Nanomedicine, defined as the application and convergence of nanotechnology in biological, pharmaceutical, and medical-related areas, offers a plethora of unprecedented tools that can revolutionize cancer therapy. Nanoparticles as chemotherapy delivery systems exhibit several advantages: i) protect the payload from premature degradation in the biological environment; ii) enhance the bioavailability; iii) prolong presence in the blood; iv) deliver to target tissues more precisely with a controlled release. In addition, the possibility to optimize NP biophysical (i.e., size, charge, shape, and material composition) and biological (i.e., ligand functionalization for targeting) properties allows for highly tailored delivery platforms. However, despite thirty years of interesting discoveries and extensive experimentation, only 15 cancer nanodrugs have been approved, and they exhibit only a moderate impact on overall survival compared to relevant standard therapies. This review aims to describe the state-of-art of cancer nanomedicine by discussing both clinical outcomes and factors that are limiting nanodrugs translation from bench to bedside.
Introduction

Cancer is one of the major public health problems worldwide, the International Agency for Research on Cancer has estimated that a total of over 18.1 million new cancer cases and 9.6 million cancer deaths have occurred globally in 2018 \[1\]. Although the cancer death rate has declined by 29% from 1991 to 2017, mainly due to advances in prevention and application of existing cancer control knowledge, the magnitude of this decline is highly variable according to age, race, and sex \[2\]. Treating cancer remains much more challenging than preventing it.

The main treatments for cancer are surgery, radiation, and chemotherapy. Although some excellent drugs are available, the efficacy of many existing chemotherapeutic drugs is limited by their poor solubility coupled to their inability to reach their therapeutic site of action in sufficient amounts to be efficacious \[3\]. The distribution into healthy organs and tissues and the depression of the immune system limit the dosage that can be given, and in turn, prevents these drugs from achieving the potential cures that they are clearly capable of \[4-6\]. Therefore, there is a need for targeted or site-specific delivery of such agents to reduce the side effects to non-targeted tissues and organs and increase the effectiveness of therapy \[6\]. In this regard, nanomedicine offers a plethora of unprecedented tools that can revolutionize the way we look at cancer, both at the diagnosis and treatment stages. Nanomedicine is defined as the application and convergence of nanotechnology in biological, pharmaceutical, and medical-related areas, and it can be traced back to the late 1990s. Nanomedicine employs nanoscale materials and principles to develop platforms for drug and gene delivery by exploiting the fact that endogenous transport at the cellular level is actively driven at nanometer length-scale \[7\]. Nanoparticles (NPs) have the nature of high surface-to-volume ratio and abundant surface chemistry \[8\]. The high surface-to-volume ratio facilitates the loading and delivery of drugs, genes, and/or imaging agents either in the interior or on their surface, while the abundant surface chemistry makes it possible to modify the surface using organic biomacromolecules or targeting ligands. Nano-medicine and its NPs offer potential solutions to the challenge of chemotherapy drug delivery, in particular, the requirements for i) protect the payload from premature degradation in the biological environment \[8, 9\]; ii) enhance the bioavailability \[10-12\]; iii) prolong presence in blood \[6, 13\]; iv) deliver to target tissues more precisely with a controlled release \[7, 14\]. This review provides an overview of nanomedicine in cancer therapy, focusing on key optimization of NPs properties size, charge, shape, material, and ligand functionalization for targeting nanodrugs that have been clinically approved and factors that are limiting their efficient translation from bench to bedside.

1. Nanoparticles

The major advantages of NP delivery systems include optimization of NP biophysical (i.e., size, charge, shape, and material composition) and biological (i.e., ligand functionalization for targeting) properties, allowing for highly tailored delivery platforms (figure 1) \[15, 16\].

![Fig 1: Nanoparticle delivery systems can be optimized in term of their biophysical (i.e. size, charge, shape and material composition) and biological (i.e. ligand functionalization for targeting) properties.](image-url)
Nanoparticle size, charge, shape and composition are strong determinants of cellular uptake \[17, 18\].

