Advanced nanomedicine and cancer: challenges and opportunities in clinical translation

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Abstract

Cancer has reached pandemic dimensions in the whole world. Although current medicine offers multiple treatment options against cancer, novel therapeutic strategies are needed due to the low specificity of chemotherapeutic drugs, undesired side effects and the presence of different incurable types of cancer. Among these new strategies, nanomedicine arises as an encouraging approach towards personalized medicine with high potential for present and future cancer patients. Therefore, nanomedicine aims to develop novel tools with wide potential in cancer treatment, imaging or even theranostic purposes. Even though numerous preclinical studies have been published with successful preliminary results, promising nanosystems have to face multiple obstacles before adoption in clinical practice as safe options for patients with cancer. In this MiniReview, we provide a short overview on the latest advances in current nanomedicine approaches, challenges and promising strategies towards more accurate cancer treatment.

1. Introduction

Cancer is considered one of the hardest health-related threats worldwide. In fact, cancer provokes 8.97 million deaths thereby being the second leading cause of death only ischemic heart disease, according to the World Health Organization (WHO) (WHO, 2020). Formerly thought of as a single mass, tumors are composed by cancer cells surrounded by non-cancer cells within the extracellular matrix (ECM) such as immune cells, adipocytes and cancer stem cells (CSCs), thereby forming the complex tumor microenvironment (TME) (Hinshaw and Shevde, 2019). Cancer is characterized by aberrant cell proliferation compared to normal cell growth (Krieghoff-Henning *et al.*, 2017). Those cells first affected determine the type of disease, being known more than 100 different types. Healthy cells are not strong enough to compete with cancer cells for nutrients from the bloodstream (DeBerardinis *et al.*, 2016; Vander Heiden *et al.*, 2017; Vazquez *et al.*, 2016). Thus, healthy cells are overcrowded by tumor cells, which are able to widely spread. Since the high amount of nutrients cannot be provided by the vasculature, some cancer cells die but most of them are able to divide in this environment where not all nutrient requirements are fulfilled (Krieghoff-Henning *et al.*, 2017).

The WHO published in 2018 the list of the most frequent cancers through the Global Cancer Observatory (GLOBOCAN) registry (WHO, 2020). Among the new cases of cancer diagnosed in 2018 (18.08 million in total), lung (2.09 million cases together with

trachea and bronchus), breast (2.09 million cases) and prostate (1.28 million cases) were the most frequent. In men, lung (1.37 million cases) and prostate (1.28 million cases) cancers ranked the first and second positions, followed by stomach and liver cancer (and intrahepatic bile ducts) with 0.68 and 0.60 million cases, respectively. In women, breast cancer is the most frequent with 2.09 million cases followed by lung (0.72 million cases), cervix uteri (0.57 million cases) and colon (0.58 million cases) cancers. However, it is worthy to highlight that colon and rectal cancers (colorectal cancer) would be the third most frequent cancer overall (1.80 million cases).

Although the administration of free chemotherapeutic drugs remains as the gold standard for cancer treatment, this therapeutic strategy still presents inherent challenges. Among the most important are the lack of specific treatments and poor drug accumulation in the tumors (Creixell and Peppas, 2012; Han *et al.*, 2017; Jain and Stylianopoulos, 2010). As a consequence, undesired side effects in healthy tissues occur, especially in the heart (Octavia *et al.*, 2012), bone marrow (Daniel and Crawford, 2006), gastrointestinal tract (Mitchell, 2006), and nervous system (Grothey, 2003).

