A review of the current state of nanomedicines for targeting and treatment of cancers - achievements and future challenges

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Highlights

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Abstract

Abstract text. 12 point, double-spaced. Maximum length 200 words. Written in the present tense and impersonal style

Keywords

Cancer, effective therapy nanomedicine, current and future challenges

1. Introduction

Nanotechnology is based on the exploitation of matter at the nanoscale [1], by the integration of the nanostructures into larger systems for real-world applications. Over the last two decades, nanotechnology has gained prominence in modern biology with the field of nanomedicine becoming one of the most prominent and vital [4]. It is both their small size and larger surface area, as well as other unique physiochemical properties, which makes them extremely desirable for medical applications [1-4]. Nanomedicine allows for drugs or delivery devices to be manipulated at the nanoscale, for improved delivery to desired destinations within the body, while at the same time, retaining the valuable pharmacological properties of the drug [5]. Importantly, efficient drug delivery and excellent release potential of drugs can never be exploited if the medicine is hindered by possible toxic side-effects. The same unique properties that make nanomaterials (NMs) so desirable often contribute to their potential toxicity [6].

In recent years, great progress has been made in the synthesis of a variety of materials that can be used as nano-vehicles (carbons, synthetic polymers, micelles, liposomes/vesicles, drug-polymer polysaccharide conjugates to name a few) [7-10]. Currently, commercial nanomedicines are predominantly generated as nanocarriers for therapeutics or stabilized solid drug NMs. These strategies have potential to target a single cell type and provide great potential for effective medicine delivery. As an example, NM surfaces can be chemically modified to influence site-specific drug delivery [9, 11]. Additional to drug delivery, the discovery of size-dependent properties that result in materials with specific emission, absorption, or light scattering spectra, has expanded potential applications in imaging and diagnosis [12]. Further benefits of the use of NMs, can include improved

drug stability and a longer shelf-life, improve pharmacokinetics and clearance [9] as compared with traditional formulations.

Cancer is a global disease with high morbidity and mortality. In 2018, it is believed that 18 million people newly diagnosed with cancer and approximately 10 million patients died due to cancer-in the same period [13]. Current traditional diagnosis and treatment approaches include magnetic resonance imaging, computer tomography imaging, the surgical removal of the tumour followed by intensive course of chemotherapy or radiotherapy. However, generally speaking, all current approaches for diagnosis and treatment are far from perfect due to lack of targeting ability NOT STRICLTY TRUE ANY MORE, PLENTY OF SPECIFC TARGETTED Abs NOW-TONE IT DOWN A BIT , a limited half-life or overt systemic toxicity.

The tumour microenvironment is associated with mild acidic condition, defective vascular structure, overexpression of certain enzymes (i.e. a number of enzymes involved in the tricarboxylic acid cycle), highly concentrated glutathione and reactive oxygen species (ROS) [14]. These unique characteristics might be targeted for stimuli-activatable nanoplatforms for cancer treatment. Nanomaterials show particular promise as candidates for cancer treatment due to their high surface to volume ratio and tuneable size, shape, composition, and surface chemistry, which in combination allow for improved tumour targeting and enhanced therapeutic efficacy. These properties as well as the strategies utilised by various nanomedicines to exploit these unique cancer characteristics, will be explored and expanded upon in the main body of the review.

The main body of the manuscript examines the progress made in utilisation of metallic nanomaterials, nano carriers or stabilized solid drug nanomaterials in medical applications intended for diagnosis,

delivery and treatments of cancers. The search criteria included a combination of the following terms: “nanomedicine”, “nanoparticles”, “nanomaterials”, “cancer”, “liposomes”, “micelles”, “solid drug nanoparticles”, “nano-delivery” “nano-carrier”, “nano-vehicles” “nano-constructs”, “nano-emulsions”, “drug delivery”, “therapeutics”, “imaging”, “*in vivo*” and “systemic”. The last literature search was conducted on 27-4-2020. The search criteria resulted in a total of 4057 abstracts being scrutinized and a total 191 papers are included in main body of the review (inclusion and exclusion criteria highlighted below). Due to the inevitable limitations and exclusionary nature of any literature search, studies that did not include the search terms in the title or did not provide adequate information in the abstract, might have been unintentionally omitted. However, all endeavours have been made to construct a comprehensive review and offer a balanced overview of the success of the current strategies for the application of nano-sized constructs for diagnosis and treatment of cancers. This review will not discuss the methodology utilised for the manufacture of the constructs or loading and encapsulation efficacy of the active pharmaceutical ingredients. The review focuses only on *in vivo* and clinical studies rather than *in vitro* experimentation, in order to capture the products that are potentially closer to market (assuming that initial screening and developmental work is conducted *in vitro*). The review concentrated on rodent, primate and human testing only and does not include fish, insect or parasitic experimental models. Moreover, engineered NMs or empty nanocarriers are not included. Finally, any manuscript that did not provide adequate experimental detail either in the main publication or as supplementary information has been excluded. Due to space constraints only a selected number of investigations are highlighted in the main text, but the conclusions are based on all 191 identified studies in the literature search and listed in tables 1-16.

The review has been structured and divided on most common cancers [15] and the proposed therapeutic use of the nanomedicine. The overall aim of the review is to recognise state of play in the

design and utilisation of cancer related nano medicines with the particular attention to ascertain the potential reasoning why the number of nanomedicines reaching clinical testing is still very low considering the incredibly large and ever increasing number of experimental investigations into the design and efficacy of manufactured nanomedicines designed for treatment and management of cancers.

2. Nanomedicines designed for targeting and treatment of cancers

2.1 Lung cancer

In order to solve the shortcomings of poor stability, easy degradation, short half-life, and low transfection efficiency of siRNA to specially deliver gene to drive expression without disrupting essential regulatory mechanism, multiple cellular and tissue barriers must be overcome. An interesting study demonstrated that inhalation, as well as IV injection, of polyester NMs containing siRNA for luciferase enzyme decreased the bioluminescence in the tumour xenograft of A549Luc cells in mice, corresponding to a 65% knockdown of the luciferase expression at 48 hr after the inhalation [16]. It stands out as a substantial effect, which is somewhat surprising as very little mass of NMs translocate across the alveolar-blood membrane, typically less than 1% of the deposited dose of inhaled nanoparticles [17].

A number of studies have reported a wide distribution of various types of nanoparticles following IV. administration, including the tumour tissue, liver and spleen, whereas the amount of NMs is less in other tissues [16, 18-22]. The majority of studies show less than accumulation of nanoparticles in the xenograft tumour tissues than other organs, particularly the liver and spleen, following IV

administration. An exception is a study by Zhang et al. who reported an effective accumulation of purpurin-loaded liposomes (80 nm) in tumour tissue and smaller uptake in other tissues after IV administration of the nanoparticles [23]. It is a somewhat surprising observation, considering the vast number of observations on selective uptake of IV administered NMs by the liver and spleen. It should be noted that the authors only used three mice per group and the standard deviations are very small (mean = 183×10^6, SD = 3.3×10^6 photons/cm/sec, estimated from data presented) [23]. The selective accumulation of NMs in the tumour should probably be interpreted cautiously until an independent repetition of the results has confirmed the results.