Size is directly related both to the cellular internalization rate and to the circulation time of the NPs \[17\]. It has been demonstrated that NPs 40-50 nm size exhibit maximum uptake in vitro \[18\], while NPs between 10 and 100 nm in diameter show optimal results in vivo applications \[19\]. NPs 70-200 nm show the tendency to accumulate in the solid tumor tissue through passive targeting \[20, 21\].

The surface charge and the hydrophobic/hydrophilic of the NPs are key factors in the interaction between NPs and biological medium, and consequently, they influence cellular uptake. Cationic NPs show significantly higher affinity with negatively charged phospholipid head groups, glycans as well as proteins on cell membranes, and in turn are more efficient in cellular uptake \[22\]. On the other hand, anionic and neutral NPs encounter poor cellular internalization \[23, 24\].

NPs which are more hydrophobic than the cell surface they are binding to, were observed to have both higher cellular uptake and protein adsorption on their surfaces \[25\]. Hydrophobic NPs, instead, adsorb less of medium proteins \[5, 21\]. According to these findings; NPs are often coated with polyethylene glycol (PEG) because this highly hydrophilic polymer enhances in vivo circulation by creating a steric hindrance for proteins, including opsonins \[26\]. Opsonins, indeed, are rapidly recognized and sequestered by cells of the mononuclear phagocyte system leading to the rapid removal of NPs from blood circulation in the kidneys (NPs smaller than 10 nm), spleen, and liver (larger NPs) \[17, 18\].

The shape is also important. Due to hydrodynamic forces, the symmetry of the NPs determines the trajectory in their journey through the circulation system, while the shape of NPs affects the cellular uptake efficiency \[27\]. Some authors have reported that since spherical NPs can accommodate cellular membrane wrapping, they are more effectively taken up than rods \[21, 24, 29\]. On the other hand, some studies have demonstrated that rods and tubes show both higher cellular uptake efficiency and drug delivery efficiency than spheres \[30, 31\]. These contradictory findings may be a result of the contribution NPs’ size, material or charge, as well as of different cell lines used for uptake experiments \[27\]. However, it is generally recognized that spherical NPs have shorter circulation times than rods or other non-spherical particles \[21\].

Many material systems have been introduced into nanomedicine to improve the performance of drug delivery systems. Despite each material exhibits unique physical-chemical and biological properties, NPs can be divided into three categories: organic, inorganic, and organic/inorganic hybrid NPs \[32\].

### 1. Organic NPs

Several organic nanostructures (i.e., liposomes, polymeric micelles, albumins, etc.) have received clinical approval for tumor chemotherapy by improving the performance of the original drugs (i.e. paclitaxel, doxorubicin, daunorubicin, etc) both in terms of efficacy and safety \[18\]. Liposomes, in particular, with a dozen approved drug products (i.e., Doxil®, Caelyx®, DaunoXome®, Myocet®, etc.) are the most successful drug delivery systems \[19, 24\]. The similarity of the liposome membrane to biological membranes provides unique opportunities for the delivery of drug molecules into the cells or at sub-cellular compartments. Moreover, liposomes size can be precisely controlled, and their surface can be easily modified. This property can be exploited both for active targeting and to improve NPs pharmacokinetics by PEGylation. They can encapsulate and store both hydrophilic and hydrophobic molecules, and they are nontoxic, nonimmunogenic, and biodegradable \[34, 35\]. On the other hand, liposomes show poor stability, low loading efficiency, and poor release profiles \[21\].