2. Biomaterials and cancer

During the last years, scientific research tries to develop novel biomedical devices in order to improve not only the diagnosis of cancer, but also its treatment (Brouillard *et al.*, 2021; Shi *et al.*, 2017; Wong *et al.*, 2020). In this context, materials´ engineering emerges as a new medical technology aimed at the obtention of proper tailor-made biomaterials. According to the definitions of N.A. Peppas and D.F. Williams, a biomaterial is "substance other than food or drugs contained in therapeutic or diagnostic systems that is in contact with tissues or biological fluids" and "a substance that has been engineered to take a form which, alone or as part of a complex system, is used to direct, by control of interactions with components of living systems, the course of any therapeutic or

diagnostic procedure, in human or veterinary medicine" (Peppas and Langer, 1994; Williams, 2009). Biomaterials are therefore materials which are synthesized from a biological source or have the final aim of interacting with the biological system in order to assist in diagnosis, therapy or to restore physiological functionality (Aamodt and Grainger, 2016; Huebsch and Mooney, 2009). Over the years, advanced biomaterials have emerged as one of the most promising tools to increase therapeutic efficiency and biocompatibility, and possess the ability to mimic properties and features found in natural macromolecules in order to be used in multiple biomedical applications, such as drug delivery (Gonzalez-Valdivieso *et al.*, 2019), gene delivery (Piña *et al.*, 2020), nanovaccines (Gonzalez-Valdivieso *et al.*, 2020), *in vivo* imaging (Oliveira *et al.*, 2019), early diagnosis (Beri *et al.*, 2018), tissue engineering (Taraballi *et al.*, 2018), regenerative medicine (Biggs *et al.*, 2018), 3D bioprinting (Murphy and Atala, 2014), biosensors (Tao *et al.*, 2019) or cell harvesting (Pierna *et al.*, 2013).
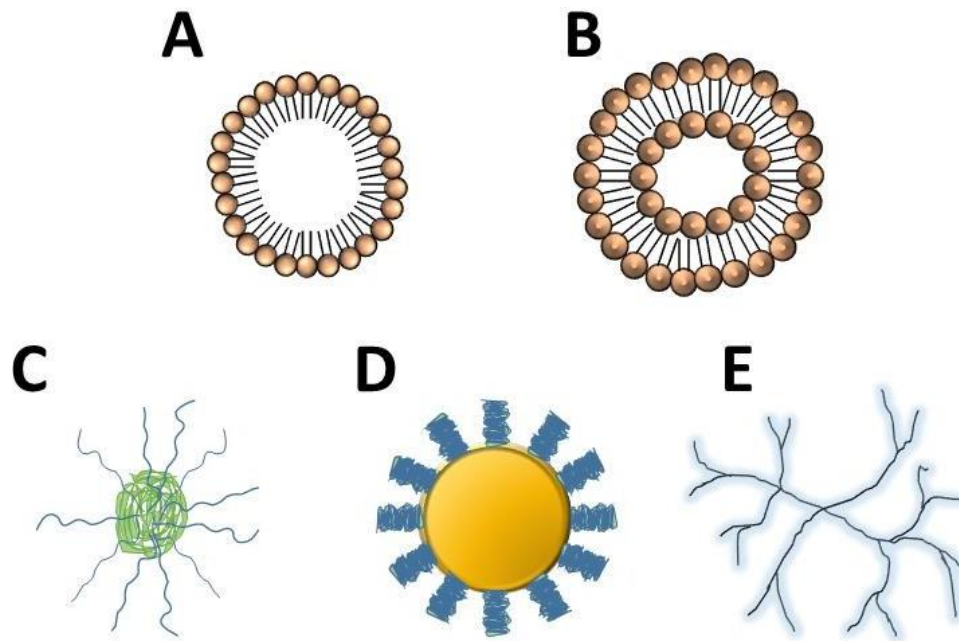
Figure 1. Schematic representation of different structures used in nanomedicine. A: Lipid nanoparticle; B: Liposome; C: Micelle; D: Gold nanoparticle; E: Dendrimer.