It has been shown that photothermal therapy or radio frequency-induced hyperthermia on subcutaneously injected lung cancer cells is highly effecting in reducing tumour growth, using chlorin-based carbon nanohorns [24], crystalline silicon NMs [25], red blood cell membrane-camouflaged melanin particles [18], MoS_2-based hyaluronic acid-functionalized nanoparticles [19], graphitic carbon nitride particles [20], black tin oxide NMs [26] and purpurin-loaded liposomes [23]. One study showed that xenograft tumour of lung cancer cells in nude mice had reduced growth after IV administration of paclitaxel-loaded nanobubbles (liposomes) as compared to the effect obtained by paclitaxel alone [27]. Another study used nanogels with polymer pylopyrryle (thermo-responsive compound) and methotrexate (antineoplastic agent); the combined treatment by direct injection of the nanogel in the tumour and phototherapy and methotrexate inhibited tumour growth more individual treatments [22]. Phototherapy following IV administration of the nanogels with polymer pylopyrryle also reduced tumour growth [22]. The combined treatment was not used for the IV administration, which might be due to the well-known adverse effects by methotrexate in cancer patients. The experimental detail of all relevant studies relating to lung cancers is summarised in table 1.

2.2 Breast cancer

With about 1.7 million new cases annually and more than 500000 deaths, breast cancer is by far the most frequent cancer malignancy in females worldwide, accounting for 25% of all new cases. Although we have seen improvements in screening and treatments, mortality remains high [28]. It is evident that new developments and therapeutic strategies for the treatment of breast cancer is absolutely essential

Recently a large number studies have used various mouse models to assess the therapeutic efficacy of newly developed nanostructures (Table 2). Structures that upon NIR radiation increase local temperature and act as photothermal therapeutics. Some constructs are also loaded with chemotherapeutics and/or chemicals with a photodynamic therapeutic potential released from the construct when heated. In general, all studies show an improved treatment result compared to negative controls (no treatment) or groups treated with chemotherapeutic, photodynamic (PDT) or photothermal (PTT alone). Synergy when combining multiple treatments are observed. Notably, 13 studies showed a complete eradication of the tumours, following NM treatment [29-41]. These experiments were mostly conducted over 14-21 days with the time to complete ablation was between 1 and 14 days .In none of the 13 studies any signs of re-growth was observed during the follow-up period. It is important to state that this was not the case in majority of investigations highlighted in table 2.

The nanomedicines are very diverse in chemistry and generally complex in construction. As they are only used in a single publication, it may not be possible to identify specific materials as most promising constructions. Although the nano-constructs may be complex, the thirteen studies overall showed a simple therapeutic plan compared to some less successful studies. Eight studies only used PTT, two only used PDT, two studies used a combination of PDT and PTT and only one study used a theranostic agent combined with PTT. Interestingly, most of the studies with the most promising potential only used a single treatment (10 with single IV injection and 3 single intratumoral injection). 15 of the remaining studies in Table 2 used multiple IV treatments (up to 15 injections), one used 5 IV and tumor adjacent injections, one used 4 tumor adjacent injections and two used daily oral gavage.

As two examples of nanomedicines designed for oral administration in a recent investigation, Paclitaxel stabilized Pluronic F-127 nanocrystals were used in an attempt to reduce the side-effects associated with traditional drug administration. Following the oral administration of the drug, no anti-tumour activity was observed in the mice treated with the commercially available PTX suspension. Nevertheless, the oral administration of the nanocrystals significantly inhibited tumour growth in breast xenograft animals. Unsurprisingly, the oral administration of the drug, resulted in less efficacy compared to the intravenous route. [42]. Elsewhere, a series of self-assembled nanostructured with the prodrug conjugates based on a commercially available Capecitabine (N-pentyloxycarbonyl-50-deoxy-5-fluorocytidine, Xeloda) were developed by substituting the pentyl group at the N^4 position with three different hydrophobic alkyl chains: palmityl (5-FCPal), oleyl (5-FCOle), and phytanyl (5-FCPhy). The efficacy of the new formulations was evaluated in female BALB/c mice injected with 4T1 cells into the third mammary fat pad. The data demonstrated that after 17 days, the 5-FCOle treatment group possessed significantly smaller tumours than all other treatment groups (~1/5 the size

of the tumours in both the 5-FCPhy and Capecitabine treatment groups and ~1/10 the size of tumours in the untreated control group [43].

2.3 Colorectal cancer

Colorectal cancer (CRC) ranks as the second most lethal cancer and the third most prevalent malignant tumour worldwide [13]. Typically, successful treatment of CRC involves complete removal of the tumour and metastases, which may require extensive surgical intervention [44]. In cases of unresectable lesions or for patients who are intolerant to surgery, maximum shrinkage of the tumour and suppression of further tumour spread, and growth is the desired outcome, and radiotherapy and chemotherapy are the leading strategies for controlling disease in such patients [45]. Nanomedicines are being developed which may offer significant advancements in the diagnosis, imaging and targeted treatment of CRC and in future lead to improvements in patient outcomes.

A key strategy for the development of nano-based diagnostic and therapeutics is the exploitation of the enhanced permeability and retention (EPR) effect whereby nanoparticles selectively extravasate and build-up in tumour tissues due to the abnormally dense and leaking vasculature and lack of effective lymphatic drainage [46]. Furthermore, structural features including high surface area and the potential for surface functionalization or hollow cores allow NMs to perform as nanoplatforms which can be manipulated to improve tumor selectivity, specificity and bioavailability of therapeutics. The choice of NM backbone can also be utilized to perform as a contrast agents to improve imaging applications. Combinations of these approaches have been developed maximize applications and therapeutic benefits within one nanoformulation. In a 2016 study, nanocapsules loaded with superparamagnetic iron oxide nanoparticles (SPIONs), a NIR fluorescent dye and the radioisotope,

Indium-111 were developed which enabled triple-model imaging (fluorescence/magnetic resonance/nuclear imaging) to provide complementary information on the spatial distribution of the tumour potentially significantly improving tumour diagnostics [47]. Furthermore, the properties of the nanomaterial itself can be employed in the targeted treatment of tumours for example through exploitation of the nanomaterial photothermal properties for the use in photothermal therapy (PTT). The enhanced photothermal properties of different NMs have been utilised in the development of a variety of non-invasive tumour ablation strategies including radiofrequency-based therapy [48] and near infrared irradiation (NIR) alone [49] or in combination with chemotherapeutic drug delivery [50-52]. Multimodal theranostics; the coupling of *in vivo* diagnostics with therapy, represent attractive prospects for the future development of more effective anti-cancer interventions. Further advancements in PTT offered by nanocarrier platforms include the targeted delivery of a sensitising agent to the tumour site as demonstrated by the reduction tumour cell tolerance to PTT after the delivery heat-shock protein inhibitor phenolic epigallocatechin 3-gallate loaded onto NiS2-coated nanoprobes [53]. Curcumin supramolecular nanofibers have also been showed to elicit superior radio-sensitization compared to free curcumin [54]. The intratumoral sensitisation to the photothermal energy can lead to the refinement of the PTT strategy by enabling the use of lower energies or shorter irradiation times preventing excessive damage to normal tissue while maintaining efficacy in destroying the tumour.