### 1.2 Inorganic NPs

Compared to organic NPs, inorganic material systems show high thermal/chemical stability and resistance to corrosion under physiological conditions. In addition to ease of synthesis, modification, and inertness, the magnetic and optical properties (fluorescence, plasmonic absorbance, etc.) make inorganic NPs attractive for both imaging and ablation of malignant tissue \[36\]. Inorganic NPs include metals (e.g., gold, silver, platinum) \[37\], semiconductors (e.g., quantum dots) \[38-40\], carbon dots/nanotubes \[41\], silica \[32, 36\] and oxides (e.g., iron oxide, titanium oxide, zinc oxide) \[41, 42\] and they have been extensively studied for diagnostic and therapeutic purposes in oncology. Among inorganic NPs, gold nanostructures have attracted much attention for their intrinsic properties (surface plasmon resonance, low toxicity, and ability to penetrate tumor tissues), and they have been studied and administered in phase I and II clinical trials for cancer treatments \[37\]. Mesoporous silica (MS) NPs has emerged as intermediary nanovehicles in the sense that they possess similar biocompatibility as the organic NPs as well as the stability and versatility of inorganic nanocarriers \[32, 36\]. MS NPs have been shown to be exceptional nanocarriers for a wide variety of drugs and biomolecules used in cancer treatments (i.e. doxorubicin, paclitaxel, small interfering RNA for gene knockdown, plasmid DNA for transfection, etc.), exhibiting good performance both in vitro and in vivo \[32\]. On the other hand, zinc oxides NPs have received attention in cancer therapy due to their wide bandgap semi-conductor capacity and non-toxic and biocompatible properties. These oxides can induce cell cytotoxicity and reactive oxygen species gene-expression resulting in the death of cancer cells \[39\]. However, the in vivo translocations of inorganic NPs have encountered great debate, large-ly related to the potential toxicity, and only a few of them have been approved by the Food and Drug Administration (FDA) (e.g., NanoTherm, aminoisilane-coated superparamagnetic iron oxide NPs, and NBTXR3, a suspension of functionalized spherical NPs of hafnium oxide) \[33\].

### 1.3 Organic-inorganic hybrid NPs

The recently developed organic-inorganic hybrid nanomaterials combine the merits of both organic and inorganic materials, excluding some of their limits. The synergistic combination of materials provides im-proved biocompatibility, high drug loading capacity, stimuli-responsive drug release, co-delivery of multi-drugs, etc \[33, 44\]. Organic-inorganic hybrid nanosystems typically present a core-shell architecture, where the inorganic core (QDs, metal NP, silica, etc.) is covered by an organic shell (liposomes, polymers, etc.) able to increase the bio-safety, biocompatibility, and biodegradability of the nanoplateform. Some of these nanosystems have been successfully employed and validated as therapeutic or diagnostic nanocarriers \[41-43\]; others more advanced, rep-rent the first prototypes of theranostic nanoplatfroms. The possibility to entrap imaging agents and therapeutic drugs in a single integrated NP allows providing medical treatment with precise spatiotemporal control while monitoring the treatment’s therapeutic efficiency. Although NP-based platforms can merge both therapeutic and diagnostic properties are the Holy Grail for nanomedicine, they have not yet been clinically approved.

### 2. Targeting strategies

Since most cancer nanodrugs are administered intravenously for systemic delivery to tumors, targeting strategies are crucial. They are cate-gorized into passive and active approaches. In passive targeting, the ac-cumulation of NPs in tumors mainly relies on highly leaky vasculature, allowing particles to enter into the tumor from surrounding tissues, and poor lymphatic drainage system, which reduces their clearance \[26, 27\].
This phenomenon, known as the enhanced permeability and retention (EPR) effect \((47)\), has been considered as the “royal gate” in the drug delivery field for a long time. Studies in animal models showed that the EPR effect could lead to a 50-fold accumulation in tumors compared to healthy tissues, however, it provides modest tumor specificity in humans, and is unlikely to be sufficient for effective drug delivery \((4, 21)\). EPR effect should be now reconsidered in the light of the tumor heterogeneity and in particular of the degree of angiogenesis, lymphangiogenesis, and perivascular tumor growth and as well as on the basis of the intratumor pressure and interpatient variability \((48)\).