3. Nanomedicine

Nanomedicine combines biomaterials, nanotechnology, biomedicine and pharmaceutical science, thereby involving nanopharmaceutics, nanodevices for imaging purposes and theranostics (Eifler and Thaxton, 2011; Spencer *et al.*, 2015; Wagner *et al.*, 2006; Wong *et al.*, 2020). Although nanomedicine is relatively new, this research field evolves very fast and is being increasingly used not only for biomedical applications, but also in many other fields of our daily life (Henderson and Shankar, 2017; MacEwan and Chilkoti, 2017; Wong *et al.*, 2020). In the medical world, "nano" materials represent one of the most promising approaches not only for therapeutic purposes, but also diagnostics and theranostics approaches (Davis *et al.*, 2008; Eifler and Thaxton, 2011; Jain and Stylianopoulos, 2010; Liu *et al.*, 2020; MacEwan and Chilkoti, 2017; Rai *et al*., 2021). According to the criteria from the US Food and Drug Administration (FDA), nanodrugs are those products that range from 1 to 100 nm, and due to their small size and high

surface area exhibit key differences compared to bulk materials or materials outside of this range that exhibit related dimension-dependent properties (Bobo *et al.*, 2016; Sainz *et al.*, 2015; Wolfram *et al.*, 2015). Biomedical nanodevices include liposomes, dendrimers, polymer nanoparticles, micelles, nanocrystals, metals, other inorganic materials and proteins (Behzadi *et al.*, 2017; Shi *et al.*, 2017). Figure 1 depicts different shapes used in nanomedicine. To overcome the abnormal physiology of tumor tissue, nanomedicine takes advantage of the so-called Enhanced Permeability and Retention (EPR) effect to improve drug accumulation within the tumor thereby reaching therapeutic drug amounts (Maeda, 2015; Matsumura and Maeda, 1986).

The options for the design and functionalization of nanomaterials are hugely varied and the list of potential applications increases more and more, so current tendency in nanomedicine points to tailor-made devices (Tran *et al.*, 2017). Nonetheless, it is important to notice that nanomedicine-based treatments are not miracle cures, as they still have challenges to overcome. As instance, bioavailability is a typical challenge when developing a nanodevice (Yang *et al.*, 2013). As the most important biological fluid, blood contains more than 3000 different proteins. Once injected in the bloodstream, nanodevices interact with plasma proteins and, as a consequence, its surface is usually covered by various biomolecules (especially proteins) and the so-called corona is formed (Shemetov *et al.*, 2012; Tenzer *et al.*, 2013). This adsorption of proteins not only alters the particle size, stability and surface properties (Hühn *et al.*, 2013), but also affects its behavior and distribution within the body (Aggarwal *et al.*, 2009; Karmali and Simberg, 2011; Monopoli *et al.*, 2012). Even though the composition of the protein corona varies, it is well known that more abundant proteins first bind to nanoparticles surface and then the composition is changed during the circulation time (Aggarwal *et al.*, 2009). Thus, non-specific interactions with serum proteins are one limiting factor in terms of

circulation time. Opsonins are some of the corona-forming proteins and are recognized by reticuloendothelial systems (RES) and the mononuclear phagocyte system (MPS), leading to rapid blood clearance and high liver and spleen accumulation, so this could be an interesting strategy when needed targeted delivery to these organs (Owens and Peppas, 2006). On the other hand, dysopsonins such as apolipoproteins and albumin, inhibit phagocytic uptake, increase blood circulation time (Walkey *et al.*, 2012). Covering the

nanoparticles surface with polymers such as polyethylene glycol (PEG) is the most used approach in order to develop long-circulating nanoparticles and therefore prevent rapid clearance, as pegylation reduces protein adsorption through hydrophilicity and steric repulsion effects thereby resulting in longer blood circulation time and lower accumulation in the liver (Gref *et al.*, 2000; Owens and Peppas, 2006). Furthermore, it has been demonstrated that increased density of PEG on the surface of gold nanoparticles can decrease the amount and change the types of the protein corona and reduce macrophage uptake *in vitro* (Walkey *et al.*, 2012).

