to date [28]. Currently there are three clinical studies taking place with BIND-014 ([www.clinicaltrials.gov](http://www.clinicaltrials.gov)) and all use established excipients including PLG and PEG co-polymers in order to hasten the regulatory pathway. One clinical trial is a Phase 2 study to evaluate the efficacy and safety of BIND-014 in patients with metastatic castration-resistant prostate cancer. There is also a Phase 1 study to find the highest safe dose of docetaxel nanoparticles for injectable suspension that can be given in the treatment of patients with advanced metastatic cancer. Lastly, it is being used to evaluate the efficacy and safety of patients with advanced non-small cell lung cancer in Phase 2. All three studies are ongoing. Like Doxil®, BIND-014 relies on its nanometer size to passively leave the tumour vasculature. Unlike Doxil®, however, the composition has been engineered to control drug release, among other things [28].

One of the challenges associated with using disease-based targets for homing of a therapeutic agent is the variability in expression of targets due to patient–patient variability and the stage of the tumor. Shastri *et al*. recently published a different approach to overcome this challenge [29]. Tumors comprise many cell types including endothelial cells that form associated blood vessels. They developed particles that are delivered to endothelial cells using a biophysical approach. By using charged polymers with the right affinity for cell lipids, the team has developed nanoparticles that can recognize specific cell types simply by their chemical properties. They took the approach that charged polymers containing aromatic sulfonate have pronounced affinity for caveolae, which are highly expressed by endothelial cells. They discovered that nanoparticles with specific affinity for caveolae are preferentially taken up by endothelial cells without the need for cell-specific targeting ligands [29]. This could overcome the variability in expression of targets due to patient–patient variability and the stage of the tumor. By further understanding the relationships between nanoparticle surface physicochemical characteristics and cell-surface domains, nanoparticle systems that can inherently discriminate between healthy and diseased cells may be better understood in the near future.

**Theranostic nanoparticles**

Much of the forecasted promise of nanotechnology in medicine takes the form of smart technologies, such as theranostic platforms that can target, diagnose, and administer optimized treatment protocols tailored to each specific patient. Nanotheranostics are submicrometer-sized carriers containing both drugs and imaging agents within a single formulation [30]. Personalized nanomedicine refers to the use of nanosized carriers to elaborate optimized treatment protocols tailored to each specific patient [31]. Theranostic nanoparticles integrate molecular imaging and drug delivery, allowing the imaging of therapeutic delivery as well as follow-up studies to assess treatment efﬁcacy [32]. Theranostic nanoparticles can serve as useful tools to explore the fundamental process of drug release after cellular internalisation of nanoparticles, which could provide key insights into the rational design of targeted nanocarriers for personalized treatment.

**Inorganic nanoparticles**

 Magnetic nanoparticles (MNPs) have generated great interest in the field of cancer nanotheranostics owing to their intrinsic magnetic property that enables them to be used as contrast agents in magnetic resonance imaging and as a therapeutic system. The unique physical properties of MNPs enable them to serve as imaging probes for locating and diagnosing cancerous lesions and simultaneously as drug delivery vehicles that deliver therapeutic agents preferentially to those lesions. The current efforts are being carried out to combine these properties and to develop MNP based nanotheranostics having imaging and therapeutic functionalities that will help towards the development of personalised medicine with scope for real time monitoring of biological responses to the therapy. There are a number of electromagnetically activated nanoparticles intended for cancer treatment are currently nearing or progressing through clinical development. Presently there are 14 nanoparticle formulations under clinical investigation for MRI imaging (US clinical trials database; URL**:**

[http://www.Clinicaltrials.Gov/ct2/results?Term=%22nanoparticles%22+and+%2](http://www.Clinicaltrials.Gov/ct2/results?Term=%22nanoparticles%22+and+%2mri%2&no_unk=y:)

[mri%2&no\_unk=y:](http://www.Clinicaltrials.Gov/ct2/results?Term=%22nanoparticles%22+and+%2mri%2&no_unk=y:)**)**.

Superparamagnetic iron oxide nanoparticles (SPIONS) act as efficient contrast agents for magnetic resonance imaging (MRI) as a result of high magnetization in an external magnetic field and prominent T2/T2 relaxation. Currently, a variety of MNPs are in early clinical trials and some formulations have been clinically approved for medical imaging and therapeutic applications. Some of them include Lumiren® and Gastromark® for bowel imaging; and Feridex® I.V and Endorem® for liver and spleen imaging among others. Iron oxide nanoparticles were highly used owing to their superparamagnetic effects and acceptable biocompatibility. NanoTherm® produced by Magforce AG, is a liquid of iron oxide that reacts to the presence of a magnetic field [33]. It is administered by intratumoral delivery and then heated by an externally applied alternating magnetic field, to provide hyperthermia treatment localized to a tumor. It has been reported that the heat generation is limited to the immediate surroundings of the NanoTherm® nanoparticles so the surrounding healthy tissue is not affected. It has been licensed in Europe since 2010 for the treatment of brain tumors.