An alternative strategy is to use active targeting that relies on affinity ligands, which will directly bind NPs to overexpressed receptors on tumor surfaces. This is achieved by “decorating” the surface of the NPs with targeting moieties such as monoclonal antibodies, peptides, proteins, amino acids and, small molecules \((46-50)\). The first applications of active targeting derived from the functionalization of the surfaces of liposomes with monoclonal antibodies, designed to bind antigens present on target cells \((51)\). Although some of these products appeared to show promise in cancer treatment, most of them were not more effective than the non-targeted versions and did not bring new nanodrugs to market \((50)\). The poor success of targeted NPs technology renewed questions about understanding limitations in targeting strategies. Among other implications, it is well recognized that the biological environment can significantly alter the NPs identity and, consequently, interfere with ligand accessibility \((52)\). When introduced in the bloodstream, NPs are coated by a dynamic biomolecular layer that is referred to as a “biomolecular corona” (BC), which has important consequences not only in terms of pharmacokinetics but also in NPs’ targeting capability \((7, 53, 54)\). The biomolecular corona formation screens the targeting molecules on the surface of nanocarriers and causes loss of specificity in targeting \((53)\).

### 3. Clinically Approved Cancer Nanomedicines

The first nanomedicine that received clinical approval was the PEGylated liposomal formulation of doxorubicin. It was approved by the FDA as Doxil® in 1995 and by the EMA as Caelyx® in 1996 \((55-57)\). Since then, 15 nanodrugs have entered the market, refer to table 1 \((33)\). With a mean particle size of 80–90 nm, Doxil® is indicated in the following conditions: (i) AIDS-related Kaposi’s sarcoma in patients with HIV; (ii) recurrent ovarian cancer; (iii) metastatic breast cancer and (vi) myeloma. Doxil® is targeted to tumors via the EPR effect, providing higher levels of doxorubicin at the tumor tissue compared to free doxorubicin. This Johnson & Johnson’s nanomedicine led to substantially reduced side-effects and to better efficacy of action by increasing the tolerated dose levels. In particular, it has been demonstrated to decrease cardiotoxicity compared to free doxorubicin. On the other hand, the treatment efficacy did not increase as expected \((6, 56, 57)\). Myocet®, another liposomal formulation of doxorubicin was approved in Europe and Canada in 2000 to treat metastatic breast cancer (with cyclophosphamide) \((58)\).

