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Bridging the Knowledge of Different Worlds to Understand the Big Picture of Cancer Nanomedicines

Vimalkumar Balasubramanian,* Zehua Liu, Jouni Hirvonen, and Hélder A. Santos*

Explosive growth of nanomedicines continues to significantly impact the therapeutic strategies for effective cancer treatment. Despite the significant progress in the development of advanced nanomedicines, successful clinical translation remains challenging. As cancer nanomedicine is a multidisciplinary field, the fundamental problem is that the knowledge gaps stem from different vantage points in the understanding of cancer nanomedicines. The complexities and heterogeneity of both nanomedicines and cancer are further demanding the integration of highly diverse expertise to develop clinically translatable cancer nanomedicines. This progress report aims to discuss the current understanding of cancer nanomedicines between different research areas in terms of nanoparticle engineering, formulation, tumor patho-physiology and clinical medicine, as well as to identify the knowledge gaps lying at the interface between the different fields of research in nanomedicine. Here we also highlight for the necessity to harmonize the multidisciplinary effort in the research of nanomedicines in order to bridge the knowledge and to advance the full understanding in cancer nanomedicines. A paradigm shift is needed in the strategic development of disease specific nanomedicines in order to foster the successful translation into clinic of future cancer nanomedicines.

nanotechnology have offered unprecedented opportunities to advance the treatment of various diseases, including cancer.^[2–7] The application of nanotechnology in cancer therapy, herein referred as cancer nanomedicines, have received wide spread attention due to the unique physicochemical properties of the nanoparticles with the ability to deliver different therapeutics (e.g., chemotherapeutics and biologics), altering their pharmacokinetic profiles, augmenting their accumulation in the tumors and reducing their toxicity profiles.^[8–11] Nanomedicines aim to improve the balance between therapeutic efficacy and systemic toxicity of conventional chemotherapeutic agents, which lack of specificity, thereby enhancing the therapeutic index of the anticancer drugs. In clinical cancer care more evidences have been suggested that nanoparticles found to be localized in solid tumors after the systemic (intravenous) administration of nanomedicines to cancer patients.^[9,12,13]

In addition, compared to the conventional anticancer drugs, nanomedicine have shown many benefits in terms of improved half-life in blood circulation, enhanced drug bioavailability with reduced side effects of the parental drugs. Anti-cancer nanomedicines are rapidly emerging as a promising approach and offers the possibilities to the clinicians to overcome the limitations of current cancer therapy.^[14–17] In this direction, an array of nanomedicines has been synthesized, engineered with different physicochemical properties, such as size, shape and surface chemistry, and formulated with a large variety of anti-cancer therapeutics, including surface modifications with, e.g., polyethylene glycol (PEG) or other coatings, in order to extend the circulation time of the nanomedicines in bloodstream.^[18–20] Various targeting moieties, such as antibodies, peptides, sugars and proteins, have also been attached to nanomedicines in different ways to further facilitate their selective accumulation within the tumors.^[21,22] Furthermore, more complex and advanced nanomedicines designs equipped with multiple functions, such as combined therapeutics, imaging, diagnostic moieties with programmed release, have also been developed to improve the therapy of cancer.^[23,24] Moreover, the pathophysiological properties of the tumors enable the preferential accumulation of the nanomedicines through leaky tumor vasculatures and poor lymphatic drainage system.^[22,25,26]

1. Introduction

Cancer remains one of the leading cause of deaths worldwide.^[1] Current therapies in the clinics such as chemotherapy, radiotherapy and surgery, can provide only limited survival benefits to the patients. In recent years, the advances in

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In the last decade, extensive active research have been done to investigate the potential of various nanomedicines with different sizes, surface chemistries, composition, targeting ligands, and anti-cancer therapeutic agents in a variety of rodent animal models of human cancers.^[15,27–29] Some nanomedicines have showed encouraging anti-tumor effects in pre-clinical studies and others have showed a promise for clinical development.^[13,30] Nevertheless, only limited nanomedicines are being investigated in humans and eventually less entered the clinic. Despite the significant progress made to develop more advanced nanomedicines to improve cancer therapy, the nanomedicines research is still mostly at an early stage of development or preclinical stage, thus growing pressure is escalating for the clinical translation of cancer nanomedicines worldwide.

The development of cancer nanomedicines is moving through different stages, i.e., from basic science to clinical applications that requires an extensive interdisciplinary effort from different fields of research ranging from material and life sciences, biomedical engineering to clinical medicine (Figure 1). Therefore, it is crucial to promote a large scale multidisciplinary effort, aiming at the clinical transformation of nanomedicines. However, understanding the development of nanomedicines for cancer therapy is so far interpreted differently, depending upon the specific research field within the interdisciplinary research in nanomedicines. Thus, bridging the knowledge base of this diverse field is key to fulfil the gaps in advancing the understanding of cancer nanomedicines and in order to assure the unified development that in turn can accelerate the translation of nanomedicines to the clinic. As nanomedicines are the convergence of multidisciplinary research fields, breaking barriers is important to identify and to understand the fundamental challenges that need to be addressed in order to link between nanomedicine's engineering, physico-chemical properties, nano-bio interactions, pharmacokinetics, biodistribution, tumor biology and patient survival. Therefore, successful clinical translation will require a re-examination of the design and development of nanomedicines with different prospects of diverse research areas.

This progress report aims to discuss the current understanding of cancer nanomedicines and its relation in different research areas, as well as to identify the knowledge gaps lying at the interface of this multidisciplinary research field. Here, we highlight the emerging nanomedicines for effective clinical translation from in the view of different disciplines, such as material engineering, pharmacy, tumor biology and clinical medicine. We also re-examine the basics in the development of nanomedicines with respect to the physicochemical properties, formulation, tumor patho-physiology and clinical care. Finally, we emphasize the necessity to harmonize the multidisciplinary effort in the research of nanomedicines in order to bridge the knowledge and to advance the full understanding in cancer nanomedicines.

2. Cancer Nanomedicines from the Nano-Engineering Perspective

Increasing interests on the application of nanotechnology for producing nanomedicines is largely driven by the rapid

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innovations and developments of various nanoparticles through nanomaterial engineering.^[31,32] Nanotechnology provides the versatile possibility to engineer a myriad of nanoparticles

Figure 1. Cancer nanomedicine is a convergence of multi-disciplinary research fields. The inter-play of many scientific disciplines need the integration of knowledge to advance the full understanding in cancer nanomedicine.

generally in the dimension range of 1–200 nm that can selectively target cancer in the body, as well as open opportunities in the development of advanced and new cancer nanomedicine strategies.^[16,33] The rationale of nanoparticle engineering is aimed to improve the therapeutic advantages of cancer nanomedicines, which include: (i) carrying and delivering high amount of therapeutic payloads ranging from small chemotherapy agents to larger biologics without leaking before it reaches the desired tissues or cells; (ii) reducing the interaction with the mononuclear phagocytic system (MPS), thereby prolonging the circulation time in the bloodstream; (iii) increasing the accumulation of nanoparticles in the active tumor sites in order to reduce the unwanted off-target side effects; (iv) attaching multiple targeting ligands to the surface of nanoparticles for high affinity and specificity for tumor tissue or cancer cell targeting; and (v) facilitating the intracellular drug delivery by overcoming the different biological barriers and by-pass the drug resistance mechanism.

In the last years, a large array of nanoparticles comprising various materials have been engineered to deliberately design customized nanomedicines with specific properties and functionalities for application in cancer diagnosis and therapy. This includes, solid lipid nanoparticles, liposomes, polymeric

micelles, hydrogels, dendrimers, polymersomes, inorganic nanoparticles (e.g., iron oxide, quantum dots, gold, silica and silicon particles), among many others (**Figure 2**).^[16,34] However, in some cases, the combination of different types of nanoparticles have also been used for nanomedicine development. In most cases, these systems are constructed with desirable biological properties, such as biocompatibility and biodegradability, for the intended biological applications.

2.1. First Generation Nanomedicines

From the nanoparticle engineering point of view, the evolution of cancer nanomedicines can be categorized into three different generations based on their ability and functionality. In the first generation of cancer nanomedicines, nanoparticles with the size up to 500 nm can take the advantages of leaky vasculatures combined with dysfunctional lymphatics present in the solid tumors, which enable them to efficiently extravasate and be retained in tumors over time. This phenomenon is known as the enhanced permeability and retention (EPR) effect.^[36,37] EPR based passive targeting strategies have been heavily investigated as a potential for nanomedicines delivery

Figure 2. Schematic representation of nanoparticle engineering that enables the design of versatile nanoplateforms with various materials, compositions, physicochemical properties (e.g., shape, size surface and surface functionalized with an array of targeting ligands) to prepare the nanomedicines for applications in cancer therapy. Tailoring the physicochemical properties of nanoparticles to overcome the various biological barriers can offer the possibility to develop more efficient cancer nanomedicines. Reproduced with permission.^[35] Copyright 2011, RSC.

in tumors.^[38] The key requirement for the first generation of nanomedicines to exploit the EPR effect in tumors is the prolonged circulation kinetics in blood. Coating the surface of nanoparticles with neural and hydrophilic polymers is needed to decrease the binding of opsonin proteins and recognition of MPS that leads to prolonged circulation times of the nanoparticles in the bloodstream. PEGylation has been widely used for the surface coating of the nanoparticles in order to introduce a stealth property to the nanoparticles, because PEG chains hinder the non-specific interaction of the nanoparticle's surface with the blood components due to tight hydrated layer and reduce MPS recognition, resulting in reduced uptake and clearance from the bloodstream.^[39] PEGylation of liposomes have shown to extended the blood circulation time from less than 30 min to 5 h after systemically administration, conferring the 'stealth effect' of PEGylation.^[40] Similarly, PEGylated poly(lactico-glycolic acid) (PLGA) nanoparticles have shown to significantly increased the blood circulation half-life together with reduced liver uptake, compared to non-PEGylated PLGA nanoparticles.^[41] PEGylated dendrimers-drug conjugates can spontaneously form into nanoparticles (60–80 nm) and have shown to prolonged the circulation time as the total plasma doxorubicin concentrations declined slowly and plasma clearance was approximately 1000 times lower than the free doxorubicin,

leading to an enhanced tumor accumulation.^[42] This PEGylation strategy led to the clinical translation of first generation of nanomedicines, such as Doxil[™] and Genexol-PM[™]. Prolonged stealth effect of PEGylation is not only dependent on molecular weight and density of the PEG chains, but also on the nanoparticle size and surface charge.^[43] However, passively targeted (long circulating) nanomedicines alone might not be able to fully control the off target toxicity, specifically because directed nanoparticles with active targeting and controlled release of drugs into tumors are expected to improve the efficiency of the nanomedicines.