A number of approaches have exploited the tumour microenvironment to improve specificity and selectivity of contrast agents for imaging and drug delivery. In 2018, a doxorubicin-loaded degradable cobalt oxide nanoprism (CoNP) was developed to facilitate MRI-monitored synergistic cancer therapy that simultaneously responds to intratumoural oxidability and acidity. Selective degradation of the CoNP backbone to Co^{3+} under H_2O_2-rich and acidic tumour microenvironment led to

significant improvement in contrast between tumour and normal tissue as visualised by MRI. Furthermore, a synergistic effect was demonstrated between the photothermal and chemotherapy induced by Co_3O_4 and DOX in mouse model upon irradiation compared to treatment with the unloaded and DOX-loaded CoNP alone [55]. A further study utilised the highly acidic tumour microenvironment to develop a nanoprobe for NIR fluorescence-guided photothermal therapy which was specifically activated in the hydrogen sulfide (H_2S)-rich tumour environment [56]. The *in situ* H_2S-mediated transformation of the administered nanoprobe into a NIR-responsive photothermal agent allowed the targeted and complete ablation of tumours in xenograft models with no destruction of the normal neighbouring tissue. Moreover, the manufacture of a mesoporous carbon-gold hybrid nanoprobe loaded with NIR fluorescent dye resulted in tumour-specific nanozyme activity in combination with enhanced photothermal therapy effect. Through the catalysis of H_2O_2, present in high levels in the tumour microenvironment, to hydroxy radicals the AuNP increased intracellular oxidative damage in the tumour cells leading to significant reduction in tumour volume with no regrowth over 30 days post exposure [57]. These studies thereby demonstrates the application of nanomedicines, tailored to be responsive to the tumour microenvironment to improve the selectivity for tumour imaging and cancer theranostics. Furthermore, specific biomarkers or cellular features of CRC tumours such as overexpression of αvβ3 integrin receptor [58], CXCR4 [59] or ABCB1 [60] have been explored as potential targets to improve tumour targeting in the development of nano-theranostics. Similarly, co-opting tumour cell biology has allowed for tumour-specific drug delivery approaches to be developed. For example, a dendrimer- doxorubicin conjugate using a cathepsin B-cleavable peptide was utilised to capitalise the over-expression of cathepsin B by cancer cells to trigger intratumoural delivery of the chemotherapeutic agent [61]. The opportunity presented by NM based platforms to combine a number of the above approaches into a single multimodal nano-theranostic was further by the use of a peptide-cargo monomer which self-assembled to encapsulate

the drug cargo in nanoshells that can be triggered by the acidic tumour microenvironment to disintegrate and switch charge [62]. The peptide-cargo monomer structure protects the therapeutic cargo in the circulation whereas the intratumoral shape and charge change allowed the integrin-mediated uptake of the cargo specifically to the tumour cells. This approach was used to successfully deliver the tumour suppressor p53 intracellularly directly targeting the tumour cells mechanism of action resulting in significant tumour growth suppression which was comparable to treatment with doxorubicin [62]. Oxaliplatin (OXA) is a third-generation platinum anti-tumour compound, which exerts its effects by interfering with DNA replication and transcription machinery through nuclear DNA adduct formation. Clinically, OXA is often utilised as a first-line chemotherapy strategy in combination with 5-fluorouracil (5-FU) for treatment of advanced colorectal cancer. Presently, both drugs are administered by intravenous infusion and exhibit poor oral bioavailability. However, a recent study aimed to develop an oral delivery system for OXA and 5-FU. In an ion-pairing complex of OXA with a deoxycholic acid derivative (Nα-deoxycholyl-l-lysyl-methylester, DCK) (OXA/DCK). On day 14, when tumours became evident, the mice were orally exposed to the nano-emulsion formulation daily for 18 days. After the treatment, the tumour mass in the nano-emulsion treated group was reduced by 43%, compared to the control animals [63].

Additional novel therapeutic strategies reliant on the use of NM based platforms include the direct *in vivo* capture and passivation of circulating tumour cells (CTC) from the blood in order to prevent metastasis [64], a major complication associated with poor prognosis in CRC [13]. Surface-functionalised dendrimers coated with antibodies against two well-characterised CRC biomarkers were demonstrated to selectively bind CTC in both *ex vivo* patient mixed blood samples and in a mouse model administered with labelled CTC. Furthermore, the captured CTC displayed a disturbed cell cycle indicative of cell cycle arrest.

As well as improving therapeutics options for diagnosis and treatment of end-stage gastric and CRC, nanomedicines are also being developed as interventions targeting inflammatory bowel disease (IBD) and colitis. The persistence of infection and chronic inflammation within the gastrointestinal tract represent a significant risk factor in the development of colorectal cancers [65]. Nanocarriers have been exploited to improve bioavailability of therapeutic agents targeting both infectious agents [66] and the overexpression of pro-inflammatory factors [67] thereby dampening the chronic inflammatory response critical in the pathogenesis of CRC tumours. Degradation of therapeutics by the gastric juices after oral administration and low bioavailability of drugs to bacterial and cellular targets protected by the mucus layer lining the stomach and intestines have in the past limited the effectiveness of promising therapeutic agents in the treatment of colitis. The ability of drug loaded-liposomes to both protect and deliver therapeutics across the mucus layer has been exploited to effectively administer the antibacterial free fatty acid, linlenoic acid, to the stomach of a mouse model of colitis [66]. Oral administration of the LipoLLA significantly reduces the bacterial burden of *Helicobacter pylori* compared to the non-liposome delivery of the free fatty acid. Upregulation of infection-induced inflammation cytokines, IL1-β, IL6 and TNF-α were also significantly reduced. The demonstrated biocompatibility of the LipoLLA nanoformulation further suggests this may be a promising approach for the treatment of colitis. Similarly, a nanocarrier platform for oral delivery of raloxifene (selective oestrogen receptor molecule and effective immunomodulatory agent) loaded into styrene maleic acid micelles to improve bioavailability had no significant improvement in the dextran sulfate sodium (DSS)-induced colitis was observed for the micelle formulation over the administration of drug alone in this model [68]. The potential to use NMs as carriers of small interfering RNAs (siRNAs) as a gene therapy approach to dampen the excessive inflammation characteristics of IBD and thereby improve the patients symptoms has been also been explored. The

overexpression of CD68 on the surface of colonic epithelial cells and macrophages and known to promote the development and progression of IBD was identified as a promising target for intervention. The administration of NMs coated with anti-CD68 antibodies, for improved targeting and loaded with anti-CD68 siRNA to disrupt signaling to mice with colitis and demonstrated significant uptake of the CD68-coated NP and a corresponding reduction in the severity of the symptoms of disease [67]. NMs may therefore also be exploited as effective platforms for improved bioavailability and specific drug targeting for treating infection and chronic inflammatory diseases reducing cancer risk. The experimental detail of all relevant studies relating to CRC is summarised in table 3 and 4.

2.4 Prostate cancer

Prostate cancer is a commonly diagnosed cancer and the second leading cause of cancer-related deaths in USA. Currently common treatments for prostate cancer include surgery, hormone therapy, radiation therapy and chemotherapy. It has been suggested that alternative therapeutic modalities such as targeted therapy with cancer specificity would be a better treatment to enhance therapeutic efficacy in patients. As such, in a recent study a polyarginine peptide labelled polyethyleneimine nanocarrier loaded with microRNA-145 was designed and utilised which showed successful delivery of therapeutic genes directly into the tumour showing promise for effective for gene therapy [69] MicroRNA (endogenously expressed non-coding RNA molecule) has emerged as an important regulator for various developmental, physiological, and pathological conditions including prostate cancer. Elsewhere intravenous administration of polyphenol loaded of poly(ethylene glycol)-modified platinum NMs [70] and doxorubicin loaded 1,2-distearoyl-sn-glycero-3-

phosphoethanolamine-N-[methoxy(polyethylene glycol)-3000] coated tantalum sulfide nanosheets [71] both completely eliminated tumours in xenograft *in vivo* models of prostate cancer.

The Mouse Double Minute 2 (MDM2) oncogene plays a critical role in the development and progression of cancer through p53-dependent and p53-independent pathways. Ginseng is a natural product with a long history of chemo-preventive use. The anti-cancer properties of ginseng have largely been attributed to the presence of surfactant, saponin, which are termed ginsenosides. However, similar to other natural compounds, the therapeutic applications of these compounds are extremely limited due to low aqueous solubility and instability under harsh GIT conditions, extensive metabolism and rapid elimination. In a recent study, a novel ginsenoside, 25-OCH_3-PPD (functions by inhibition of Mouse double minute 2 homolog (MDM2)) isolated from *Panax notoginseng* was successfully encapsulated into Poly(ethylene glycol)- poly(lactic-co-glycolic acid) NMs. The 4 week oral treatment of a ginsenoside loaded Poly(ethylene glycol)- poly(lactic-co-glycolic acid) NMs inhibited the growth xenograft tumours by up to 87% [72]. Finally, in a unique study human prostate adenocarcinoma cells derived tumours were transplanted to pelvis of mice. The authors designed and utilised a prostate-specific membrane antigen -targeted manganese oxide–mesoporous silica NM and showed specific delivery of the nanocarrier to the tumour cells. Unfortunately, due to the carriers being empty in this study no therapeutic activity was investigated [73]. The experimental detail of all relevant studies relating to prostate cancer are summarised in table 5.