Blood circulation time is directly related to the efficient extravasation of a nanoparticle. Thus, short blood circulation half-life may be sufficient for tissues with relatively large blood flow. Contrary, longer circulation half-lives are necessary to progressively extravasate in poorly perfused tissues (Shi *et al.*, 2017). Moreover, nanosystems biodistribution within the body is dramatically affected by their size. Thus, nanodevices smaller than 10 nm are cleared by renal filtration (Owens and Peppas, 2006). Contrary, it is well known that molecules bigger than 100 nm are accumulated in the liver, which is one of the most problematic side effects of current drugs.

Different sizes of nanodevices are preferred for overcoming biological barriers and achieving their target. As instance, 11–30 nm size nanoparticles are suitable for liver and brain, whereas nanodevices with 31–80 nm diameter are appropriate for lungs, tumors and inflamed tissue (Souris *et al.*, 2010). Therefore, nanosystems between 10 and 100 nm are preferred due to their accurate accumulation and effect in desired tissues and organs.
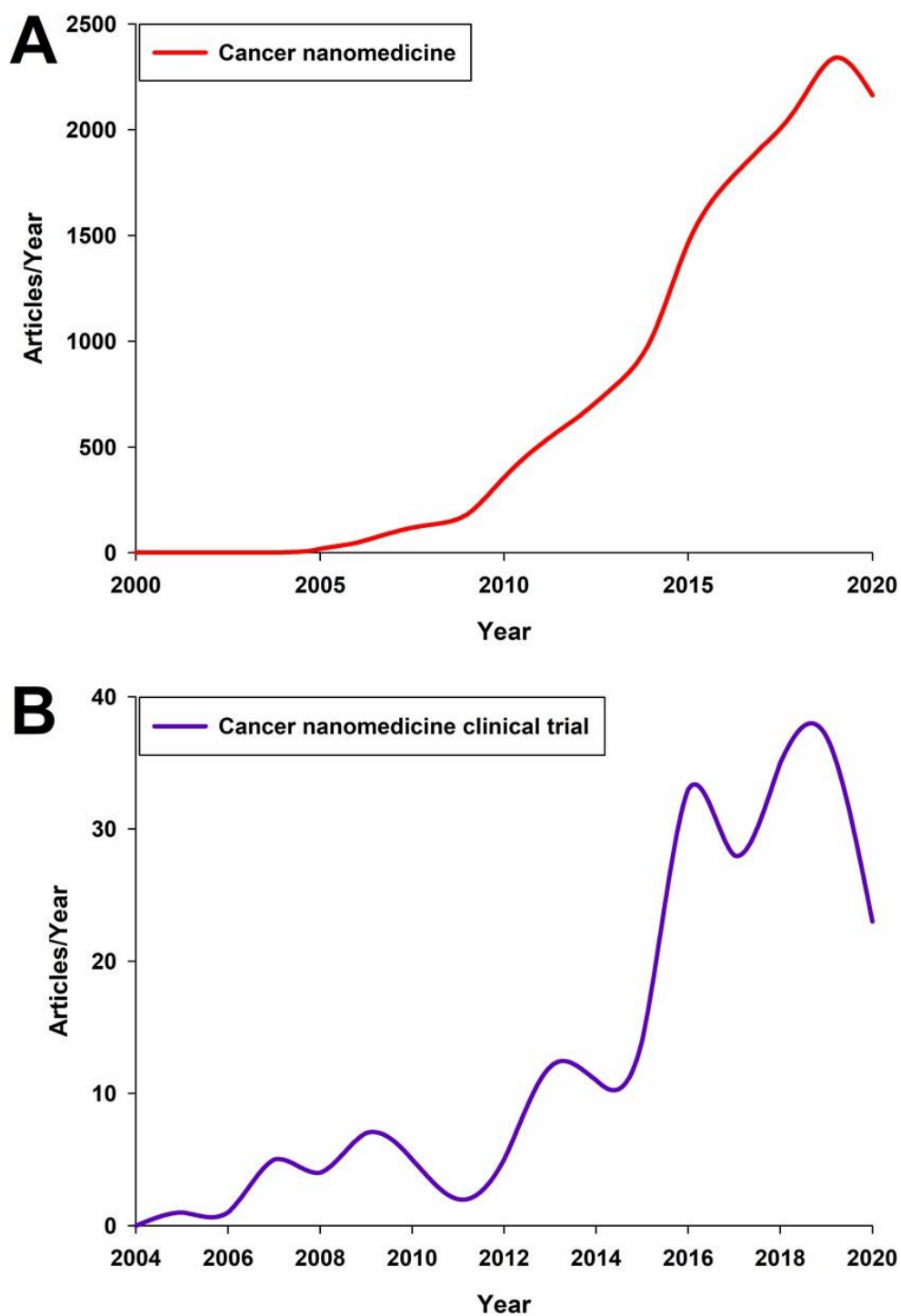
Figure 2. Scientific articles published referring to "Cancer nanomedicine" (A) or "Cancer nanomedicine clinical trial" to 2020 (B). The number of articles published in each year was identified by searching the terms referred in the legend in the PubMed database (https://pubmed.ncbi.nlm.nih.gov/), queried on 29 November 2020.