2.2. Second Generation Nanomedicines

The second generation of cancer nanomedicines is consisted of nanoparticles, similar to the first generation, with additional functionality presented by means of active targeting moieties to specifically bind to the receptors over expressed in cancer cells or smart stimuli-responsiveness to precisely control the release of anticancer therapeutic agents. In the meantime, the development of antibody technology allowed the next growth of nanomedicines through active nanoparticle targeting strategies using different antibodies, peptides, aptamers and small

molecules as a targeting affinity ligands by conjugating them to the surface of the nanoparticles for different tumors that are extensively reviewed elsewhere.^[21,44,45] Active targeting is dependent on the specific ligand-receptor recognition, where nanoparticles attached with targeting moieties can bind to specific targeting cancer cells, and as a result, anchored nanoparticles enter the cells through an endocytosis pathway and release the drug within the intracellular compartments of the cells.^[46] For example, compared to non-targeted magnetic nanoparticles, targeted ones with anti-HER2 monoclonal antibody specific for breast cancer cells have demonstrated 10–30-fold increased concentrations in tumor tissues.^[47] Similarly, nanoparticles have also been conjugated with RGD (Arg-Gly-Asp) peptides due to their high affinity to $\alpha\beta3$ integrin receptors that are highly expressed in tumor cells, thus enhancing the intratumoral drug delivery.^[48] Aptamers are small oligonucleotides that can be selected to bind tightly and specifically to a target molecule, are also widely applied into nanoparticle formation besides the surface modification. Doxorubicin can efficiently intercalate into DNA aptamer structure without affecting the aptamer's three-dimensional structure. Aptamer-Dox nanoparticle have shown to efficiently reversed the resistance of human breast cancer by cell cycle arrest in S phase.^[49] Note that the density of the targeting moieties on the nanoparticle's surface play a vital role in determining the targeting efficiency, uptake and maintenance of stealth properties. In addition, for effective targeted nanomedicines, the targeting ligands must be carefully selected in order to be specific for highly and preferentially expressed surface markers in tumor tissues or cancer cells and at the same time minimize the binding to healthy tissues or cells. Although active targeting can increase the cell specific tumor uptake, passive targeting is still a prerequisite to first accumulate the nanoparticle in the tumors and to reach the vicinity of the targeted cancer cells. Various studies have shown that active targeting enhances the in vivo tumor accumulation in many instances, but comparing the advantage of active targeting in terms of tumor accumulation and therapeutic benefit over the passive targeting is still a matter of debate. However, alternatively, selecting the pharmacologically active targeting ligands can bring additional anticancer activity to the nanoparticles besides the targeting, which can be beneficial. For example, doxorubicin-loaded polymeric micelles conjugated with EGa1 (nanobody), selectively binds to the epidermal growth factor receptors (EGFR) and blocks the EGFR signaling in tumors, which have demonstrated the substantially enhanced antitumor activity and survival in animal cancer tumor models.^[50]

Advances in nanoscale engineering allows to design smart nanosystems to target tumors and to deliver the drugs only in response to specific stimuli, namely passive-stimuli responsive and active-stimuli responsive drug release.^[24] Passive-stimuli responsiveness refers to how by applying the physiological changes, the nanoparticle will have a corresponding transformation, thus causing the release of the drugs. For example, considering the pH difference between the extra- and intra-cellular environments, several systems that have responded to low pH conditions were created by different methods, including pH sensitive polymer coatings,^[51] conjugation of pH-sensitive chemical bonds,^[52] and pH-responsive valve cappings.^[53] Other strategies, such as using of DNA as molecular keys to assemble

and transform colloidal nanoparticle systems, the conformation of which can be transformed in response to DNA via a toe-hold displacement mechanism and further mediate the cellular–particle interactions for navigating complex biological environments by changing the morphology of nanoparticles, the cellular uptake from glioma U87-MG cells can thus be enhanced up to 2.5 folds than conventional systems.^[54] Furthermore, stimuli-responsive materials sensitive to increased glutathione concentration inside the cells, specific enzymes or adenosine triphosphate (ATP), have also been largely applied into nanomedicines that are detailed elsewhere.^[55–57]

Active-stimuli responsive drug release is a more precise and easily controllable strategy by using external stimuli. The design of these nanosystems usually takes advantage of photo-activated,^[58] thermo-activated^[59] and magnetic-activated materials^[60] to achieve drug delivery under a specific external signal. Photolabile bonds or photoisomerization materials have been vastly investigated to fulfil the light inducible nanosystems. Another strategy is by the exposure of magnetic particles to oscillating magnetic field resulting in heat generation due to superparamagnetic property, where this temperature increase can be used to allow opening of a nanovalve, further triggering the drug release.^[61] DNA-assembled gold-nanorod superstructures are also applied to tune the drug loading and releasing process due to its unique NIR induced photothermal effect.^[62] These stimuli-responsive nanomedicines can precisely control the spatio-temporal drug release that offers the possibility to protect the drugs from degradation, allows direct localization or release of the payloads, and facilitates the maximum release at the target tissue/cell. Together with the advantage of a more precise and accurate drug release control, the active-stimuli responsive strategy often has to face the limitation of unsatisfied tissue penetration property for the external stimuli source. However, currently, multiple combinations of stimuli responsive nanosystems have been developed to further enhance the specificity for targeting and controlled drug delivery.^[63,64]

2.3. Third Generation Nanomedicines

The third generation of cancer nanomedicines comprise the strategically engineered multiple component nanosystems equipped with multiple functions designed to overcome different biological barriers to reach the target—tumors. These multifunctional nanoparticles are capable of performing many functions either in parallel or sequentially, such as multi-targeted nanoparticles with stimuli-responsive drug delivery, combined diagnosis and therapeutic function (theranostic), among many others.^[23,34,65,66] Combinatorial delivery of doxorubicin, paclitaxel together with nucleic acids (DNA and siRNA) using multifunctional polymeric nanoparticles evidenced the more therapeutic effect in terms of suppressing tumor growth in in vivo animal models, compared to the single delivery of each therapeutics, separately.^[67,68] Multifunctional receptor-targeted porous silicon (PSi) nanoparticles containing a RGD-targeting peptide, an anticancer agent, a fluorophore and ¹¹¹In have been used for tumor targeting and imaging combined with drug delivery in prostate cancer xenograft mouse model.^[69] Similarly, targeted theranostic liposomes consisting of gadolinium

and doxorubicin with peptide targeted to neural cell adhesion molecules showed high drug concentration in tumors, inhibiting the tumor growth with enhanced MRI imaging of Kaposi's tumours in mice.^[70] Moreover, porous silica coated quantum dots loading doxorubicin can spontaneously achieve cathepsin B enzyme targeting drug release and real-time fluorescence imaging in lung carcinoma A549 cells.^[71] Recently, an advanced targeted and multi-stimuli responsive of a theranostic nano-system consisting of pH-responsive polymeric-drug conjugate, iron oxide nanoparticles and conjugated with a tumor homing iRGD peptide was developed for the intracellular triggered delivery of doxorubicin targeted to endothelial and metastatic cancer cells.^[72] In this direction, multi-stage PSi vectors (MSV) have also been developed, in which the first-stage of the vectors is made of PSi microparticles containing the second stage therapeutic nanoparticles.^[73] This nano-in-micro multistage systems can cross different biological barriers in a sequential manner to achieve the targeting specificity to tumors: the first stage system goes through the circulation and is deposited in the tumor vasculature, whereas the second stage nanoparticles are released from the first-stage into the tumor interstitium.^[74] Currently, most of these advanced third generation multifunctional nanomedicines are in the early stages of pre-clinical development. Moreover, tailoring the physicochemical properties of nanoparticles, such as morphology (geometry and shape), size, surface charge, surface chemistry, composition, hydrophobicity, porosity, roughness, rigidity and colloidal stability can influence the series of biological processes that in turn determine the overall therapeutic efficacy of cancer nanomedicines (Figure 2).^[22,75,76] Thus, in order to utilize the potential of these advanced multifunctional, stimuli-responsive and theranostic nanoparticles that are showing promising therapeutic advantages at the preclinical stages in order to accelerate their clinical translation, from the nanoparticle engineering prospects focus should be at the practical challenges in the design, development of advanced targeted nanoparticle engineering, which include: (i) optimization of the preparation of

complex nanoparticle designs using simple steps without the requirement of multi-step processes; (ii) full characterization of the main physicochemical properties of the nanoparticles using quantitative analytical methods and ensure the quality of the nanoparticle characterization; (iii) optimization of the loading and release of payloads and assessment of the potential cross reactions in case of combination of payloads; (iv) utilization of controllable, site specific, robust and reproducible bioconjugation chemistries for attaching targeting ligands on the surface of the nanoparticles; (v) optimization of the bio-physicochemical properties of the nanoparticles to achieve long half-life in blood circulation, favourable biodistribution and pharmacokinetics, differential accumulation in target tissue; (vi) development of scalable manufacturing processes that can adopted to large scale production.