2.5 Skin cancer

Melanoma develops from the pigment-producing cells (i.e. melanocytes). They typically develop on the skin, although they may also develop in the mouth, intestine or eye. Exposure to ultraviolet light

is considered to be the major cause of malignant melanoma. A number of studies have used a mouse melanoma model to assess the therapeutic effect of nanomedicine subcutaneously inoculated melanocytes (Table 5). Studies on the distribution of particles after IV or IP injection show some uptake in the tumour, but also a distribution to other organs [74-77]. In general, all studies have shown almost or complete inhibition of tumour growth following IV or IP administration of the nanomedicine [74-78, 79-81]. The studies do not indicate that a particular type of nanomedicine is more promising than other. An interesting study used magnesium-GaIn alloy nanoparticles to treat a xenograft of melanoma cells in nude mice, demonstrating a complete growth inhibition over a 22 day period with repeated topical applications of the agent and irradiation [82]. The authors also noted that the treated tumour-bearing nude mice lived longer (up to 48 days) than untreated, irradiated or nanoparticle only mice (between 22 and 30 days). Although this may be interpreted improved survival, the mice have an overtly low survival rate as all mice in the treated group were dead at less than 20 weeks of age (8 weeks at the start of the experiment and 48 days amounts to less than 20 weeks). In comparison, nude mice live normally 26-52 weeks (or even 18-24 months in a germ-free environment). Thus, in this perspective the survival of 3 weeks after complete tumour growth inhibition is a meagre result. It should also be noted that the effect of sham-treatment with e.g. inactivated tumour cells were not tested. The experimental detail of all relevant studies relating to skin cancers are summarised in table 6.

2.6 Leukaemia

Historically, 90% of cases of acute lymphocytic leukaemia (ALL) has historically has very poor prognosis and limited treatment options in particular due to significant chemotherapy-associated toxicity. Furthermore, chronic lymphocytic leukaemia/small lymphocytic lymphoma is the most prevalent lymphoid malignancy in the USA, with approximately 140000 people living with the

disease [83]. In two recent studies, nanomedicines were utilised to target experimental model of leukaemia [84, 85]. Firstly, Au NMs extracted from *Thymus vulgaris* were used to treat 2,4-Dimethoxybenzaldehyde induced leukaemia. In this trial repeated NM administration reduced leukaemia related immunological and haematological parameters which were on the same level as a doxorubicin control [84]. This study was interesting as the authors utilise an actual leukaemia model and not a xenograft. In the second of the above mentioned investigations, a vascular endothelial growth factor 2 antibody labelled Indium phosphate QD was used to deliver miR-92a inhibitor to the cancer cells in a xenograft model. The authors showed efficient targeting and mages potential for the NMs as well as a 50% suppression of tumour volume after repeated treatment [85]. The experimental detail of all relevant studies relating to leukaemia is summarised in table 7.

2.7 Hepatocellular carcinoma

Human hepatocellular carcinoma (HCC) is one of the leading cause of cancer-related deaths with ~750 000 new cases reported annually [86]. The cancer is associated with very high morbidity and mortality predominately as a result of late diagnosis and a limited efficacy of currently available therapies [86]. Often due to the lack of available transplant donors, surgery is not usually an option for HCC patients leaving transcatheter arterial chemoembolization as the best viable option. Unfortunately, this course of treatment is associated with severe systemic side effects due to the systemic administration of the drugs. Taking this toxicity into account, more effective and safer strategies for treatment of HCC are urgently required. To this end the utilisation of nanotechnology can be highly beneficial. Therefore, a step towards overcoming the toxic side-effects of traditional chemotherapy for HCC is the utilisation of nanotechnology. From the scrutinization of the literature it is abundantly clear that the utilisation of nanomedicines have been explored for potentially safer and more effective targeted delivery systems for the clinical treatment of HCC. In one such study, a

series of well-designed designs experiments an intravenously administered PEG modified radiolabelled palladium nanosheet to liver xenograft, orthotropic and Mst1/1 (Mst1 and Mst2 kinases are tumour suppressors and regulators of liver size in adults) knock out mice models. The data from this data showed complete ablation of the tumours in all models following 18 day repeated treatment [87]. Elsewhere, the photothermal and photodynamic therapy based on the utilisation of PEGylated pompon Ruthenium NMs in a liver xenograft cancer model completely destroyed the tumour after 15 days of treatment [88]. MicroRNAs (miRNAs) are endogenous, evolutionarily conserved, small noncoding RNAs that post-transcriptionally regulate the expression of genes. Dysregulation of miRNAs appears to play fundamental roles in many cancers, and replacement of downregulated miRNAs in tumour cells may result in positive therapeutic responses. Furthermore, their small size makes them attractive for drug development. In a 2017 study a different therapy approach was based on the utilisation of polyethyleneimine-poly(epsilon-caprolactone) micelles as a nanocarrier for targeted delivery of 2'-hydroxy-2,4,4,5,6-pentamethoxyxhalcone (upregulates miR-34a - inhibits growth of tumours) to the tumours in a liver xenograft test model. The data demonstrated significant inhibition of tumour growth at day 20 following repeated IV NM administration [89]. Elsewhere, an enzyme instructed self-assembly hydrogel was used to deliver a p53 targeting peptide directly to tumour in a liver xenograft model resulted in inhibited tumour growth following repeated nano construct administration (85% smaller than non-treated animals [90]. As a final example, in a unique study a doxorubicin and Bcl-2 siRNA loaded cationic poly[2-(dimethylamino)ethyl methacrylate] and poly(3-azido-2-hydroxypropyl methacrylate) and galactose micelle was intravenously administered into xenograft and orthotropic *in vivo* test models. The authors showed that the NM induced combination chemotherapy inhibited tumour volume by 84% as compared to negative control after 21 days of treatment. Interestingly, in the orthotropic model, tumour numbers and volumes were considerably reduced in the NM treated animals as compared to PBS and non-nano formulation

treated animals [91]. The experimental detail of all relevant studies related to HCC are summarised in table 8.

2.8 Pancreatic cancer

Pancreatic cancer is still regarded as amongst the deadliest among all cancer related deaths worldwide with only 1-7% five year survival rates. Recently it was reported that an estimated 250000 global deaths attributed to the cancer. Furthermore, in developed countries, the incidences of pancreatic cancer has increased annually by the rate of 2% [92]. Pancreatic cancer is associated with late diagnosis and poor prognosis which are the principal reasons for the fatality of the disease. In pancreatic cancer there is very complex vesicular structure in the tumour as well as thick stromal architecture which generally prevents effective delivery of anticancer drugs to the target site. Considering the current challenges of targeted therapies in terms of minimizing toxicities and improving efficacies, reports from several groups including ours suggest the potential of nanomedicine strategies for targeted drug delivery in cancer patients. However, despite tremendous potential, cancer nanomedicine is also faced with considerable challenges regarding the design of the nanomaterials, as well as an incomplete understanding of tumour biology and the nano-bio-interface. To address these issues, in a 2017 study, folic acid/PEG-coated graphene oxide nanosheets used as a gene delivery system to co-deliver HDAC1 and K-Ras siRNAs (targeting the HDAC1 gene and the G12C mutant K-Ras gene respectively) were administered to a pancreatic derived cells xenograft in vivo mouse model. The data demonstrated that Combination of gene delivery and photothermal treatment supressed tumour growth at a rate of over 80% [93]. Elsewhere, intraperitoneally administered 5-Fluorouracil loaded Carboxymethyl inulin tethered silver-graphene quantum dots destroyed 100% of tumours after 30 days of treatment [94]. Moreover, doxorubicin loaded PEG

functionalized nano diamonds decreased tumour volume by 66% in a pancreatic derived xenograft model [95]. Finally, Poly (12-(methacryloyloxy) dodecylphosphorylcholine) micelles [96], arginine–glycine–aspartic acid conjugated quantum dots [97] and arginine–glycine–aspartic acid peptide conjugated to CdSe/ZnS quantum dots [98] all showed effective tumour specific accumulation in subcutaneous pancreatic derived cell xenografts. The experimental detail of all relevant studies relating to pancreatic cancer are summarised in table 9.