Nanomedicine has emerged as an encouraging approach against cancer (Figure 2). In fact, there are 110 clinical trials involving the application of nanotechnology for cancer

treatment nowadays, according to the NIH (NIH, 2020). The development of accurate drug delivery systems is a promising strategy in order to improve the selective action of unspecific drugs and, in fact, most encapsulated drugs in novel nanodevices are clinical chemotherapeutic agents, such as doxorubicin, paclitaxel and docetaxel (Han *et al.*, 2017; Kushwah *et al.*, 2018; Saw *et al.*, 2017). This fact is due not only to the high incidence of cancer, but also because tumors present a characteristic physiology which is a huge challenge for biomedical research and demands therapeutic agents to have special features (Spencer *et al.*, 2015). Thus, nanotechnology has explored over the past several decades different approaches in order to achieve better encapsulation devices, such as liposomes, nanoparticles, micelles or dendrimers (Brannon-Peppas and Blanchette, 2004; Howes *et al.*, 2014; MacEwan and Chilkoti, 2017; Minelli *et al.*, 2010; Shi *et al.*, 2017). Furthermore, some of these promising nanodevices have been used in clinical trials. In fact, the chemotherapeutic drug doxorubicin, which is currently used for the treatment of breast cancer among others, is administered with liposomal nature. As most clinically used chemotherapeutic agents are highly hydrophobic, drug encapsulation inside nanocarriers allow us to achieve higher concentrations within tumor cells (Behzadi *et al.*, 2017; Kushwah *et al.*, 2018; Luginbuhl *et al.*, 2017; Yousefpour *et al.*, 2019).

Table 1. A summary of different types of biomedical nanodevices for cancer therapy described in this review.

Type	Example	Chemotherapeutic agent	Targeted nanosystem	Indication
Liposome	Doxil®	Doxorubicin	No	AIDS-related Kaposi's sarcoma, Acute myeloid leukemia and ovarian cancer
	MbP-426	Oxaliplatin	Yes	Gastric cancer
	SGT-53	p53 gene	Yes	Solid tumors
	MCC-465	Doxorubicin	Yes	Colorectal and stomach cancer
PEGylated protein	Oncaspar®	PEG-l-asparaginase,	No	Acute lymphocytic leukemia, Lymphoblastic leukemia, Lymphoma

Polymer-drug conjugate		PK2	Doxorubicin	Yes	Liver cancer
Particle	Albumin-based	Abraxane®	Paclitaxel	No	Breast Cancer, Non-Small Cell Lung Cancer, Pancreatic Cancer
	Polymer	CAlAA-01	siRNA	Yes	Solid tumors

4. Clinically approved therapeutics

Table 1 summarizes the uses and content of nanosystems for drug delivery purposes described in this review. Doxil® is a representative example of non-targeted nanotherapeutic agent, as it has been used in the clinic for over two decades (Green and Rose, 2006; O'Brien, 2008). This small PEG-liposome (100 nm) containing the cytotoxic drug doxorubicin was first approved against AIDS-related Kaposi's sarcoma and is now approved for clinical use in ovarian cancer and multiple myeloma (Chanan-Khan and Lee, 2007). Although Doxil® also has important advantages for the clinic when compared to free doxorubicin, such as a 100-times longer half-life inside the body circulation and a reduction in cardiotoxicity, on the other hand it provokes skin toxicity that is not observed after administration of the free drug (Uziely *et al.*, 1995).