2.4. Next Generation Nanomedicines

Cancer immunotherapy is rapidly emerging as a next generation in the cancer treatment that is based on the activation of patient's immune systems to fight against cancer.^[77,78] In immunotherapy, nanoparticles offer the advantages to delivery various immuno-stimulatory and modulatory agents, simultaneously protect them from complex biological environments and target to appropriate immune cells to elicit immune responses through antigen presenting cells (APCs) or direct activation of tumor associated antigen (TAA) specific T cells (Figure 3).^[79–81] In addition, nanoparticles may serve as adjuvants depending on the material compositions that can avoid the necessity to co-administer the adjuvants and antigens. For example, nanoparticles composed of mesoporous silica/silicon, acetylated dextran were reported to possess adjuvant properties as well as able to activate the DCs.^[82–84]

As APCs like DCs are the key players in initiation of immune response at early stages, particularly for the cytotoxic T lymphocytes (CTLs) response that has a potential to kill tumor cells,

Figure 3. Schematic representation of nanoparticle strategies to stimulate the immune response. Nanoparticle have been used to deliver TAA and/or adjuvants (Toll like receptor (TLR) ligands) to APCs process, where they promote the major histocompatibility complexes (MHC) formation, thereby cognate the CD8⁺ cells, resulting in generation of tumor- cytotoxic T lymphocytes (CTLs) that has a potential to kill respective cancer cells. Reproduced with permission.^[85] Copyright 2015, ACS.

different nanoparticles have been designed to target DCs to deliver antigens and adjuvants. For example, PLGA nanoparticle loaded with ovalbumin (OVA) and TLR-4 agonist, 7-acyl lipid A stimulated the immune cells and increase the number of CD4⁺ and CD8⁺ T cells in both in vitro and in vivo.^[86] Similarly, PLGA nanoparticle co-encapsulating antigen (OVA), Pam3Csk4 and Poly(I:C) as adjuvants was targeted to CD-40 receptors on DCs and was shown to increase the nanoparticle uptake in DCs, prime the CTLs in murine tumor model, which led to prolonged control over the tumor growth.^[87] In addition, polymeric micelles composed of PEGylated poly-(L-Lysine-L-Leucine) co-loaded with model antigen (OVA), adjuvant (poly I:C), and siRNA were shown to activate the DCs and prime the CTLs in melanoma mouse model with increased survival rate.^[88] Interestingly, nanoparticle based artificial APCs have also been developed to mimic the APC-T cell interaction and to induce the CTL responses.^[89] In this direction, as an artificial APC, sub 100 nm sized iron oxide nanoparticles coated with dextran and conjugated with stimulatory molecules have shown to induce the T-cell receptor clustering under magnetic field and activate naïve T cells.^[90] More details on various nanoparticle strategies developed for cancer immunotherapy have been extensively reviewed elsewhere.^[15,85,91]

2.5. Alternative Nanomedicines

Besides the abovementioned generations of conventional nanomedicines, there are also new trends by taking advantage of the inherent properties of the nanoparticle to achieve the directly anti-cancer therapy. Nowadays, the use of specific nanoparticles for photothermal therapy has emerged as one of the important therapeutic options in management of cancer and other diseases. Due to strong electric fields at the surface, the absorption and scattering of electromagnetic radiation by noble metal nanoparticles are strongly enhanced, and these unique properties provide the potential of designing novel nanoparticles for simultaneous molecular imaging and photothermal cancer therapy. For example, gold nanorods with suitable aspect ratios (length divided by width) can absorb and scatter strongly in the NIR region (650–900 nm). As a new photothermal therapeutic platform for treating brain tumors, rabies virus-mimetic silica coated gold nanorods with an aspect ratio of 2.34 have demonstrated the reduction in tumor size, which is almost 20-times smaller than control groups after 7 days treatment.^[92] Similarly, Mo-based polyoxometalate cluster (up to tens of nanometers) have shown to enhance the photothermal conversion in response to the intratumoral acidity and reducibility. Under 808 nm irradiation for 1 h, the tumor temperature reached up to over 47 °C, where as for the healthy tissue the temperature still under 42 °C, suggesting a tumor specific targeting ability.^[93] Besides photothermal therapy, new strategies like manipulating the oxidation/reduction reaction of the nanoparticles at the specific site to achieve specific functions, have also received attention. Recently, magnesium silicate nanoparticles have been utilized to facilitate oxygen depletion to accomplish the cancer starvation therapy, which can potentially stop the tumor growth in 4T1 tumor bearing mice. The SiH₄ released from the particles can function as an oxygen scavenger and the

following SiO₂ aggregates generated in situ could block tumour capillaries and maintain intratumoral hypoxia by choking off the undesirable blood supplies.^[94] Similarly, another strategy is using upconversion nanoparticles to trigger the photodynamic therapy and thereby generate a reduction environment, further inducing the activation of bio-reductive pro-drug, and tumor to background ratio (T/B) value of hypoxic volumn in HeLa cell xenograft tumor significantly increased from 1.0 to 2.15 within 30 min.^[95] Moreover, by using iron nanometallic materials, it will enable the disproportionation of hydrogen peroxide, which is usually over-produced within the tumor area, to efficiently generate hydroxyl radicals in the Fenton reaction, chemodynamic therapy (CDT) can thus be achieved by using endogenous chemical energy to produce reactive oxygen species, which can vanish the existence of tumor within 4T1 xenograft bearing mice.^[96]

3. Cancer Nanomedicine from the Pharmaceutical Perspective

In conventional drug therapy, chemotherapeutic agents often encounter the problem of decreased selectivity, low concentration at the tumor tissues or cells, and higher systemic exposure that leads to reduced therapeutic efficiency and dose limiting toxicity.^[97] In this regard, nanotechnology has shown tremendous potential to develop and design various nanoparticles as a carrier for improved drug delivery, thereby reducing the undesired toxicity of the systemic delivery, increasing the drug dose at the tumor site and improve the overall efficacy of the drugs.^[98–100] Loading of anticancer agents in nanoparticles have a number of advantages, including: (i) enhanced drug solubility and chemical stability; (ii) protection of the drug from degradation/metabolism and/or excretion; (iii) extended circulation half-life; (iv) improved tissue distribution; and (iv) controlled drug release properties. Furthermore, the nanoparticles can alter the pharmacokinetic (biodistribution) and pharmacodynamic (drug action) profiles of the anticancer drugs, resulting in enhanced therapeutic index. After all, nanomedicines are nano-sized suspension formulations, and all their features should contribute to a common goal, that is to improve the therapeutic index of the active pharmaceutical ingredients (API), i.e., anti-cancer drugs. Thus, the development of efficient nanoparticle drug delivery systems is crucial for the development of nanomedicines for cancer therapy.

It has been estimated that newly identified API entities (more than 40%) may suffer from solubility issues presenting a challenge to develop pharmaceutical formulations of these drugs.^[101] Nanoparticles have shown to enhance the solubility of hydrophobic and poorly water-soluble drugs or by nanocrystal formation.^[102,103] Nanoparticles assisting the drug solubilization are highly desired to significantly improve the bioavailability of the APIs. For example, FDA approved Doxil®, which encapsulate 10,000 doxorubicin drug molecules in single 100 nm sized liposome as a result of the increased drug solubility, allowing for high drug doses, and at the same time minimizing the side effect of cardiotoxicity.^[104] However, high doxorubicin loaded in liposomes was achieved beyond the solubility limit, thus most of them are in a solid phase. It was suggested that more than 98% of the

circulating drug remaining inside the liposomes after systemic administration due to the presence of cholesterol in the liposomal formulation that contributed to the enhanced drug stability.^[105]

Nanomedicines can also be benefited from formulating the drugs in nanoparticles without the need of any additional toxic excipients. These toxic excipients are often used in already existing marketed drug formulations, causing dose limiting toxicities of the drug.^[106] Thus, nanoparticles can offer the advantages of improved drug tolerability and administration of high dose of anti-cancer drugs. For example, Cremophor™ is a dose-limiting toxic excipient commonly used in the currently marketed Taxol™ formulation. Clinical nanomedicines like Abraxane™ and Genexol® PM are able to achieve the administration of higher doses of paclitaxel in human patients due to the increased drug solubilization effect from the nanoparticles and by avoiding this toxic excipient.^[106–108] In addition to the traditional small drug molecules, nanoparticles can also entrap large macromolecules, such as proteins, peptides, DNAs and RNAs to protect them from enzymatic degradation and to improve their stability during the transport and until they reach the active cancer tumor sites.^[109,110]

3.1. Pharmacokinetics of Nanomedicines

The pharmacokinetic (PK) evaluation of drug loaded nanoparticle is the most important aspect for both preclinical and clinical studies in the development stage of cancer nanomedicines.^[111–113] Classical PK study is aimed to measure the concentration of drugs in almost all tissues over a period of time after the administration of the drugs until the phase of elimination. The PK of the free drug is largely altered by the nanoparticle at least until it is released from the nanoparticle, whereas the nanoparticle's PK is mainly dictated by their physicochemical properties, such as size, charge, and surface chemistry.^[111] Subsequently, when the drug is released from the nanoparticles in the bloodstream, intrinsic drug PK will followed by the released drugs. Therefore, for the nanomedicines' formulation the PK profiles of both loaded and unloaded drugs (released) are crucial to understand the PK properties of the nanomedicines and how it affects both their pharmacodynamic and toxicodynamics.^[112]