<table>
<thead>
<tr>
<th>Product</th>
<th>Drug</th>
<th>Composition</th>
<th>Size</th>
<th>Indications</th>
<th>First Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxil®/Caelyx®</td>
<td>Doxorubicin</td>
<td>PEGylated liposome</td>
<td>80–90 nm</td>
<td>Myeloma, Kaposi’s sarcoma, breast, ovarian cancer</td>
<td>1995 US</td>
</tr>
<tr>
<td>DaunoXome®</td>
<td>Daunorubicin</td>
<td>Liposome</td>
<td>40-50 nm</td>
<td>Advanced Kaposi’s sarcoma</td>
<td>1996 US</td>
</tr>
<tr>
<td>DepoCyt®</td>
<td>Cytarbine</td>
<td>Liposome</td>
<td>-</td>
<td>Lymphoma, Leukemia</td>
<td>1999 US</td>
</tr>
<tr>
<td>Myocet®</td>
<td>Doxorubicin</td>
<td>Liposome</td>
<td>150 nm</td>
<td>Breast cancer</td>
<td>2000 Europe/Canada</td>
</tr>
<tr>
<td>Abraxane®</td>
<td>Paclitaxel</td>
<td>Human serum albu-min NPs</td>
<td>130 nm</td>
<td>Breast, non-small-cell lung, pancreatic cancer</td>
<td>2005 US</td>
</tr>
<tr>
<td>Lipusu®</td>
<td>Paclitaxel</td>
<td>Liposome</td>
<td>150 nm</td>
<td>Breast and non-small-cell lung cancer</td>
<td>2006 China</td>
</tr>
<tr>
<td>Oncaspar®</td>
<td>Asparagine specific enzyme</td>
<td>PEG-L-Asparginase</td>
<td>-</td>
<td>Acute lymphoblastic leukemia</td>
<td>2006 US</td>
</tr>
<tr>
<td>Genexol-PM®</td>
<td>Paclitaxel</td>
<td>Micelle</td>
<td>25 nm</td>
<td>Breast, non-small-cell lung, ovarian, gastric cancer</td>
<td>2007 Korea</td>
</tr>
<tr>
<td>Mepact®</td>
<td>Mifamurtide</td>
<td>Liposome</td>
<td>-</td>
<td>Osteogenic sarcoma</td>
<td>2009 Europe</td>
</tr>
<tr>
<td>NanoTherm®</td>
<td>-</td>
<td>Iron oxide</td>
<td>-</td>
<td>Brain tumors</td>
<td>2011 Europe</td>
</tr>
<tr>
<td>Marqibo®</td>
<td>Vincristine sulfate</td>
<td>Liposome</td>
<td>115 nm</td>
<td>Acute lymphoblastic leukemia</td>
<td>2012 US</td>
</tr>
<tr>
<td>Onivyde®</td>
<td>Irinotecan</td>
<td>PEGylated liposome</td>
<td>110 nm</td>
<td>Advanced pancreatic cancer</td>
<td>2015 US</td>
</tr>
<tr>
<td>DHP107®</td>
<td>Paclitaxel</td>
<td>Lipid NPs</td>
<td>-</td>
<td>Gastric cancer</td>
<td>2016 Korea</td>
</tr>
<tr>
<td>Vyxeos®</td>
<td>Daunorubicin and Cy- tarabine</td>
<td>Liposome</td>
<td>100 nm</td>
<td>High-risk acute myeloid leukemia</td>
<td>2017 US</td>
</tr>
</tbody>
</table>

Table 1. Clinically approved cancer nanodrugs \([6, 33, 55-67]\)
Abraxane® was the top-selling nanomedicine in 2018 with $950 M (Doxil®, $252 M) [39]. It is a human serum albumin-bound paclitaxel NP formulation approved by the FDA in 2005. Abraxane® is indicated for: (i) breast cancer; (ii) non-small-cell lung cancer and (iii) metastatic adenocarcinoma of the pancreas [60-62]. The albumin-bound paclitaxel NPs have an average particle size of about 130 nm, and they enhanced paclitaxel tolerance, allowing drug administration without the use of castor oil—cremophor EL®, a toxic surfactant used to improve paclitaxel solubility [63]. Clinical studies have demonstrated a significant increase in the maximum tolerated dose (with similar toxicity to Taxol) [6]. Other nanodrugs of paclitaxel have been developed: Lipusu® (liposomal nanodrug for breast and non-small-cell lung cancer) [64], Genexol-PM® (micellar nanodrug for breast, non-small-cell lung, ovarian, and gastric cancer) [65], DHP107® (lipid nanoparticles for gastric cancer) [33] and Apealea® (micellar nanodrug for ovarian, peritoneal, and fallopian tube cancer) [69].

Vyxeos®, approved by the FDA in 2017 and by the EMA in 2018, is the first dual drug nanomedicine: it is a liposomal formulation of co-encapsulated cytarabine and daunorubicin at a 5:1 molar ratio. It is indicated for the treatment of adults with newly-diagnosed therapy-related acute myeloid leukemia or acute myeloid leukemia with myelodysplasia-related changes [66]. Clinical studies showed that Vyxeos® significantly prolonged overall survival and event-free survival relative to conventional chemotherapy with cytarabine plus daunorubicin. Moreover, it was also associated with significantly higher rates of complete remission [67]. Both daunorubicin and cytarabine chemotherapy regimens had previously been marketed as nanomedicines: DaunoXome®, a liposomal daunorubicin formulation indicated for Kaposi’s sarcoma, was approved in 1996 by FDA while DepoCyt®, liposomal cytarabine used for lymphoma and leukemia, was approved in 1999 [33].