Along this same line, Abraxane®, a 120 nm size albumin nanoparticle containing paclitaxel, was designed and developed to retain the therapeutic activity of paclitaxel without the toxicity associated with the emulsifier Cremophor El® involved in the paclitaxel formulation (Taxol®) (Sparreboom *et al.*, 2005). A phase III study involving 454 patients with metastatic breast cancer compared Abraxane® and Taxol® (Gradishar *et al.*, 2005). Results showed up to 80% higher maximally tolerated dose (MTD) of Abraxane® and significantly greater response rates compared to patients treated with Taxol®. Furthermore, the Abraxane® group showed significantly lower incidence of

grade 4 neutropenia compared to patients treated with Taxol®. Therefore, the clinical advantage associated with Abraxane® is not only due to its "nano" form but also to the lack in the formulation of toxic Cremophor El® (Henderson and Bhatia, 2007). Interestingly, and as a direct consequence of this, Abraxane® does not require the use of pre-medications that are normally required for Taxol® treatment.

Multiple nanotherapeutic agents based on PEGylated proteins have been also approved for clinical use. PEGylation strategy is widely used as it increases the solubility, prevents rapid renal clearance, reduces immunogenicity and increases circulation times (Harris and Chess, 2003; Posey *et al.*, 2005; Rowinsky *et al.*, 2003). For these reasons, different proteins, such as enzymes, cytokines and monoclonal antibody Fab fragments, have been typically PEGylated. The US Food and Drug Administration approved Oncaspar®, a PEG-l-asparaginase, in 1994 to treat acute lymphoblastic leukaemia (Graham, 2003). Although the naked form of the drug accurately depletes asparagine and is active against acute lymphoblastic leukaemia and lymphoma, a hypersensitivity reaction and antibody production are induced, thereby leading to rapid clearance from the circulation. Oncaspar® was shown to have increased plasma half-life compared to the naked l-asparaginase and reduced the hypersensitivity reaction in patients with refractory lymphoma (Abshire *et al.*, 2000; Agrawal *et al.*, 2003; Ho *et al.*, 1986).

Furthermore, cancer cells are characterized by higher expression of multiple proteins, not only cytoplasmic proteins, but also cell membrane receptors (Byrne *et al.*, 2008). These cancer markers are of huge interest, as we can use different targets depending on the type of tumor and we can even differentiate primary tumors from distant metastases (Byrne *et al.*, 2008). The surface of nanoparticles can therefore be decorated with molecules as

targeting systems in order to specifically drive these therapeutic nanodevices to cancer cells and thereby avoid undesired effects in healthy cells (Shi *et al.*, 2017). Thus, nanotechnology can take advantage of cancer markers in order to develop advanced nanocarriers that allow us to achieve personalized biomedical therapeutics (Eskandari *et al.*, 2020; Henderson and Shankar, 2017).