The PK profile of the formulation can quantitatively describe how the body handles the drugs and/or nanoparticles. Important parameters for this include, $C_{\max}$ (maximum concentration), $t_{1/2}$ (half-life), Cl (clearance), AUC (area under the curve) and, most importantly, the maximum tolerated dose (MTD).^[111] Generally, most of the nanomedicines tend to show a prolonged $t_{1/2}$ and AUC, partly suggesting the maintenance of a drug concentration within the therapeutic window with reduced fluctuations, caused by the protection of the nanoparticle or the retained drug release. Thus, PK can provide understanding on the bio-fate of the nanoparticle and also further indicate the potential side effects. For example, PK of the Doxil® has high AUC, long $t_{1/2}$, and low Cl with relatively small volume of distribution than the free drug.^[104] A much longer $t_{1/2}$ of Doxil than the free drug may be due to the low release rate, thus even though the cardiotoxicity of doxorubicin is reduced, the prolonged tissue retention induces

other side effects like foot and hand syndrome.^[114] Also, Doxil® (liposomal doxorubicin) and DaunoXome® (liposomal daunorubicin), basically share a similar formulation form (liposomes), but the former one contains PEG coating to avoid the MPS and to stabilize the lipid drug encapsulation, and where the free drug can merely be released within extracellular environment; nevertheless, the latter one has a totally different design strategy, aiming at promoting the uptake by the MPS, followed by providing a reservoir from which the free drug can then enter the circulation, thereby DaunoXome® does not have PEGylation. On one hand, compared to Doxil®, DaunoXome® exhibits a higher $C_{\max}$ and a much shorter $t_{1/2}$ and a faster Cl.^[115] It is obvious for the nanomedicines formulation that has a longer $t_{1/2}$ and mean resident time, the drugs are protected both from metabolizing enzymes in the liver before they are released, and also from renal clearance due to the increased size; this leads to the longer exposure time of the drug to the tumor, which partly explains the promoted drug therapeutic index. On other hand, Abraxane® has a fast Cl than DaunoXome® with large volume of distribution, and $t_{1/2}$ similar to DaunoXome®. Nevertheless, Abraxane's PK is similar to free paclitaxel: low AUC, high Cl, high volume of distribution, and short $t_{1/2}$.^[116]

3.2. Controlled Drug Release

To achieve therapeutic efficacy, a drug should be released from the nanoparticles to the target tumor tissue or cancer cells, which is one of the main obstacles for nanomedicines. For example, passively targeted PEGylated liposomes (Doxil®) nanomedicines have demonstrated to be an efficient nanocarrier with high drug loading to deliver the doxorubicin with enhanced tumor accumulation.^[104] However, a modest anticancer activity was observed due to low drug release rate in both circulation and tumor resulting in only about 40–50% bioavailability of Doxil® in the tumor.^[114,117] In another clinical studies, liposomal cisplatin formulation (SPI-077) shown a substantial tumor accumulation with almost no anticancer activity due to diffusional limitation of cisplatin through the intact liposomal membrane.^[118,119]

Active targeting to tumor cells have been envisioned to increase the intracellular delivery and bioavailability of drugs. In recent Phase II clinical trials, actively targeted BIND-014 nanomedicines showed higher accumulation in tumor, yet better therapeutic efficacy was not evidenced.^[120] Therefore, enhancing the accumulation of nanomedicines in the tumors are not directly correlated with the bioavailability of the drugs in the tumors, being rather dependent on the rate of drug released. As the drug is main driver for the therapy, the key here is how to formulate the nanomedicines in such a way that is not only having a high accumulation in the tumor, but also releasing effectively the drug to exert its action/therapy. However, this needs to be accomplished by simultaneously maintaining the stability of the nanomedicines in the systemic circulation and achieve enhanced tumor bioavailability by the released drug only upon reaching the tumor tissue, which is very challenging.

In order to overcome this issue, various stimuli-responsive nanoparticles have been developed to respond to various environmental changes in the tumor and its microenvironment, such as enzymes, pH, redox conditions or external stimuli (e.g., magnetic field, light, heat and ultrasound) to precisely control the release of the drugs from the nanoparticles after reaching the tumors.^[66] One stimuli-responsive nanomedicine to reach the advanced clinical stage is the thermosensitive lyso-liposomal formulation (Thermodox) encapsulating doxorubicin and releasing the drug upon heating to 40–45 °C due to the structural changes (pore formation) in the liposomes.^[121] Despite of this advanced stimuli-responsive nanomedicine, the majority of the nanomedicines are regarded to slowly release the drugs in the systemic circulation, as a result of the long circulating time and slow extravasation, which most likely lead to a lower drug concentration when they reach the tumor and associated tumor microenvironment (TME). In addition, given that recent analysis showed only about 0.7% of the injected dose of nanomedicines actually accumulate in the tumors, suggesting that less amount of nanomedicines reaching the tumor site may further reduce the drug dose at the tumor.^[122] Therefore, aligning the simultaneous drug release, PK and extravasation of nanomedicines will offer great advantages to achieve an optimal therapeutic outcome.

3.3. Combination Therapy

Long-term outcomes for patients with malignant tumor have improved with the addition of combination chemotherapy, due to the great potential in enhancing the drug's therapeutic efficacy, lowering the drug dosage, and overcoming drug resistance.^[123] Nanomedicines have the potential to load different drugs within one single carrier, therefore co-delivery of several drugs using functional nanoparticles show great potential in improving the therapeutic efficacy, while lowering the side effects.^[124–126] However, the combination therapy is not only using several different drugs at the same time, it is a rather complicated process from the administration time to the drug dosage, and thus, the sequence of different drugs are greatly affecting the therapeutic outcomes.

In the area of nanomedicines, the dosage ratio between different drugs is especially important. Recent studies systematically comparing the high drug dose monotherapy and multi-agent combination therapy, suggested the importance of alternating drug dose ratio at different tumor progression, thus plays an essential role in personalized therapy.^[127] For co-delivery of nanomedicines, most of the drug are simultaneously co-loaded or subsequently loaded at different stages. However, few studies are focusing on manipulating the dosage ratio of different drugs within the nanoparticles. Besides modifying the drug loading techniques, there are also great demands for investigating the parameters influencing loading capacity and in the end one can flexibly manipulating the concentration of different drugs within nanoparticles to further fulfil the personalized nanomedicines concept, namely, nanomedicines prescription can best suit for an individual based on the

progression of the cancer, as well as on both the personal pharmacogenetic and -genomic information.^[128]

In addition to the drug dosage manipulation, the other problem commonly found within the combination therapy area is how to evaluate the synergistic effect of the drugs. A combined effect greater than each drug alone does not necessarily indicate synergism. Sometimes this can be a result of additive effects or even a slight antagonism. $A + B > A$ or $A + B > B$ is a simple axiom, which does not require elaborate proof, such as P values. A claimed “synergistic effect” should be properly elucidated by calculating the combination index (CI) of two or more drugs, which is sometimes neglected.^[129] It will be of great importance to have a deeper understanding of difference or even the advantage of nanomedicines based drug combination therapy against conventional drug combination therapy.

3.4. Maximum Tolerated Dose (MTD)

MTD is the largest dose that does not produce dose-limiting toxicities in a substantial number of subjects, i.e., MTD is a direct index to value the toxicity of one formulation, and it is also one important parameter to be investigated during the phase I clinical trials.^[130] One main advantage of nanomedicines is the claim that it can greatly decrease the toxicity of anti-cancer agents by reducing the random distribution of the drug, which has already been vastly investigated during the past years. Also, there are studies suggesting that the MTD of Abraxane® was higher than that reported for Taxol®, this is partly the reason during the phase III clinical trials, where the response rate among the metastatic breast cancer patients treated with Abraxane® was higher than Taxol®.^[131] This example demonstrates that different formulation of nanomedicines also has the possibility of a much varied MTD performance. Despite several controlled drug release nanosystems have already been fabricated and tested, whether different design or drug release strategies have the impact on the MTD is still not clear. For example, comparing to the unmodified ones, does the ligand facilitate the active targeting can really promote the MTD by reducing the side distribution? Or, whether the designed tumor-specific release behavior, such as pH-sensitive or enzymatic-sensitive drug release, can be fulfilled within the in vivo tumor microenvironment? MTD can perform as an indirect, but useful tool, to give a rough answer to these questions, which is rather indispensable for further clinical studies. Yet there is a lack of systematic investigation around this topic.

It is however unwise and unrealistic to test the MTD for every single nanomedicine in vivo, thus there is a huge demand to build-up ex/in vivo and in silico platforms with satisfied correlation curves. Recently, there has been several studies applying microfluidics as a new paradigm to simulate the organ-on-chip studies.^[132,133] Microscale cell cultures elicit a more authentic response from conventional cultured cells, enabling physiologically realistic in vitro tissue models to be constructed. In addition, the precise control over the flow rate allow a more persuasive replication of the blood circulation, and last but not the least, one microfluidic chip containing multiple chambers can represent different organs and these compartments can be

connected via fluidic conduits designed to recapture the blood circulation pattern, therefore mimicking the complex multi-organ interactions.^[134,135] However, the possibility of using this tool as a new paradigm to study the MTD and the drug metabolism it still needs further investigation.

4. Cancer Nanomedicines from the Tumor Biology Perspective

Although various cancer nanomedicines showed tremendous therapeutic benefits in the preclinical stages, their clinical translation is very limited due to the sub-optimal therapeutic efficacy.^[136–138] To overcome the bottlenecks in improving the therapeutic efficacy of nanomedicines, for a long time, nanoparticle engineering took the central stage and more light was shed on understanding the relationship between different bio-physicochemical properties of the nanomedicines design, thereby controlling their therapeutic efficiency. Despite the progress in the nanomedicines development, achieving high therapeutic efficacy is persisting challenge due to the complex tumor pathophysiology that hinders the therapeutic effect of nanomedicines.^[139] In the tumor, the vasculatures are fairly irregular structures and the surrounding tissues are largely dysfunctional due to overwhelming pro-angiogenic signals present in the TME that cause heterogeneous, disordered and leaky immature blood vessels.^[140,141] Leakiness in vasculatures are a result of large gaps/pores between the endothelial cell junctions caused by improper coverage of supporting pericytes that enhance the vasculature permeability and allow the extravasation of nanoparticles.^[15] Furthermore, proliferating cancer, stromal cells and extracellular matrix (ECM), raises compressive forces and cause the impairment in lymphatic flow.^[142] Thus, after reaching the tumor, the nanoparticle clearance is reduced due to the poor lymphatic flow that allows the retention of nanoparticles within a tumor area.^[22] These pathophysiological properties of the tumor and their microenvironment is the solid foundation for the pillar concept of EPR in the design and development of cancer nanomedicines.