2.9 Osteosarcoma

The most commonly utilised therapeutic method for treatment of bone cancer is the surgical intervention. However, surgical intervention will usually lead to formation of bone defects with addition complication that bone tumour cells might remain in surrounding regions of the defects. Unless treated the residual bone tumour cells will proliferate and will result in the recurrence of the cancer. Therefore, it is imperative, that to biomaterials are developed with not only the capacity for efficient for bone formation but also the capacity to repair the large defects induced by the surgery, but just as importantly to have the capacity to kill remaining tumour cells around the original site of cancer. As touched upon in recent years, photothermal therapy has been utilised as a promising tool for tumour treatment including bone cancer. Compared with the traditional tumour therapy approaches such as radiotherapy and chemotherapy, photothermal therapy could kill tumour cells in a targeted area through hyperthermia with clear advantage of minimal invasiveness, permitting fast recovery and preventing damage to the nontargeted regions. In this review three studies were identified which utilised osteosarcoma cell xenograft models to assess the photothermal performance of a number of candidate formulations *in vivo* (Table 8). In these investigations bioactive glass scaffolds functionalized by the $CuFeSe_2$ nanocrystals [99], doxorubicin loaded bovine serum

albumin-iridium oxide NMs [100] and black phosphorus reinforced 3D-printed scaffold [101] all exhibited complete abolition of the tumours with very little adverse side effects. The experimental detail of all relevant studies relating to bone cancer are summarised in table 10.

2.10 Brain cancers

There are a number of publications that have used brain cells for studies on imaging of tumours and therapy. The majority of studies using brain cells have assessed the uptake of materials subcutaneous tumours of inoculated cancerous glioblastoma cells in nude mice. Following, IV administration it has been demonstrated that NMs are delivered to the tumour tissues as well as other organs, in particular the liver [102-105]. However, in relation to brain cancer, the observations in these studies are obviously limited by the fact that the model does not incorporate translocation the blood brain barrier. In fact, the studies do not appear to have targeted specifically brain cancer, but rather used brain cells as model. Interestingly, one study demonstrated that fluoromagnetic nanotubes, administered by IV injection, crossed the blood brain barrier and located to the tumour site in Nod/Scid mice [106].

The use of NMs as a therapeutic tool to eradicate brain cancer cells has also used subcutaneously xenografted cells in nude mice. Utilisation of topical photothermal therapy has demonstrated that the tumour size is dramatically reduced in 12-14 days after irradiation [105, 107-109]. It has also been shown that mice treated with nanocomposite encapsulated doxorubicin had smaller tumour volume than mice treated only with doxorubicin, suggesting an improved delivery or activity of the drug at the tumour site [103]. The experimental detail of all relevant studies relating to brain tumours are summarised in table 11.

2.11 Ovarian cancer

Ovarian cancer is one of the most lethal gynaecological malignancies principally due to late stage diagnosis and reduced therapeutic efficacy. Currently, the standard management of ovarian cancer combines cytoreductive surgery and chemotherapy. Although rapid advances exist in multiple therapy strategies, the clinical outcome has not been improved in ovarian cancer patients, so novel therapeutic strategies are required to archive successful management of ovarian cancer. As some examples of this in two recent studies NM related photothermal therapy was utilised in ovarian xenograft cancer models in mice. In 2016, multiple intravenous treatments with a thermo responsive poly(N-isopropylacrylamide) based dendritic nanogel supressed ovarian tumour volume by 60% after 10 days of repeated treatment [110]. Elsewhere, a manganese and gallium capped copper sulfide nanodots almost entirely stopped tumour growth for up to 13 days post commencement of treatment. Interestingly, the authors showed clearance of materials via the renal route [111]. The experimental detail of all relevant studies relating to ovarian cancer are summarised in table 12.

2.12 Bladder cancer

Combinations of multiple therapeutic approaches have gained increasing attention for optimizing clinical disease management. As touched upon above there is considerable evidence for hyperthermia being very promising for multidisciplinary approaches for cancer therapy (synergy of combined hyperthermia and chemotherapy. In particular the optical property of near-infrared (NIR) resonant

NMs have improved antitumor efficacy through combined photothermal therapy and chemotherapy. This approach was utilised in a 2013 in an attempt to treat bladder cancer in an *in vivo* xenograft model. Firstly, 5-fluorouracil and anti-human epidermal growth factor receptor 2 antibody loaded magnetite nanocrystal photothermal treatment resulted in significant and persistent remission of the tumour mass (almost 100%) after 14 days of treatment following intratumoral and IV treatment [112]. Elsewhere, dioleoyl phosphatidic acid-gemcitabine monophosphate and cisplatin loaded PLGA NMs intravenously administered in a bladder cancer xenograft model for 14 days inhibited the growth of tumours by almost 100%) after 14 days of treatment [113]. The experimental detail of all relevant studies relating to bladder cancer are summarised in table 13.

2.13 Oral cancer

Nanotechnology applications in cancer detection and treatment have the potential to replace highly invasive conventional cancer detection and treatment, which often includes biopsies, irradiation, and painful therapies. The ability to diagnose malignant disease at the earliest opportunity allows treatment options to be planned as early as possible and hence directly affects the morbidity and mortality of head and neck cancer. Nanomedicine represents a great hope for improving cancer treatments by acting at least at two main levels: namely by conferring new properties to a pharmaceutical agent and targeting the agent directly to the tumour. As with many cancers, there is a need to deliver therapeutic agents with greater efficiency to improve the treatment of oral cancers and to improve patient outcomes. In 2016, a -styrenesulfonate and positively-charged poly (diallyldimethylammonium chloride) gold nanorod was utilised as BAG3 siRNA platform in a xenograft model of oral cancer. In said study, BAG3 was selected as it is strongly induced on the mRNA and increases greatly on the protein level, indicating its critical role in the heat shock response at least in PTT of oral cancer cells. Additionally, BAG3 gene expression was shown to be significantly

increased in oral cancer cells compared to normal cells and hence was favourable for improve the therapeutic efficacy. The data demonstrated that intratumoral administered NM-mediated gene therapy and photothermal treatment resulted in significant and persistent remission of the tumour mass by 100% after 18 days [114]. Next, intravenous exposure of a Sorafenib (drug used to inhibit tumour angiogenesis) and chlorin e6 multifunctional NM in an oral cancer xenograft model for 12 days resulted in significant reduction of the tumour mass [115]. The experimental detail of all relevant studies relating to oral cancer are summarised in table 14.