PK2, a HPMA polymer-doxorubicin conjugate, was the first targeted nanotherapeutic agent to reach the clinic. The nanoparticle includes galactosamine to target the asialoglycoprotein receptor (ASGPR), which is typically expressed in hepatocytes (Reshitko *et al.*, 2020). As ASGPR is expressed in both healthy hepatocytes and primary liver cancer cells, the targeted nanoparticles get accumulated in normal liver cells as well as in the tumor (Hopewel *et al.*, 2001). Concentrations of the drug in the liver were 15–20% of the administered dose after 24 hours (Julyan *et al.*, 1999) and the concentrations within the tumor tissue were up to 50-fold higher than would have been achieved through free doxorubicin. Currently, the only targeted nanoparticles in the clinic are specifically driven to the transferrin receptor, which is known to be upregulated in many types of cancer (Gatter *et al.*, 1983). Thus, we can find MbP-426, a liposome containing the cytotoxic platinum-based drug oxaliplatin (Sankhala *et al.*, 2009); SGT-53, which contains a plasmid encoding for the tumor suppressor p53 in a liposome (Pirollo *et al.*, 2016; Senzer *et al.*, 2013); and CAlAA-01, a 70 nm polymer-based nanoparticle containing small interfering RNA (siRNA) (Davis, 2009; Eifler and Thaxton, 2011, Zuckerman *et al.*, 2014). MCC-465, an immunoliposome-encapsulated doxorubicin with encouraging results in clinical trials against colorectal and stomach cancer (Fernandes *et al.*, 2015; Hamaguchi *et al.*, 2004; Matsumura *et al.*, 2004), is not in use yet. Other examples of clinically approved nanodrugs are summarized in Table 2.

Table 2. Examples of clinically approved biomedical nanodevices for cancer therapy.

Product	Type	Chemotherapeutic agent	Size (nm)	Indication	Approved by	Biologic License Application
Adagen®	Polymeric nanoparticle	Bovine pegademase	n/a	Severe Combined Immunodeficiency (SCID)	FDA	019818
Bexxar®	Antibody-radioactive element conjugate	iodine-131	n/a	Non-Hodgkin's lymphoma	FDA	125011
DaunoXome®	Liposome	Daunorubicin	45	AIDS-related Kaposi's sarcoma, metastatic ovarian cancer, metastatic breast cancer, multiple myeloma	FDA	050704
DepoCyt®	Liposome	Cytarabine	n/a	Lymphomas or leukemia with meningeal spread add neoplastic meningitis	FDA	21-041
Eligard®	Polymeric nanoparticle	Leuprolide acetate	n/a	Prostate cancer	FDA	021731
Kadcyla®	Antibody-drug conjugate	DM1	n/a	Metastatic breast cancer	FDA	125427/0
Marqibo®	Liposome	Vincristine	163	Acute lymphoid leukemia	FDA	202497
Mepact®	Liposome	Mifamurtide	n/a	Osteosarcoma	EMA	EMEA/H/C/000802
Myocet®	Liposome	Doxorubicin	150	Breast	EMA	EMEA/H/C/000297
Mylotarg®	Antibody-drug conjugate	Calicheamicin	n/a	Acute myeloid leukemia.	FDA	761060
Onivyde®	Liposome	Irinotecan	n/a	Pancreatic cancer	FDA	207793
Ontak®	Fusion protein	Denileukin diftito	n/a	Cutaneous T-cell lymphoma	FDA; EMA	103767; EU/3/01/075
Vyxeos®	Liposome	Daunorubicin and Cytarabine	n/a	Acute Myeloid Leukemia	FDA	209401
Zevalin®	Antibody-radioactive element conjugate	yttrium-90	n/a	Non-Hodgkin's lymphoma	FDA; EMA	125019; EMEA/H/C/000547

5. Challenges

Table 3 shows different nanoformulations currently used in clinical trials. One of the main disappointing obstacles is the stark contrast between the high amount of successful nanotherapeutics in preclinical studies in the laboratory at both *in vitro* and *in vivo* level and the outcomes from clinical trials. Despite multiple animal models are currently available, from cell line-based subcutaneous and orthotopic xenografts or patient-derived xenografts (PDXs) to genetically engineered mouse models (GEMMs), there is a lack of tumour models able to fully reproduce all aspects of human cancer (Choi *et al.*, 2014; Sharpless and Depinho, 2006). Furthermore, it is of great importance to highlight the major contribution of tumor metastases to cancer mortality, whereas models of human tumor metastasis are not valid for the nanotherapeutic penetration within metastatic tissues compared to primary tumors. Therefore, the translation of therapeutic nanosystems could be improved by the development of novel animal models able to mimic the heterogeneity and special physiology of human tumors (Hubbard *et al.*, 2016; Lin *et al.*, 2014; Rongvaux *et al.*, 2014).