Several studies pinpointed that varying the different physicochemical properties of the nanoparticles, such as shape, size, and surface can impact the tumor accumulation and retention in different tumors.^[22,143,144] Although, increasing number of nanomedicines have been reported based on the EPR principle, it is often over simplified and unified virtually for all type of tumors, whereas it is substantially more complex in reality.^[145] In murine cancer models, polymeric micelles with different sizes (30, 50, 70, and 100 nm) showed similar extravasation and anti-tumor activities in highly permeable colon adenocarcinoma, whereas in less permeable pancreatic tumors, only polymeric micelles with 30 nm size in diameter showed significant tumor accumulation.^[146] Similarly, in another preclinical study, the tumor type dependent EPR effect was reported in carcinomas and sarcomas with a heterogeneous uptake level of liposomes.^[147] In cancer patients, the tumor accumulation of indium-labelled PEGylated liposomes showed significantly different degrees of tumor accumulation depending on the type of cancer. The highest uptake of PEGylated liposomes (33±16% of injected dose per kilogram (ID/Kg)) was observed in head and

neck cancer, whereas only 18±6% and 5±3% of ID/Kg in lung and breast cancers, respectively, were observed.^[148] These pre-clinical data revealed that the EPR effect can be greatly varied from tumor to tumor and suggests that differences in the EPR effect is clearly dependent on the tumor type. Interestingly, the accumulation of PEGylated liposomes is significantly differed between patients with same type of cancer. Thus, accumulating evidences of nanomedicines indicate that the EPR is markedly varied between tumor types, patients, within same tumor or patients, and dependent on the stage of cancer progression. In addition to the consideration of tailoring the distinctive physicochemical properties of the nanomedicines, as differences in the EPR effect largely affected by properties of the tumor, which critically raises the concern of investigating pathophysiology of tumors. Therefore, more than ever, it is crucial to understand the behaviour of nanomedicines in relation to the tumor micro-environment properties.

One of the most restricting factor for nanomedicines is the limited nanoparticle accumulation at the active site of the solid tumor. Generally, the accumulation of nanoparticles within the tumor sites includes two phases: (1) the extravasation of the nanoparticle from the blood vessel into tumor microenvironment, and (2) the intratumoral distribution of nanoparticles within the tumor ECM, followed by cellular uptake. Meanwhile, the vast majority of the nanoparticles are recognized and phagocytized by stationary or circulating monocytes. Due to the variable physiological barriers and microenvironment properties, designing principles of nanomedicines should be varied accordingly.

Currently, to further enhance the treatment index of nanomedicines, several strategies aiming at different prospects are proposed. Tumor growth and progression not entirely depend on the cancer cells, and also the pathophysiology in the surrounding TME. The complexity of TME are posed by the network of various types of cells, ECM, blood and lymphatic vasculatures (Figure 4).^[149] Emerging evidences suggest that the TME play a vital role in regulating tumorigenesis, including tumor initiation, development, proliferation and metastasis, and important response to cancer therapy.^[150,151] TME is sought to be one of main drivers for the accumulation of nanoparticles/nanomedicines in the tumor and highly heterogeneous TME contribute to the differential distribution of nanomedicines within tumor. In TME, the aberrant tumor vasculatures, elevated interstitial fluid pressure (IFP) and abnormalities in ECM are major hurdles in terms of effective penetration of the nanoparticles into the tumor tissue.^[140] Therefore, understanding the multifaceted TME will allow to ascertain the abnormal physiological process that can be modulated to improve the therapeutic efficacy in cancer therapy. Various approaches have been developed to modulate the aberrant TME that have shown promising results in enhancement of anti-cancer effect of nanomedicines.^[145,152]

4.1. Modulating the Tumor Microenvironment for Cancer Therapy

The varying degrees of tumor vascularization and angiogenesis are also thought to be the influential parameters for

Figure 4. Schematic representation of the cancer tumor microenvironment. In primary tumors, cancer cells are surrounded by complex TME, which comprises various types of cells, such as endothelial cells (blood and lymphatic), fibroblasts, macrophages, pericytes, extracellular matrixes and various signaling molecules. The interplay of all these components collectively contribute to the cancer tumor growth and progression. Reproduced with permission.^[153] Copyright 2014, Elsevier B.V.

the optimal accumulation of nanoparticles in the tumor. It is suggested that even though the leaky and irregular tumor vasculatures seems to provide larger gap to allow the nanoparticles traversing through the tumor interstitial and, eventually, nearby the tumor cells, it also reduces the amount of blood flow resulting in flow stasis and causing high IFP.^[154] It is known that most of the tumors have high IFP resulting from irregular vasculatures, which can be a barrier for effective nanoparticle delivery in the tumors.^[37] On contrary, to enhance the vascular permeability, vascular normalization strategies aim to transforming the aberrant tumor vasculatures into closely resembling normal vasculatures in order to enhance the structural and functional integrity of the vasculature networks by increasing the pericytes coverage, reducing the IFP and leakiness of the vessels (**Figure 5A**).^[155] Thus, by normalizing the tumor vasculature, the solid tumor stress may be reduced and promote the nanoparticle penetration efficiency. Proangiogenic proteins like vascular endothelial growth factors (VEGF) are over-expressed in many tumors that are primarily driving the angiogenesis process.^[156] Therefore, VEGF can be a ther-

apeutic target for the vascular normalization approach.^[155] Normalizing the tumor vasculature using anti-VEGFR-2 antibodies in mouse tumor, blocked the VEGFR-2 receptors and decreased the pore size of tumor vessel wall, which in turn allowed the enhanced delivery of small nanoparticles (12 nm) and at same time hindered the delivery of 60 and 125 nm sized nanoparticles.^[157] However, the normalized vessels presenting the size restrictions for this strategy and allowed only smaller nanoparticles (< 60 nm) to be rapidly transported to the tumor tissue. Even though this approach has been mainly investigated in animal models, anti-angiogenic based vascular normalization has been reported in clinical trials of cancer patients. Thus, normalizing the vasculature can facilitate the enhanced delivery of smaller nanoparticles, while preserving the EPR effect and reducing the IFP. In addition, it was also demonstrated that the vascular normalization approach by using the anti-VEGFR-2 antibodies restored the vascular functions after 5 days of treatment in a breast adenocarcinoma xenograft model, resulting in increased tumor perfusion, pericytes coverage, and accumulation of different sized nanoparticles

Figure 5. Schematic representation of different approaches to modulate the cancer tumor microenvironment for effective cancer therapy. A) Normalizing the aberrant cancer tumor vasculatures to recover the structural and functional integrity of the vasculatures in order to improve the penetration of nanomedicines. B) Normalizing the stress of the cells by inducing cell apoptosis using anticancer drugs that can reduce the tumor cell densities and blood vessel compression in order to restore the perfusion in tumors. C) Matrix normalization is to weaken or degrade the extracellular matrix (ECM) components using ECM degrading enzymes that can facilitate the distribution of nanomedicines. Reproduced with permission.^[155] Copyright 2015, Elsevier B.V.

(20 and 40 nm in diameter).^[158] However, the smaller nanoparticles (20 nm) shown a homogenous distribution within the tumor tissue compared to larger nanoparticles (40 nm), suggesting that the interstitial transport of nanoparticles also presents a significant barrier for most of the developed nanomedicines. Note that VEGF blockade for long period of time can prune more tumors vessels and cause resistance, thereby limiting the treatment efficacy.^[159,160] In addition, increasing evidences suggest that vascular normalization by VEGF blockade may also facilitate the metastasis.^[161,162] Therefore, VEGF blockade in cancer treatment clearly warrants further investigations.

Rapidly proliferating tumor cells in the confined blood vessels can lead to a decreased blood flow as a result of reduced diameter of blood vessels. To promote the blood vessel decompression, anticancer drugs have been employed to reduce the tumor cell densities by causing apoptosis and

increasing the interstitial space resulted in enhanced tumor perfusion due to reduced IFP, and temporary vascular normalization (Figure 5B).^[163] Interestingly, pre-treatment of polymeric micelles loaded with paclitaxel (after 24 h) have shown to increase the blood flow and tumor oxygenation that further effectively increased the delivery of different other cancer nanomedicines, such as polymeric micelles composed of (PEG-poly(caprolactone -co- trimethylene carbonate) (mmePEG₇₅₀-p(CL-co-TMC)) (20 nm), PLGA nanoparticles grafted with RGD peptides (230 nm) and doxorubicin loaded liposomes (CaelixTM) (size of 100 nm).^[164,165] As micellar paclitaxel increased the MTD of paclitaxel compared to free drug, micellar paclitaxel can effectively be utilized to induce effective and safer tumor priming. This approach has been demonstrated in clinical study with breast cancer patients, where the tumor priming with paclitaxel reduced the IFP, improved the oxygenation of the tumor and also partly

downregulated the VEGF expression.^[166] Alternatively, an active vascular targeting approach has been developed using PLGA-lipid nanoparticles, in which doxorubicin was linked to the PLGA core, and combretastatin, an anti-angiogenic agent, was entrapped in the outer lipid envelope.^[167] After the release of combretastatin from the lipid layer, it induced the vasculature disruption and further the trapped PLGA core nanoparticle released the doxorubicin to tumor cells, demonstrating the enhanced therapeutic index of the drug with reduced toxicity.