Collectively, clinically approved nanodrugs exhibited improved bioavailability, longer circulation times, and reduced side-effects compared to free chemotherapeutics. However, the majority of approved cancer nanomedicines exhibited only a moderate impact on overall survival as compared to relevant standard therapies. The treatment efficacy did not increase as expected, and it represents the main weakness in the nanodrugs’ clinical translation [6, 31, 59].

### 4. Is cancer nanomedicine lost in translation?

The success rates for nanodrug candidates for phase I, II, and III trials significantly plunge from 94% to 48% to 14%, respectively. The high success of phase I trials suggests good material safety, while the fact that only 14% of nanodrugs concluded phase III with positive outcomes is due to the low efficacy [39]. The drop in the success rate of clinical trials is in analogy to the gap between the huge number of published papers and the poor clinical outcome of these technologies. Over 42,500 articles (more than 5000 only in 2020) appear in a PubMed search for “nanoparticles for cancer,” yet only 15 nanoparticle-based cancer nanomedicines are approved globally.

What is limiting the efficient translation of cancer nanomedicine from bench to bedside?

Before nanotechnology can truly become a valuable tool for clinical medicine and revolutionize cancer treatments, some difficulties must be overcome.

One of the main factors for the disappointing efficacy of cancer nanomedicine is the poor understanding of the interactions between NPs and the biological environment, which results in their insufficient accumulation in the tumor. An interesting analysis of 117 cancer nanoparticle papers has demonstrated that only 0.7% (median) of the administered NPs is delivered to a solid tumor [68]. These results can be explained on the one hand, with the failure of the EPR effect in the clinic and, on the other hand, with BC formation, which makes ineffective active targeting strategies [69]. However, in light of the fact that the BC composition is strictly correlated to the NPs synthetic identity, the possibility to design the NPs with the goal to manipulate the corona composition to make them able to acquire the desired targeting capability once in vivo opens to new, intriguing targeting strategies. A properly designed NP could ensure the uptake of proteins specifically recognized by receptors on target cells in the protein corona. In this manner, the protein corona could be transformed from a problem to a targeting moiety [7].

Another crucial factor that is preventing the efficient translation of NPs technology from bench to bedside is the limited reliability of cancer animal models which fail to reproduce the complexity of human tumors in term of their mutation, proliferation, metastasis, size, and heterogeneity [31, 68]. EPR effect, which works well in animal models but not in humans, is a good example of the discrepancy between the therapeutic efficacies observed in preclinical studies and the lack of positive clinical outcomes.

### Conclusions

Despite thirty years of exciting discoveries, coupled with extensive clinical experimentation, cancer nanomedicine did not revolutionize the way we look at cancer treatment. Nanodrugs clinical application is still limited; however, the lessons learned from the current failure are now the driving force for the next generation of nanomedicines. A better understanding of the in vivo BC opens the intriguing possibility to exploit it both for targeting and to tailor drugs according to each person leading to personalized clinical therapy. On the other hand, significant progress has been made in drug controlled release and stimuli-sensitive drug delivery systems. Thermo-Dox®, a thermosensitive liposomal-doxorubicin formulation that is undergoing clinical trials, is showing impressive performance in comparison with both free doxorubicin and standard liposomal formulations of the drug [33].

In conclusion, the optimization of active targeted, stimuli-sensitive and multi-therapeutic agents nanodrugs is expected to enhance the clinical efficacy of nanomedicine to treat cancer.
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