Moreover, the manufacture and the escalating complexity are important challenges for clinical development of therapeutic nanosystems. The transition from preclinical to clinical development and subsequent commercialization requires predetermined standards of quality, controls and good manufacturing practice, which can be achieved

by means of manufacturing unit operations already available in the pharmaceutical industry.

Table 3. Examples of biomedical nanosytems in clinical trials for cancer therapy.

Type of nanomaterial	Product	Chemotherapeutic agent	Indication	Status	Clinical trial reference
Dendrimer	AZD4320	AZD4320	Advanced solid tumors; lymphoma; multiple myeloma; Hematologic malignancies	Phase I	NCT04214093
Gold nanoparticle	Aurimmune	TNF	Solid tumor	Phase I	NCT00356980
Liposome	CPX1	Irinotecan	Colorectal cancer	Phase II	NCT00361842
Liposome	LE-SN38	Sn-38	Neoplasms	Phase II	NCT00046540
Liposome	Lipoplatin^{TM}	Cisplatin	Non-small cell lung cancer; breast cancer; gastric cancer	Phase III	NCT02702700
Liposome	LNDDP	Cisplatin	Malignant mesothelioma	Phase II	NCT00004033
Liposome	2B3-101	Doxorubicin	Glioma	Phase I,II	NCT01386580
Polymeric conjugate	XMT1001	Camptothecin	Small cell lung cancer; Non-small cell lung cancer;	Phase I	NCT00455052
Polymeric conjugate	Cpc634	Docetaxel	Ovarian cancer	Phase II	NCT03742713
Polymeric conjugate	CRLX101-Olaparib	Olaparib	Urothelial cancer; Small cell lung cancer; Non-small cell lung cancer; prostate cancer	Phase I; Phase II	NCT02769962
Polymeric micelle	Nk105	Paclitaxel	Breast cancer nor metastatic recurrent	Phase III	NCT01644890
Polymeric micelle	Nanoxel® M	Docetaxel	Head and neck squamous cell carcinoma	Phase II	NCT02639858

	Lipusu®	Paclitaxel	Breast cancer	Phase IV	NCT02142790
	Nanoplatin	Gemcitabine	Locally advanced and metastatic pancreatic cancer	Phase I; Phase II	NCT00910741
	E7389-e044-112	Eribulin-lf	Solid tumors	Phase I	NCT01945710
	Nc6004	Cisplatin	Head and neck cancer	Phase II	NCT03771820
	Paclical	Paclitaxel	Ovarian cancer	Phase III	NCT00989131
Targeted minicell	TargomiRs	miRNA mimic	Malignant pleural mesothelioma; Non-small cell lung cancer	Phase I	NCT02369198

6. Conclusion

Despite the numerous advances in oncology, chemotherapeutic drugs currently used in the clinic present important limitations, such as low specificity of therapeutic agents with important side effects on healthy tissues. Thus, novel strategies for achieving an accurate action on targeted cells are needed. Nanotechnology and medicine have been combined thereby constituting the nanomedicine field, which consists of the development of therapeutic devices at the "nano" scale aiming to tackle cancer cells specifically. Even though key steps are still needed to improve its accuracy, nanomedicine is becoming more and more promising, as demonstrated by the increasing number of clinical trials involving nanodrugs.

Nanomedicine is continuously evolving and more sophisticated multifunctional nanotherapeutics are reaching the clinical practice. Even though many challenges still exist for the translation of nanodevices to clinically approved products, their potential advantages should lead to their successful development. Moreover, the continuing need

of novel classes of anticancer therapies mandates scientific research to achieve improved

nano-based approaches. Ideally, nanomedicine will contribute to improve patient survival

in the foreseeable future.

Conflict of Interest

The authors declare no conflict of interest, financial or otherwise.

Funding

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