In solid tumors, highly dense and abnormal ECM presents also a transport barrier, causing an inefficient penetration of the nanoparticles that ultimately will reduce the therapeutic efficacy of the nanomedicines. TME associated ECM is a complex meshwork consisting of collagen fiber network, microfibrillar elastins, glycosaminoglycan and proteoglycans.^[168] Different biomacromolecules crosslinked into gel-like structures resulted in a viscous matrix that reduce the fluid flow and limits the diffusion of nanoparticles from blood toward cancer cells. In addition, the tumor ECM has also increased the level of lysyl oxidase that crosslink the collagens and increase the stiffness of the ECM.^[169] Therefore, often therapeutic nanoparticles accumulate in the periphery without reaching the core of the tumor due to the diffusion limitation. ECM is involved in the proliferation of cancer cells, migration, invasion, and angiogenesis, and also in the resistance of apoptotic stimuli.^[170] Collagen fibers are the main structural proteins in ECM that are building a migration tract for the tumor cells. In addition, hyaluronic acid (HA) has contributed to the increased IFP and hindered the diffusion and penetration of nanoparticles.^[150,171,172] Therefore, modifying the components of ECM has been employed as an alternative strategy to increase the intratumoral delivery of nanomedicines (Figure 5C).^[172] By weakening or degrading the dense ECM matrix and reducing the IFP, the nanoparticle's transport in the tumor interstitium can be improved. For example, it has been shown that the penetration of nanoparticles in the solid tumors can be improved by utilizing the ECM degrading enzymes like collagenase and hyaluronidase to degrade the ECM components.^[173] As the ECM and their components can vary between different types of tumors and their localization, effects of modifying different components in ECM can be largely varied in terms of nanoparticle diffusion and penetration in relation to the type of tumors. It is noteworthy that using the ECM degrading enzymes possibly can increase the occurrence of metastasis. Treatment of hyaluronidase to degrade the HA in tumor ECM has been employed to enhance the penetration of liposomes (Doxil) into tumor after both intravenous and intratumoral administration.^[174] In xenograft mice, hyaluronidase reduced the IFP by 40% and increased the tumor distribution of doxorubicin (2–8 times more) compared to Doxil alone. Other enzymes like lysyl oxidase (LOX) and matrix metalloproteinases have been also used for ECM remodeling in tumor. PLGA nanoparticles (size of 200 nm) coated with anti-LOX antibody were able to specifically bind to ECM and inhibited the in vivo tumor growth with enhanced drug therapeutic index (effective at 50 times less dose of free anti-LOX antibody).^[175] Alternatively, as fibronectin is one of the component of ECM, particularly in glioma, polylactic acid based nanoparticles loaded

with paclitaxel and surface functionalized with fibronectin targeting peptide have shown 70% more survival time than other treatment groups.^[176] Besides the enzymes, other drugs like losartan, which blocks the angiotensin II receptor and reduces the tumor collagen, have been used to increase the diffusive transport and therapeutic efficacy of intravenously administered liposomal Doxil.^[177]

5. Cancer Nanomedicines from the Clinical Medicine Perspective

Currently, many nanomedicines are under clinical development in various stages of clinical trials or some have already been approved for clinical use by FDA in USA or the European Medicines Agency in Europe (Table 1).

Some nanomedicines are used in clinic for the therapy of various cancers at different stages, including Doxil[™], Dau-Xome[™], Myocet[™], Depocyt[™], Aberxane[™], Genexol-PM[™], and Onivyde[™].^[13,204] However, liposome-based nanomedicines represent the dominant class among all FDA-approved nanomedicines. For example, PEGylated liposome loaded with doxorubicin (Doxil/Caelyx) was the first nanomedicine approved by FDA for clinical use. Compared to standard clinical therapies, Doxil showed superior clinical therapeutic efficacy in ovarian cancer and AIDS-related Kaposi's sarcoma.^[104,205] Furthermore, in other cancers like multiple myeloma and metastatic breast cancer, the therapeutic efficacy was equivalent to that of standard clinical therapies.^[206,207] The main advantage of the Doxil in the therapy of solid tumors is the reduced cardiotoxicity, which is the adverse side effect caused by doxorubicin, as a result of the limited doxorubicin accumulation in heart. Nevertheless, Doxil have shown other side effects like hand-foot syndrome due to the extravasation into the skin facilitated by the prolonged circulation properties of Doxil. Similarly, albumin nanoparticles bound paclitaxel (Aberxane[™]) and polymeric micelle based nanomedicines loaded with paclitaxel (Genexol-PM[™]), are another classes of nanomedicines that are clinically approved to enable the administration of high doses of paclitaxel without increasing further the drug toxicity in patients, but the higher drug dose still fail to enhance the therapeutic drug efficacy.^[208,209] Thus, so far, the clinically approved nanomedicines have been mostly relying on improving the safety drug profile that can improve the quality of life in patients, but the patient survival rate remained equivalent to that of standard cancer therapies available at the clinical care. Although liposomal-based nanomedicines existing in the market have demonstrated the enhance tumor accumulation and improved toxicity profiles, none of them exhibited long term overall patient survival benefits compared with treatment of parental drugs.^[210] Recently, liposomal-based nanomedicines combining cytarabine and daunorubicin (Vyxeos/CPX-351) in clinical trial phase III have shown improved overall survival benefits in patients with high risk acute myeloid leukaemia, increased from 5.95 to 9.56 months.^[14] Thus, these nanomedicines can only provide modest overall survival benefits to the patients. The majority of the clinically approved cancer nanomedicines are based on the concept of EPR, while some of them designed with ligand mediated active targeting to alter the behaviour in tumors are

Table 1. Some examples of cancer nanomedicines that are already approved for clinical care and in the clinical trials under investigation.

Nanomedicine product	Type of nanoparticle	Drug	Type of cancer	Clinical status	References
Clinically approved nanomedicines					
Doxil/Caelyx	Liposome	Doxorubicin	Kaposi sarcoma Ovarian cancer Breast cancer Multiple myeloma	Approved (1995,1999,2003,2007)	[178]
DaunoXome	Liposome	Daunorubicin	Kaposi sarcoma	Approved (1996)	[179]
Myocet	Liposome	Doxorubicin	Breast cancer	Approved (2000)	[180]
Abaxane	Nanoparticle albumin bound	Paclitaxel	Breast cancer Pancreatic cancer Lung cancer	Approved (2005)	[181]
Genexol-PM	Polymeric micelle	Paclitaxel	Breast cancer Lung cancer Ovarian cancer	Approved (2007)	[108]
Mepact	Liposome	Mifamuride Muramyl tripeptide phosphatidylethanol- amine	Osteosarcoma	Approved (2009)	[182]
NanoTherm	Iron oxide nanoparticle	Thermal ablation	Glioblastoma	Approved (2010)	[183]
Marqibo	Liposome	Vincristine	Acute lymphoid leukemia	Approved (2012)	[184]
Nanomedicines in clinically trials (targeted)					
MM-302	Liposome (Target: HER-2)	Doxorubicin	HER-2 positive breast cancer	Phase II/III	[185]
BIND-014	Polymeric nanoparticle (Target: PSMA)	Docetaxel	Lung cancer (NSCLC) Prostate cancer	Phase II	[186]
2B3-101-BBB	Liposome (Target: Glutathione)	Doxorubicin	Brain metastases of breast cancer	Phase I/II	[187]
Anti-EGFR immuno liposomes	Liposome (Target: EGFR)	Doxorubicin	Solid tumors	Phase I	[188]
MBP-426	Liposome (Target: transferrin receptor)	Oxaliplatin	Gastric tumors	Phase I/II	[189]
SP1049C	Polymeric micelle (Target: P-Glycoprotein)	Doxorubicin	Adenocarcinoma	Phase II/III	[190]
Nanomedicines in clinically trials (non-targeted)					
MBT-0206 (Endo-Tag1)	Liposome	Paclitaxel	Pancreatic cancer Breast cancer (triple negative) Head and neck cancer	Phase I/II	[191]
ATI-1123	Liposome	Docetaxel	Solid tumors	Phase I	[192]
Lipoplatin	Liposome	Cisplatin	Lung cancer (NSCLC)	Phase III	[193]
CPX-1	Liposome	Irinotecan & Floxuridine	Colorectal cancer	Phase II	[194]
CPX-351	Liposome	Cytarabine & Daunorubicin	Acute Myeloid leukemia	Phase III	[195]
Lipusu	Liposome	Paclitaxel	Solid tumors	Phase II	[196]
Onco-TCS	Liposome	Vincristin	Non-Hodgkin Lymphoma	Phase II/III	[197]
ThermoDox	Liposome	Doxorubicin	hepatocellular carcinoma	Phase III	[198]
NK-105	Polymeric micelle	Paclitaxel	Gastric cancer Breast cancer	Phase II/III	[199]
ABI-008	Albumin nanoparticle	Docetaxel	Prostate cancer Breast cancer (metastatic)	Phase II	[200]
CLR-101	Polymeric nanoparticle	Camptothecin	Solid tumors Lung cancer (NSCLC) Renal cell carcinoma Rectal cancer	Phase II	[201]
Nanoplatin	Polymeric micelle	Cisplatin	Pancreas cancer	Phase II/III	[202]
DHAD-PBCA-NP	Polymeric nanoparticle	Mitoxantrone	Hepatocellular carcinoma	Phase II	[203]

in clinical trials, such as BIND-014 (Bind therapeutics),^[211] MM-302 (Merrimack Pharmaceuticals),^[212] and anti-EGFR immunoliposomes.^[213] Recently, BIND-014, which is a tumor prostate-specific membrane antigen (PSMA)-targeted nanoparticle containing docetaxel, has shown disappointing results in Phase II clinical trials. Although, clinical results demonstrated the enhanced tumor accumulation with reduced side effects as compared to the free drugs, the higher drug concentration achieved was unable to provide better therapeutic efficacy.^[19,120] Furthermore, polymeric micelles (NK105)^[199] and nanoparticles (CRLX101)^[214] have also shown disappointing clinical outcomes pressing the importance of reconsidering the design strategies of nanomedicines that will have significant impact on improving therapeutic efficacy and ultimately long term overall survival rates of patients.