2.14 Soft tissue sarcomas

Soft tissue sarcomas term a number of rare cancers affecting the tissue which connect and support body's main organs. Tissues that can be affected by soft tissue sarcomas include, muscle (leiomyosarcoma), blood vessels (angiosarcoma), tendons, ligaments and fat (liposarcoma). It is understood that sarcomas can develop in any part of the body. The utilisation of nanomedicines in treatment of experimental models of sarcomas has been untaken by [116-118]. Firstly, doxorubicin loaded mesoporous bioactive glass nanosphere treatment inhibited tumour growth inhibition by 80% in a xenograft model of sarcoma [116]. Similarly, photothermal and doxorubicin treatment using redox-sensitive nano constructed from hyaluronic acid, single-walled carbon nanotubes and gadolinium for 10 days of treatment and chemotherapy inhibited tumour growth by 70% [117]. Finally, the intravenous repeated exposure to Ag_2S amorphous nanodots and photothermal treatment for 13 days inhibited tumour growth by 75% (xenograft model of sarcoma) [118]. The experimental detail of all relevant studies relating to sarcomas are summarised in table 15.

Finally, table 16 depicts a number of studies in which nanomedicines were designed and utilised against numerous cancer types.

TABLE 1-16

3. Summarising remarks

With ever-increasing incidences of cancer globally, the clinical management of the disease continues to be a challenge. Fortunately, due to better understanding of the biological processes involved in cancer initiation and progression over the last two decades has triggered a significant body of research into anti-cancer therapeutics, which includes massive expansion of the field of cancer related nanomedicines. As highlighted above a number of different types of NMs are used to deliver therapeutics or image to varying cancers in experimental models. These include dendrimers, micelles, liposomes, polymeric NMs, ceramic NMs, metallic NMs, carbon nanotubes, protein NMs and viral NMs. The holy grail in the field of cancer nanomedicine is the total destruction of cancer governed by specific targeted delivery of high doses of drug molecules to tumour sites with minimum adverse effects to healthy tissues.

3.1 Traditional cancer therapy and its limitations

The conventional therapeutic approaches for treating various cancers are principled on repairing the defective genes involved, destroying the cancer cells or inhibiting blood supply to the tumour. Additional treatment options include the surgical removal of the tumour, radiation and chemotherapy all of which have substantial limitations [119]. As some example of these accompanying confines: a) surgery is not applicable to all cancer types; b) radiation therapy does not distinguish between cancer

cells or healthy surrounding tissue and c) chemotherapy is often unsuccessful in advanced stages of numerous cancers, the drugs have poor targeting and specificity and generally associated with significant toxicity as an undesired side-effect [120].

In 2020 there are over 550 drugs licensed for clinical use in treatment of differing cancers [121] with only four of these classified as a nanomedicine (Table 17).

Table 17

3.2 Advantages of utilisation of NM based cancer therapy

Due to the better targeting potential, biocompatibility, biodegradability and biosafety, nanoplatforms have great promise for clinical applications. First and foremost, NMs offer great promise for specific targeted delivery of anti-cancer drugs which ultimately diminishes the side effects. From scrutinization of the available literature and discussed above and highlighted in table 1-16, it is clear that utilisation of targeting moieties and surface functionalisation has been a great success in allowing specific delivery of nanomedicines to the desired destination in rodent cancer models (albeit predominately xenograft models - this issue will be deliberated in great detail below).

Secondly, a number of studies have designed nanomedicine to overcome multi-drug resistance (MDR) in cancers [i.e. 122, 123]. It is now well established that MDR is a fundamental obstacle of

conventional clinical cancer treatment. MDR may occur via different mechanisms: a) new mutation of oncogenes that become resistant to former treatments; b) ATP-binding cassette transporters that pump out chemotherapeutics; c) survival of cancer stem cells that escape from conventional therapies and d) evolution of cancer cells in their microenvironment [124]. It is important to note that certain cancers such as colorectal cancers or non-small-cell lung cancers do not respond effectively to standard chemotherapy [45]. Finally, many of the traditional anti-cancer drugs have low solubility which results in the drug exhibiting reduced bioavailability. In clinical settings this limitation is associated with low bio-availability of drug and insufficient delivery of doses reaching the desired destination. As an additional complication, there is potential for significant interpatient variability in the drug pharmacokinetics [125].

3.3 Different strategies for use of nanomedicines in combating cancer

3.3.1 Nanocarriers

Liposomes are colloidal carriers produced spontaneously by hydration of a combination of lipids in a number of aqueous media. These nanocarriers are composed of hydrophilic core entrapped by bilayers of natural and/or synthetic lipids. These nano constructs are stable, biocompatible, biodegradable and exhibit very little toxicity. As for nanomedicines, hydrophilic drugs are often encapsulated in the self-assembled phospholipid membrane. These carriers are heavily relied upon in the literature as the means of delivering therapeutics to the cancers in experimental settings [i.e. 27, 66]. As an important note, all cancer related nanomedicines that are currently on the market and in clinical use are formulated using liposomes as the carrier.

Experimental data suggests that carbon nanotubes could be exploited for targeted drug delivery at the nanoscale. One of the principal reason for the popularity of CNTs in nanomedicine is that the drug can either be attached to the outer surface of the material or be loaded inside the NM. The poor solubility of SWCNTs could be overcome by functionalization of the surface which has been regularly utilised for targeting of the nanomedicine to the preferred destination [i.e. 117].

Similarly, Nanodiamonds are often utilised as nanocarriers due to their biocompatibility, stability and very low as compared to other carbon based nanomaterials (i.e. MWCNT - 9] than other carbon nanomaterials. As with other nanocarriers, these materials can be easily functionalised, labelled and conjugated to improve solubility and allow for specific targeting to cancerous tissue [i.e. 95].

Dendrimers are a class of repeatedly branched polymeric macromolecules extending from the core, combining in a 3D geometric pattern. These materials can be manipulated to alter shape and size to best suit its intended use. Dendrimers possess a number of unique properties which make them very attractive in the field of nanomedicine: a) number of terminal surface groups which can be modified for bioconjugation of drugs or targeting moieties; b) NM Surfaces modifiable to incorporate functional groups to augment or resist epithelial, or vascular bio-permeability; c) Surface groups that can be modified to optimize biodistribution, receptor-mediated targeting or controlled release of drug; d) interior empty space which can be utilised to encapsulate small-molecule drugs; e) low immunogenicity particularly due to the ability to surface modify the materials [126]. The use of dendrimers has been heavily exploited in the design of cancer nanomedicines in rodent experimental models [i.e. 61, 109].

Gold NMs are size controllable colloidal suspensions. The scrutiny of *in vivo* and *in vitro* literature depicts that multifunctional gold NMs are highly desirable and manipulated in design of novel nanomedicines due to their stability, versatility and low toxicity. The use of gold NMs holds great promise as a "magic bullet" approach against cancer. As clearly demonstrated in tables 1-14 gold NMs have been used extensively as nanocarriers to combat cancers in experimental rodent models [i.e. 37, 53].

Quantum dots (QDs) (also known as nanoscale semiconductor crystals) are spherical light-emitting NMs composed of a semiconductor material. These materials contain unique optical and electronic properties such as bright and intensive fluorescence and often utilised as fluorescent probes for cancer screening from biological fluids, classification of tumours and for high-resolution biomolecular and cellular imaging [i.e. 35, 97].

3.3.1 Nanomaterials designed for use in photothermal therapy

In cancer like many other diseases in humans, there is an urgent necessity to develop non-invasive treatment options to conventional therapy. As such NM-induced photothermal treatment is an area of research which has gained popularity over the last decade. Photothermal treatment at the nanoscale is principled on non-invasive heating of tumour cells to cytotoxic levels. Biologically temperature above 42°C induce undergo apoptotic cells with temperatures above 50°C with non-programmed necrotic cell destruction [127].