GastroMARK® (ferumoxsil) is an oral gastrointestinal imaging agent composed of an aqueous suspension of silicone-coated, superparamagnetic iron oxide particles 400 nm approximately in size. It is designed to distinguish the loops of the bowel from other abdominal structures and physiology. Images of organs and tissues in the abdomen using MRI without contrast agents can be difficult to read because the abdominal organs and tissues cannot be easily distinguished from the loops of the bowel. GastroMARK® flows through and darkens the bowel when ingested. By more clearly identifying the intestinal loops, GastroMARK® enhances the ability to distinguish the bowel from adjacent tissues and organs in the upper gastrointestinal tract. GastroMARK® is marketed in the US by Mallinckrodt Inc. and in the EU by Guerbet S.A. under the tradename Lumirem™.

Two other interesting products in which iron oxide nanoparticles are used for magnetic detection of cells *in vitro* are CellSearch® and NanoDXTM. The magnetic nanopartcles are tagged with cell-specific markers, and an external field is used to separate or aggregate the bound cells in solution, allowing detection.

Ferumoxytol (AMAG Pharmaceuticals, Lexington, MA, USA) are SPIONs with a nonstoichiometric magnetite core covered by a polyglucose sorbitol carboxymethylether coating. It has an average colloidal particle size of 30 nm. It is an approved iron replacement therapy agent that has also shown potential for use as a contrast agent in imaging studies for tumors. Ferumoxytol, by virtue of its cellular uptake, is more relevant than conventional MRI, which cannot provide information on the tumor margin of aggressive tumors like pancreatic carcinoma. Ferumoxytol-enhanced MRI scans in patients receiving preoperative neoadjuvant therapy may offer enhanced primary tumor delineation, contributing towards achieving disease-free margin at the time of surgery, and thus improving the prognosis of pancreatic carcinomas [34].

Ferumoxytol has also potential for use as a contrast agent in imaging studies of the lymph

system, especially involving lymph nodes that have been affected by cancer. Ferumoxytol is

taken up by normal lymph nodes, but excluded from cancerous lymph node tissue. It is not

yet been approved for use as an imaging agent, however researchers are interested in testing

its effectiveness as a contrast agent for studies of normal lymph tissue and cancer tissue in

lymph nodes of individuals with prostate cancer. It is currently in Phase 1 trials (US

clinical trials database; URL:<http://clinicaltrials.gov/show/NCT01296139>).

Besides cancer, SPIONs more recently can also be applied to labeling of stem cells. Stem cells hold great promise for the treatment of multiple human diseases and disorders. Tracking and monitoring of stem cells *in vivo* after transplantation can supply important information for determining the efficacy of stem cell therapy. Li et al., have analysed the applications and future development of SPIONs in this interesting field [35]. However, it is still in the early stages of development. The potential toxicity of SPIONs *in vivo* needs to be investigated. For instance, after the SPION labeled cells are transplanted into the host, they influence not only the labeled cells, but also the liver and spleen of the host [36]. Systematic preclinical studies need to be conducted with standardized assays to assess the potential long-term toxicity of the *in vivo* use of SPIONs. How to translate stem cell tracking from preclinical models to human is another issue. There have been very few clinical studies, however, a more thorough understanding of label particle-cell-host interactions will greatly improve the applicability of SPIONs-based stem cell tracking and monitoring.

**Conclusions**

Nanomedicine research represents significant investment on drug delivery. Global government spending for 2010-11 in nanotechnology research was estimated at 67 billion USD. This sector is expected to grow from a current value of USD 2.3 billion to 136 billion USD by the year 2021 (Swiss Biotech Roundtable on nano-based drug delivery report; URL: <http://cgd.swissre.com/events/Swiss_Biotech_Roundtable_on_nano-based_drug_delivery.html>). Over recent years, several non-targeted nanomedicines have reached clinical development. Other complex targeted nanosystems are being investigated to address to various cancers, some of which combine diagnostic and therapeutic agents. Others can trigger drug release at the target site when exposed to external stimuli, and these are currently in clinical development. A categorical analysis of the identified applications and products also provides insight into the future directions of the field. We found an overwhelming focus on development of nanoparticle constructs for cancer applications. This is likely due to investment available in this area, the prevalence and impact of cancer in society, and the reality that the risks of many nanomedicine trials may be offset by the benefit sought in treating life-threatening cancers. While nanomedicines are being tested in late stage cancers due to the patient running out of options, this presents a major challenge to show efficacy of the nano-drug Although nanomedicine has already established a substantial presence in today's markets, a large portion of the nanomedicine applications identified are still in the research and development stage. The key to success is an interdisciplinary and open-minded approach, complemented with the partnership and knowledge exchange between academia, industry, and regulatory agencies.

**Acknowledgements**

This work was supported by Department of Agriculture, Food and Marine under FIRM (Food Institutional Research Measure) Project References: 11/F/042 and 13/F/510. It was also supported by the EU FP7 Grant “TRANS-INT” number 281035.

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