5.1. EPR in Humans

The development of nanomedicines largely relies on the EPR phenomenon by considering the positive correlation between EPR mediated preferential accumulation of nanomedicines in the tumors and their therapeutic efficacy.^[38,215] Although the EPR effect is attested to be a universal phenomenon for all type of solid cancer tumors, the EPR-assisted tumor accumulation of nanomedicines has been demonstrated only in limited type of cancers.^[38] However, the EPR phenomenon is implausible to be present, if not equally present in all types of tumors. Therefore, the EPR effect alone cannot contribute to the clinical efficacy of the nanomedicines.^[152] In addition, increasing evidence suggests that the EPR effect is heterogeneous and largely varies between patients and tumor types, particularly within the same patient and tumor over a period of time.^[38,106,145] In a human tumor analysis study carried out in more than 200 patients with eight different types of cancer have shown large variation in tumor vasculatures, their location within the tumor, stroma and density, macrophage counts and distribution between patients and tumor types.^[106] More importantly, marked difference was evidenced within the same patient or tumors. However, there has been only limited effect made to address the effect of EPR in improving the therapeutic efficacy of nanomedicines.

While the EPR effect is well addressed in many preclinical studies using animal orthotopic and subcutaneous xenografts, and genetically engineered rodent models, there is inconsistency presented between therapeutic efficacy of nanomedicines gained in preclinical and clinical trial studies.^[216,217] This is mainly due to the difference in tumor models associated with species variation that fails to represent human cancers. Rodent tumor models are quite different from human cancers in many ways, including tumor growth rate, tumor size, rate of metabolism and lifespan of the host.^[152] In addition, the tumor development, microenvironment, and tumor-body-weight ratio also present a major difference between both species. Compared to rodent models, in humans the tumor growth speed is relative slow, thus the EPR effect within human body does not expect to function as in rodents tumor models. For example, subcutaneously injected tumor in rodents can grow up to ± 1 cm within few weeks, if this is related to the human tumors, it represents ± 20 cm tumor growth.^[8] As the tumor growth is more rapid in

murine tumor models, blood vessels are not developed properly, instead are highly vascularized and leaky, simple stromal structure with low density, whereas in humans all tumor vessels are not necessarily leaky, highly dense stroma, which leads to heterogeneous distribution. Nevertheless, although pre-clinical studies from murine tumor models are consistent, yet insufficient to correlate the clinical outcome in human patients. Therefore, enhanced therapeutic efficacy of nanomedicines achieved using those tumor models may not produce the same therapeutic efficacy in therapy of human solid tumors. It is noteworthy that currently none of the available tumor models have the capacity to replicate all aspects of human tumor that are clinically relevant.^[22] In this regard, clinical translation can be improved by the development of animal tumor models, such as patient-derived tumor explant and humanized murine tumor models that are more closely imitate human tumors in terms of morphology, heterogeneity, and complexity of matured, dense and less permeable than xenograft models in relation to clinical condition.^[218,219] As the EPR effect is diverse in patient tumors and the lack of detailed understanding in patient variability and tumor heterogeneity of the EPR effect in humans, clinical evaluation of the EPR effect in human is highly challenging, yet valuable for the long term success of the development of nanomedicines.

5.2. Patient Pre-Selection

Although cancer nanomedicines are progressing exponentially at the preclinical level, clinical therapeutic efficacy studies are still rather insufficient, which may slow down the acceleration of further clinical development of nanomedicines. Main key drivers for the clinical failure of the nanomedicines are the poor understanding of heterogeneity in the diseases, patient population, and inability to tailor the nanomedicines according to the tumor biology or the cancer progression stage of the target patients.^[106] Thus, understanding the correlation between patient, biology, tumor and the nanomedicines' behaviour is critical for the optimal clinical outcome of the nanomedicines. In this respect, implementing the concept of patient pre-selection allows to identify the right patients for a better therapeutic response from the nanomedicine therapy, which can contribute to the success of cancer nanomedicines in the clinic (Figure 6).^[106,220] Identifying clinically relevant companion diagnostic/imaging modalities or clinical biomarkers can be a useful strategies for preselecting the patients by screening, thereby helping to predict the therapeutic outcomes of the cancer nanomedicines. Eventually, it may help clinicians to determine whether the patient will respond to the nanomedicine therapy prior to the initiation of the cancer treatment process. However, the patient preselection is highly challenging for nanomedicines as it should be aligned for both nanoparticles and payload anti-cancer drugs. So far, efforts to utilize the patients preselection in the development of nanomedicines is gained only limited attention. Recently, it was shown that carboxymethyl dextran-coated magnetic particle (MNP) (size of 30 nm) can be used as companion diagnostics to stratify the tumors accumulation rate and predict the therapeutic response of the subsequent paclitaxel/docetaxel loaded PEG-PLG nanoparticle (size of 100 nm) as a

Figure 6. Rationale of patient pre-selection strategy for choosing the right patients to predict the maximum therapeutic benefit of cancer nanomedicines. Identifying the patients likely to respond to the nanomedicines therapy using companion diagnostic/imaging agents or theranostic nanomedicines that can help to obtain the information about the cancer tumor accumulation and EPR characteristics (as predictive marker) and potential anticancer activity in heterogeneous patient populations. The nanomedicines can be assigned if the patient shows significant accumulation (moderate to high) and excluded if the patient shows both low and high off-target accumulation. Based on reference [220].

model nanomedicine treatment in xenograft tumor models.^[221] Tumor accumulation and distribution of MNP was imaged by clinical MRI and high resolution intravital microscopy to categorize the different levels of tumor accumulation (high-moderate-low). While tumors with low accumulation of diagnostic MNPs after the treatment with nanomedicines shown less therapeutic response, faster tumor growth, whereas high-MNP accumulation had higher therapeutic response and did not show any increase in the tumor size. Furthermore, different tumor accumulation levels of diagnostic MNPs were significantly correlated with docetaxel loaded nanomedicines, where the high MNP accumulation evidence 25-fold high docetaxel. Although these two nanoparticles are different in size, composition and cellular level distribution in tumors, MNPs can be highly useful in predicting the suitability of nanomedicines treatment that can greatly increase the clinical efficacy. In this line, some early stage clinical studies suggest that the pre-selecting specific population of cancer patients based on their likelihood of being susceptibility to the EPR and accumulation of nanomedicines via the ERP, may eventually enable the clinical success of cancer nanomedicines.^[222,223] For example, in human patients, in order to predict the therapeutic response of irinotecan-based liposomal nanomedicines (MM-398), the same patients were pretreated with ferumoxytol (Feraheme™), a FDA approved nanomedicine for iron deficiency anaemia, as marker to predict the EPR

characteristics in human patients.^[88,224] A positive correlation between the uptake of ferumoxytol in tumors and tumor regression following the irinotecan liposome treatment was observed. Although this pilot clinical data suggests that such a companion diagnostic tools can be highly beneficial for patient pre-selection, this also warrants large studies to clinically validate them. Investigating in the development of a generalized approach of such companion diagnostics to other nanomedicines (mostly for passively targeted), where the higher accumulation is the prerequisite for the therapeutic efficacy, can be beneficial for increasing the translation potential of nanomedicines. These clinically relevant companion diagnostics/imaging modalities can also be used to predict the potential side effects for patients preselection in addition to the tumor accumulation and therapeutic response. For example, the patients can be excluded from the nanomedicines treatment if they are predicted to accumulate at very high levels in vital organs like brain, heart and other healthy tissues due to altered renal clearance, hepatic excretion or co-morbidities of the patients.^[220]

In addition to the companion diagnostics, screening the patients for clinically relevant biomarkers that are indicative of specific tumor characteristics or correlate with increased therapeutic response of any specific patient population can be highly useful to predict clinical outcomes and to identify the patient respond to the therapy.^[225] For example, FDA approval

of anti-cancer treatment of trastuzumab (Genentech/Roche) in breast cancer patients is based on their ability to predict the treatment response by preselecting the patients using biomarker analysis of ERBB2(HER-2) tyrosine kinase receptor over expression, which is found to be in only 25–30% breast cancers and determine the decision of therapy.^[226] Recent studies also attempt to identify the biomarkers for predicting the EPR, in which tumor accumulation of PEGylated liposomes was shown to significantly correlate with the ratio of serum matrix metalloproteinase (MMP-9) and tissue inhibitor of metalloproteinase (TIMP1) levels in the systemic circulation.^[227] All these can be used as potential biomarkers for predicting the EPR response in tumors. However, the predictive biomarkers may also differ in levels depending on the tumor biology, progression stage and anticancer drugs response in individual patients. Thus, using single biomarkers might not be sufficient to effectively predict the treatment outcome of diverse patient population, demanding for developing combination of biomarkers. Indeed, it is challenging to identify the predictive biomarkers in humans to better correlate the nanomedicines' efficiency in cancer therapy, and as tumor genotyping progresses rapidly, it can most likely facilitate the patient screening to optimize the therapeutic outcome towards personalized therapy in the future. In this respect, the advances in molecular targeted therapies offer the possibility to patient preselection and personalized therapeutic options that can dramatically improve the clinical outcome of the nanomedicines in cancer patients.