In particular, numerous factors make Near infrared (NIR) light-activated phototherapeutic strategy (photothermal and photodynamic therapy photothermal therapy extremely attractive for potential

treatment of cancers [128, 129]. Firstly, nuclear proteins are highly sensitivity to heat, hence hyperthermia can affect inhibition of DNA repair and replication as well as RNA and protein synthesis [130]. It is understood, high temperatures can also disaggregate microfilaments and microtubules. Moreover, cells in the S- and M-phase of replication exhibit high heat sensitivity. Importantly, a tumour and the healthy tissue behave differently in response to heat-induced damage. In healthy tissue at temperatures of up to 45°C, vasculature readily increases the blood flow which dispels heat [131]. On the other hand, tumour vasculature is hyperpermeable, disorganized and often have excess blind ends and abnormal bulges, making them greatly inefficient in heat dissipation. Thus, at the same thermal dose, the healthy tissue can remain at a lower temperature than the tumour. This physiological difference means that hyperthermia does not damage adjacent tissues/organs to the tumour being targeted [132]. Additionally, in principal, a high temperature within the malignant mass might induce the inhibition of blood perfusion and increase the rigidity of red blood cells, which in turn proceed vasodilatation, blood stasis, endothelial swelling, and plasma leakage or haemorrhage, with red blood cell and platelet aggregation leading to coagulative necrosis. Importantly, the abnormal blood flow also affects oxygen and nutrient delivery within the tumour leading to severe tissue acidosis. Furthermore, in addition to action on tumour cells and vasculature hyperthermia might affect the extracellular matrix. It has been demonstrated that hyperthermia can relax collagen fibres which in principal might allow for better transport of the therapeutics to the tumour [133]. Finally, hyperthermia might induce cell death through lysosomal death pathways [134]. Compared with traditional small molecular photothermal agents (PTA) and photosensitizer agents (PSA), biocompatible inorganic nanomaterials usually can exhibit more potent performance based on their intrinsic physicochemical properties, which potentially can be used as promising nanocarriers to load various functional molecules for combined therapy. Among various physicochemical properties, the electronic properties of these nanomaterials play critical roles in endowing and improving the PTT

and PDT performance. The literature shows that targeted hyperthermia is achievable by using nanoscale metallic NMs that convert electromagnetic energy into heat. As examples iron oxide, gold, gold-silica nanoshells, and carbon nanotubes have all been successfully been utilised for this purpose.

3.3.2 Nanotechnology and gene therapy

The foundation of precision medicine in tumour theranostics is the identification of the oncogene that is responsible for a class of common cancers regardless of anatomical sites. Gene therapy refers to transfer of genetic material to the cells of an individual to ensure targeted molecular intervention. In the last few years, gene-silencing has gained popularity as an alternative treatment for a number of cancers. There major nucleic acid-based gene-silencing molecules are categorised into siRNA, micro RNA and antisense oligodeoxyribonucleic acids [135; 136]. Despite great promise, the limited tumour targeting ability and poor cellular attachment and internalisation of these molecules remains a great challenge for further advancement of gene therapy approaches. As demonstrated above numerous NMs have been employed readily for gene delivery and have included liposomes, gold NMs and CNTs. The nanomedicine literature shows the utilisation of microRNA replacement therapy to treat cancers at molecular level shows great promise. As an example, MicroRNA-34 is found to be a down-regulated for numerous cancers. It is believed that it is involved in regulation of more than 20 oncogenes, therefore, capable of treating multiple cancers. Furthermore, a significant body of research into microRNA replacement therapy has shown that various cancers correspond to specific microRNAs (Figure 1).

Fig 1. Diagram depicting the different microRNA replacement therapies with potential for use for treatment of various cancer types

3.4 Disparity between nanomedicine basic research and promising candidates being approved for clinical use

3.4.1 The selection of appropriate physiologically relevant *in vivo* test models

As demonstrated above, the cancer scientific community relies heavily on preclinical research. Traditionally, nanomedicine research has used conventional xenograft mouse models which, despite great promise in the design and validation of novel anti-cancer nanoformulations, the majority of the phase 3 clinical trials fail [137]. It is abundantly clear, that traditional *in vivo* xenograft models are extremely poor for predicting clinical outcomes as they do not faithfully holistically represent the human body; they are not suitable models to evaluate all research questions nor model drug efficacy. Moreover, the high number of therapeutic compounds that fail to translate in clinical trials highlights the need and importance for models that are more physiologically relevant to the human body, in order to personalise treatments and better predict patient outcomes Therefore, there is a real necessity for development of more advanced *in vitro* and pre-clinical *in vivo* models with better predictive power.

As conveyed in tables 1-16, the traditional xenograft rodent models are the principal *in vivo* tumour models in cancer related nanomedicine research. These transplantation models are comparatively cheap, fast and easy to establish and allow for rapid testing of potential cancer related

(nano)therapeutics. Historically, *in vivo* xenotransplantation models have been fundamental in cancer related scientific discoveries. As an example, ground-breaking research into anti-tumour immunity, T-lymphocyte tolerance mechanisms, and immune-escape routes for different tumours were all conducted in such models [138]. Unfortunately, however, traditional xenograft *in vivo* models have major restrictions which might contribute to the limited success in the advancement of promising nanomedicines discovered in the laboratory settings to clinical success. The cells in these models often lack important cell surface receptors (i.e. oestrogen receptors on prostate cancer cells [139]). Additionally, xenografts must be implemented in immunocompromised animals often non-orthotopically, thereby circumventing the natural environment and the physiological immune system responses which are crucial in the tumour micro-environment [140]. It is now understood that the crosstalk between adaptive immune components, the innate immune system, microbiome, epigenome, and tumour environment with cancer cells, is critical in tumour physiology. It is important to state that the immune incompatibility issue can be partially surmounted by the introduction of transgenes encoding human cytokines, chemokines, and growth factors can support the development of human myeloid cells in test rodents [141]. Moreover, to develop HLA-restricted T cells, recipient immunodeficient mice can be further optimized by transgenic expression of human HLA molecules [138]. Unfortunately, the scrutinization of literature demonstrates that neither of these two approaches were undertaken in any of the 191 studies identified.

To address these limitations, it stands to reason that the pre-clinical tumour models should reflect human disease as closely as possible. Ideally, a good experimental animal model should contain the patient-specific mutations that initiate a malignancy and drive its progression orthotopically, such that *de novo* tumorigenesis occurs in the natural microenvironment reflecting the crosstalk of cells with the tumour microenvironment (i.e. microbiome, physical forces, infiltrating immune cells from

lymphatic and blood vasculature) [142]. In other words, as an example, a hepatocyte cell line induced sub-cutaneous xenograft will never be representative of the complexities of human hepatocellular carcinoma. Finally, due to late prognosis of many cancers, the majority of patients might only be diagnosed after the cancer has metastasised. Therefore, preclinical drug discovery and efficacy investigations should be preferably conducted in models that reflect both early and late stage of disease.

Over the last two decades, technological advancements have led to the generation of more physiologically relevant test systems. The advent of embryonic stem cell technology and transgenesis has allowed the generation of sophisticated mouse models that better mimic human cancer in terms of genetic composition, interactions of cancer cells within their microenvironment and potential therapeutic responses. In brief, some of these models have included: a) patient-derived tumour xenograft models - based on direct implantation of human tumour fragments in immunodeficient mice [143]; b) tumour suppressor gene KO mice - *de novo* tumorigenesis induced by germline inactivation of a tumour suppressor gene [144]; c) conditional *in vivo* models - de novo formation of sporadic tumours is induced by tissue-specific Cre-loxP (site specific recombinase technology to delete, inset, translocate or inverse specific sites in the DNA) [145] d) oncogene models based upon *de novo* tumorigenesis induced by transgenic expression of an oncogene from a tissue-specific promoter; e) embryonic stem cell-based mouse cancer models genetically altered and used to produce cohorts of non-germline test models - stem cells can be utilised for rapid introduction of genetic modifications and subsequent production of chimeric mice that show the same characteristics as the established modified test animals which can include additional genetic modifications [146] and f) use of CRISPR/Cas9 technology for rapid cancer modelling in mice for efficient gene-targeting strategies

with the potential for multiplexed genome editing to induce target gene inhibition (CRISPRi) or activation (CRISPRa) [147].

As mentioned, until recently the progress in the field of cancer research was hampered by the lack of physiologically relevant pre-clinical animal models that only poorly resembled human cancer. However, the advancements of next-generation *in vitro/ex vivo* culture techniques and genetically engineered mouse models have been highly advantageous and allowed for better translation of new therapeutic strategies from the bench to clinical testing. Unfortunately, the research into cancer related nanomedicine is well and truly lagging - with the majority (if almost all) of the current investigations still being conducted in the traditional xenograft models. Although many studies effectively demonstrate the proof-of -concept underlying a promising theragnostic nanomedicine approach, they universally represent very early stages in drug development and do not address issues and road-blocks in the translation of therapy to the clinic. For any real and meaningful progression in the field of cancer nanotherapeutics, it is imperative that traditional xenografts are replaced or supplemented with next-generation genetically engineered mouse models which are better representative of human cancers.

3.4.2 Toxicological considerations

In a physiological environment, NMs acquire a new identity, which might alter their size, surface charge and aggregation, along with a constantly changing and devolving deposited protein corona. It is noteworthy that a material's acquired biological identity can be dramatically different from the material designed in the laboratory. The biological attributes afforded by the corona can affect physiological and toxicological responses to the nano-formulations *in vivo.* Both the required medical

and toxic effects of the nano-sized delivery systems are fundamentally governed by their physicochemical characteristics, including their bio-available surface area, specific surface properties (e.g. chemistry and charge), solubility and shape [148]. Moreover, nanocarriers can alter the physicochemical properties of the cargo drugs, peptides and genes, as well as altering the solubility and pharmacokinetic disposition upon delivery compared to unmodified drug [42, 149-151].

These adverse effects are principally caused by the nanoparticulate delivery directly interacting with biological surroundings or as a result of unwanted bio-accumulation in the case of insoluble carriers. Interestingly and importantly, from a toxicological perspective, numerous studies that were scrutinised in this review, safety evaluation was either entirely lacking for the manufactured formulation or the toxicity testing was only restricted to simple *in vitro* models or acute *in vivo* studies. This might be one of the reasons why despite considerable therapeutic promise demonstrated by many of the manufactured nano-constructs in experimental settings, the use and translation of nanomedicines from laboratory to clinical settings has been extremely slow. It is important that appropriate and comprehensive risk reduction strategies are incorporated for all materials proposed for medical applications. Any pre-clinical toxicological assessment should include *in vitro* and *in vivo* long term physiologically relevant exposures of the delivery formats; although this would have to be tailored and designed to take into account the intended therapeutic application of the medicine. Currently, the majority of toxicological strategies are influenced by route of delivery rather than mode of action.

3.4.3. Other considerations

It is important to recognize that rodents have a different metabolism than humans and they might exhibit a different metabolic rate compared with humans for certain drugs. These interspecies

differences must be considered in the evaluation of the pharmacokinetic benefits and toxic potential of a given formulations [152]. As an additional complication, nanocarriers can alter the physicochemical properties of a variety of drugs, peptides, genes, pharmaceutical changes in stability, solubility and pharmacokinetic disposition can occur upon delivery which need to be considered.

As part of our strategy in ascertaining the potential reasons for the disparity between the success of nanomedicines in experimental settings and the same formulations not moving forward to clinical testing, we contacted 24 research groups with what we perceived to be the most promising and advanced nanomedicines (studies were selected across different cancers and experimental test models). From the contacted list, 5 principal investigators responded. It was interesting to discover that only one group were still actively working on the published nanomedicine (further improving its therapeutic performance as well as investigating the potential long-term safety aspects of the formulation). The remainder of the groups had no immediate plans to pursue the development of the medicines, despite the highly promising data presented in the respective published manuscripts with some of the reasons offered the lack of available funding, research focus being moved to other nanomedicines and loss of expertise/collaborations from the group in question.

Furthermore, the analysis of the literature resulted in three very important observations: a: to the best of our knowledge none of the of the almost 200 investigations highlighted in the review had pharmaceutical/industrial backing; b) did not mention any approved or applied patents for their formulation and c) all studies were publicly funded. This suggests that in most part the studies were conducted solely as academic endeavours and disseminated as stand-alone publications rather than the experimental data laying the ground-work to get the nanomedicines approved for clinical use where they are most needed.

3.5 Future perspectives and conclusions

The utilisation of nanomedicines has the potential to have an outstanding impact in treating various diseases including cancers as well as various applications in tissue regeneration, biological sensors. Additionally, combinations of imaging and therapeutic agents, incorporated into the same nano-formulation can be beneficial if approved is gained for clinical use. The literature clearly demonstrates the potential of nano-sized carrier systems over traditional approaches (at the molecular level) for specific targeting of the tumours. Among the most successful of such approaches are the development of nano-emulsions, nanocrystals, and polymeric NMs. In addition, the interest in self-emulsifying drug delivery systems, liposomes, micelles and dendrimers is increasing.

Due to increasing understanding and new tools for genetically engineering mice there are now numerous models available to study all aspects of cancer biology. However, as with all models, rodent models have limitations in their ability to imitate all aspects of the human condition. In an attempt to overcome this, there is an ever growing body of research into the development and combination of 3D organoids, humanised mouse models and organs on a chip technology. 3D patient derived organoids or tumoroids faithfully retain the organisation, architecture, cellular and genetic diversity of the primary tissue served and better mimic the patient responses to drugs. These are now extensively used tool for studying both basic and clinical biology. Standardised collections of patient

samples, reflecting population disease profiles, can now be tested against panels of compounds in drug titration assays to determine their potential efficacy. Alternatively, CRISPR-Cas9 gene editing technology has generated intestinal organoids, which mimic the sequential loss and gain of functions of genes involved in human colorectal cancer, that after orthotopic engraftment could metastasise to the liver. Thus, organoid models can be utilised to study advanced aspects of cancer development in a more complexed *in vivo* scenario; especially when combined with orthotopic transplantation and humanised animal immune systems. However, caution must be taken, while humanised mouse models have improved the ability to study human diseases the process of humanisation has limitations, such as poor B-cell maturation and antibody responses that can impair translational research. To overcome this, organs-on-a-chip are beginning to offer a human focussed solution that better predicts patient outcomes to therapy and understand the mechanisms that underpin disease. The development and integration of microfluidics and microengineering into *in vitro/ex vivo* culture is replicating the key features of human tissues and organs, such as the multicellular structures, cell-cell and tissue-tissue interactions and the native microenvironment. Furthermore, microfluidics can be utilised to mimic blood and nutrient flow and remove waste products. Transwell culture have been used to grow a 2D polarised organoid monolayer of human cells allowing treatment of the apical cell surface with immune cells added to the basolateral side of the monolayer culture. With the latest intestinal models used colorectal cancer cells cultured under physiologically relevant conditions including peristalsis-like motions, intraluminal fluid flow, the use of 3D scaffolds that supported the growth of the naturally occurring microbiome without diminishing cell viability.

Despite the plethora of advantages that nanomedicine offers, the systems still have limitations, one of which is potential to adversely affect human health, which needs to be thoroughly addressed and is still regarded as an afterthought in the majority of studies scrutinized in this review. Furthermore,

to allow for real and meaningful progress in the field of nanomedicine (advancing formulations from the laboratory to clinical testing) there is an urgent necessity to replace and refine traditional testing preclinical research animal models to get in line with the rest of the cancer research. Additionally, other considerations such as patenting the formulations before publication and establishing collaborations with industrial partners with the required expertise and resources are key.

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