Given that the average success rate from clinical trial studies to approval of therapeutics is very low (10%),^[228] the risk of failure in clinical studies is very high. Therefore, a small mistake in selecting the appropriate patient population can lead to disappointing clinical results. For example, Opaxio™, a polyglutamic acid-paclitaxel conjugate that is based on the cathepsin-B activation, has been developed for the treatment of non-small lung cancer. Interestingly, in phase III clinical trials, the patient survival benefits have been observed only in women and an underlying reason was found to be the role of oestrogen levels in cathepsin-B activation.^[229] From this clinical trial results, Opaxio™ developed a strategy to restrict the clinical studies only in women with specific oestrogen levels, which allowed them to go the next stage of clinical translation. However, unlike Opaxio™, most of the nanomedicines fail in the clinical translation due to the depressing clinical efficacy or toxicity that are unknown. Often, the route cause for the devastating clinical translation are mainly associated with various biological factors that are multifactorial and further complexities exist in individual patients with different stage of cancers, pre-treatments and co-morbidities.^[106] It is noteworthy that forecasting all these multiple variable factors solely from preclinical studies is highly challenging. Thus, it is highly important to understand the clinical process and to integrate the clinicians in the development of nanomedicines to develop a successful translation strategy in the early stages of research.

6. Challenges in Clinical Translation of Cancer Nanomedicines

Therapeutic success of nanomedicines mainly relies on the optimal physicochemical characteristics of the nanomedicines.

Controllable and reproducible synthesis of the nanoparticles in terms of precise control over maintaining different physicochemical properties in parallel, is still challenging. In this direction, microfluidics platforms have gaining increasing interest due to ability of rapid production, narrow size distribution with better polydispersity, increased batch-to-batch reproducibility, thereby exhibiting better controllability over the physicochemical properties of nanomedicines.^[230–232] In addition, the microfluidics platform is more promising to fulfill scale-up and on-line quality control processes.^[233,234] The characterization of nanomedicines is the key to correlate the physicochemical properties to toxicological and biological responses.^[235,236] The nanomedicine characterization and their quality control is highly challenging due to the intrinsic polydispersity of nanoparticles (heterogeneity) that can cause the discrepancy in the nanomedicine properties. Furthermore, often characterization of the properties of nanomedicines has been performed without considering the encountering of complex physiological environments, where nanomedicines can interact with blood, biological fluids and cause aggregation/agglomeration, and protein corona formation that can alter their properties.^[237,238] As a consequence of the alterations in the physicochemical properties, the in vivo biological effects like biological functions and therapeutic performance of the nanomedicines can be largely affected. Thus, it is important to develop more efficient quantitative analytical methods and standardized characterization methods that are reflecting clinically relevant conditions.

Developing more advanced and new nanomedicines, such as theranostic, multifunctional and multistage nanoparticles also potentially bring additional technical challenges in large scale manufacturing. the preparation of this complex design nanomedicines involves often multi-step processes or intricate technologies that can increase the complexities in chemistry, manufacturing and control (CMC). While large scale manufacturing of simple nanomedicines with single drugs, such as liposomes or polymeric systems was possible due to their simplicity and ability to be easily adopted to standard manufacturing unit operations available in pharmaceutical industries, the advanced nanomedicine might demand a large rearrangements in the standard manufacturing unit operations or even require development of new manufacturing processes/units that present further CMC and good manufacturing practice challenges in industrial level production. Thus, the optimization of the preparation of complex designs of nanomedicines using simple steps without the requirement of multi-step processes and development of scalable manufacturing processes that can be adopted to large scale production or in line with standard manufacturing unit operations, is highly crucial in the pipeline in the development of nanomedicines. In scale-up production of nanomedicines, reproducibility is the constant challenge, particularly in terms of batch-to-batch variation. In addition, lack of standard methods to analyze the impurities and contaminations in the final product can compromise the quality control process. Controlled scale-up manufacturing process is also challenging that requires to identify and evaluate the sensitivity of the product to subjected manufacturing process and related processing conditions that can influence properties and functions of the product and, ultimately, the therapeutic performance. Prolonged storage conditions may

cause aggregation behaviour, releasing of therapeutics (biodegradability) that affects the properties or therapeutic activity of nanomedicines. Therefore, after the scale-up process, analyse and validation on long term stability and shelf-life upon storage conditions, are highly required.

7. Future Perspectives of Cancer Nanomedicines

7.1. Bridging the Knowledge

Only by understanding the problem, solutions can be developed. Likewise, only by gaining a deeper understanding in cancer nanomedicines it can be possible to develop efficacious cancer nanomedicines for clinical translation. As cancer nanomedicines are a multidisciplinary area of research, the fundamental problem is the knowledge gaps that exist in understanding the cancer nanomedicines from a vantage point. Material scientists, chemists and engineers can develop more robust methods/technologies to design, synthesize, characterize and engineer versatile nanoparticles/nanosystems with increasing complexities, which in turn alleviate the obstacles in complex chemistry, manufacturing and control during the late stage of the nanomedicines development toward commercialization. Engineered nanoparticles with versatile bio-physicochemical properties can serve to improve the understanding of interactions between the nanoparticles with both physiological and biological environments.

The expertise of pharmacists can dictate the suitability of anticancer agents, nanoparticle drug delivery systems, and drug release rate. Understanding both the pharmacokinetics and -dynamics is highly required to tune the therapeutically active concentration of drugs in target tissue. For tumor biologists, tumors are highly complex and heterogeneous both pathophysiologically and genetically. It is now clear that the cancer tumor microenvironment differentially varies depending on multiple parameters in distinct tumor, which determines the EPR characteristics and the nanomedicines' behaviour after reaching the tumors. Therefore, understanding the tumor and the multifaceted TME will allow to ascertain the abnormal pathophysiological process that can be modulated for efficacious cancer therapy.

From the clinicians' prospective, heterogeneous cancer tumor features with inter- and -intra patient variation can significantly influence the therapeutic outcome in targeting the patient population. Patient stratification to pre-selecting the right patients, who are expected to gain maximum benefit from the therapy, is highly required to improve the clinical performance of the cancer nanomedicines.

Undoubtedly, extensive efforts have been made to advance the understanding of cancer nanomedicines in terms of preparation/formulation development and cancer biology. These advancements in knowledge is rather segmented in specific research areas and challenges, yet interconnecting the knowledge to understand the big picture of cancer nanomedicines is still limited. A multidisciplinary effort is required to bridge the knowledge by cross cutting the borders of the different related research fields to advance our full understanding in cancer nanomedicines. Taken all together, the diversified cancer

nanomedicine field, complexities and heterogeneity of both nanomedicines and cancer tissue, it requires highly diverse expertise to develop clinically translatable cancer nanomedicines (Figure 7). Therefore, it is compelling to build a multidisciplinary and strategic collaborative frameworks between different research areas by integrating material scientists, chemists, engineers, pharmacists, biologists and clinicians to capitalize the knowledge and expertise of each partner in the very early preclinical development phase of nanomedicines for a common goal. Overall, investing in fulfilling the knowledge gaps by reinforcing the fundamental principles and understanding in cancer nanomedicines can have great impact on bringing the efficacious cancer nanomedicines to the therapy of cancer patients.

7.2. Paradigm Shift to Disease Specific Nanomedicines

In the past years, the development practices of standard cancer nanomedicines has been mainly driven by the technological development: generally, it starts with the design and development of nanoparticles/nanosystems with possible variety of advanced functionalities and then evaluated in a series of in vitro assays (e.g., cytotoxicity, cell uptake, and anti-cancer activity studies), followed by in vivo pharmacokinetic, biodistribution and anti-tumor targeting studies using xenograft models. Various attempts have been made to surmount the obstacles in attaining maximum therapeutic efficacy in patients by developing wide varieties of new nanomedicines. From this large pool of promising preclinical nanomedicines only few managed to reach the clinical care. Although this archetype greatly generated extensive preclinical information in the proof-of-concept stages that can allow the optimization in the further development of new nanomedicines, the late stage development remains stagnant. Therefore, this practice has not effectively enabled the successful clinical transformation of cancer nanomedicines and yet not fulfilled the expected therapeutic benefits for the patients. The huge gap in translating cancer nanomedicines is calling for a paradigm shift to change the current development practices of nanomedicines toward a disease (cancer)-specific development strategies of nanomedicines in an early phase of the development process. A cancer-specific strategy must focus on aligning anticancer agents, nanoparticle systems, drug release, tumor characteristics, and target patient population to balance the multiple variables in order to augment the therapeutic benefits in patients.

For such a cancer-specific strategy, the first key step is to choose the cancer type that is intended for developing nanomedicines for cancer treatment. For example, the knowledge of clinicians and tumor biologists is required to understand the tumor characteristics of specific tumor types, whether tumor is complex with highly dense stroma like in pancreatic cancers or highly vascularized like in renal cancers, which can either limit the penetration or retention of nanomedicines, respectively. This can be interconnected to pharmacists to determine whether sustained release or rapid release of drugs from nanomedicines is required depending on what kind of limitations tumors presenting to the nanomedicines. Furthermore, the input from pharmacist is vital to select suitable anti-cancer

Figure 7. Multi-disciplinary effort for creating nanomedicines by integrating material scientists, chemists, engineers, pharmacists, biologists and clinicians aiming at the development of clinically translatable strategies. Bridging the knowledge gaps by cross-cutting the borders of the different related research fields is the key to advance our full understanding in cancer nanomedicines.

drugs (single or combination) sensitive to specific tumors, to achieve therapeutically active doses and to avoid off target effects. With these prerequisite, material scientists, chemists, engineers can design and develop appropriate nanoparticles with desired bio-physicochemical properties required for specific cancers.

Cancer specific nanomedicines aiming to address well-defined challenges in any particular cancer may have more chances of success than a standard technology based on nanomedicines development. Taken all together, the availability of a large array of nanoparticle designs, advancements in nano-engineering, the bio-physicochemical properties of nanoparticles, increasing understanding of nano-bio interactions, tumor and patient biology, can embrace to adopt a disease-specific nanomedicines practice for a particular cancer from the upfront of the developmental stage of cancer nanomedicines. Even though complex to consider the cancer and patient specific parameters in an early design, this can certainly foster the successful translation of cancer nanomedicines to the clinical care.

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Conflict of Interest

The authors declare no conflict of interest.

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