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Cancer Nanomedicine and Immune System—Interactions and Challenges

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Nanoparticles have tremendous therapeutic potential in the treatment of cancer as they increase drug delivery, attenuate drug toxicity, and protect drugs from rapid clearance. Since Doxil®, the first FDA-approved nanomedicine, several other cancer nanomedicines have been approved and have successfully increased the efficacy over their free drug counterparts. Although their mechanisms of action are well established, their effects towards our immune system, particularly in the tumor microenvironment (TME), still warrant further investigation. Herein, we review the interactions between an approved cancer nanomedicine with TME immunology. We also discuss the challenges that need to be addressed for the full clinical potential of ongoing cancer nanomedicines despite the encouraging preclinical data.

Keywords: tumor micoenvironment, immunogenicity, hypersensitivity, cytotoxicity, drug development

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TUMOR IMMUNOLOGY

Tumor immunology is the interaction between cells of the immune system with tumor cells which lead to our understanding in the mechanisms of both tumor rejection and tumor progression (Copier and Dalgleish, 2013). In cancer, tumors may undergo "spontaneous regression" in which a tumor disappears on its own. This phenomenon can be attributed to the active immune system that is triggered by a secondary immune stimulation such as an active infection, which can then initiate an antitumor cell immune response (Tadmor, 2019).

In principle, our immune system protects us against cancer through three primary roles which are 1) elimination of the potentially virus-induced tumor infection, 2) prompt resolution of inflammation that is conducive for tumorigenesis, and 3) identification and elimination of tumor cells based on their expression of tumor-specific antigens (Swann and Smyth, 2007). The third process is called immune surveillance that ideally eliminates all tumors promptly upon identification of their antigen. However, some malignancies appear to escape immune surveillance by either inducing tolerance rather than an active immune response or the immune system eventually is too overwhelmed and hence the tumor progresses (Ostrand-Rosenberg, 2008; Mak et al., 2014).

In immune surveillance, tumor antigens (TAs) play important parts in the development of the tumor microenvironment (TME). They generally fall into two classes, tumor-associated antigens (TAAs) and tumor-specific antigens (TSAs), TAs are presented by major histocompatibility complex (MHC) I and II on the surface of tumor cells and trigger immune response in the host (Mak et al.,

2014). TAAs are normal proteins or carbohydrates expressed in a way that is abnormal relative to its status in the healthy, fully differentiated cells in the surrounding tissue of origin. For example, they may be expressed in abnormal concentrations and at wrong locations and times. Meanwhile, TSAs are new macromolecules that are unique to the tumor and are not produced by any type of normal cells. Due to their non-self nature, TSAs constitute true immunogens capable of eliciting an immune response. Overall, TAs can be categorized into several types including oncofetal, oncoviral, overexpressed or accumulated, cancer-testis, lineage-restricted, mutated, post-translationally altered, and idiotypic (Zarour et al., 2003). Hence, identification of TAAs and TSAs serve as a reliable biomarker for tumor diagnosis as well as a target for the development of cancer vaccines (Aly, 2012).

In the TME, there are two possible interactions that might happen. First is the antitumor immunity that works to prevent tumorigenesis in the first place (Munhoz and Postow, 2016). In antitumor immunity, both innate and adaptive immune responses are activated by TAs leading to tumor control. In this immunity, leukocytes such as tumor-infiltrating lymphocytes (TILs) which are mature $CD4^+$ or $CD8^+$ or B cells directly respond to the presence of a tumor cell (Mak et al., 2014). The second interaction is the evasion of antitumor immunity or immune escape as the immune system does not always succeed in controlling tumorigenesis. It is widely accepted that tumor immunoediting is a dynamic process that not only involves antitumor immunity, but shapes the immunogenicity of developing tumors as well. There are three distinct phases of tumor immunoediting which are elimination, equilibrium, and escape (Muenst et al., 2016). All three phases of tumor immunoediting are manifested through metabolic and cellular changes, in which the differences influence different types of cancer (Teng et al., 2008; Wenbo and Wang, 2017).

Elimination is a phase where evolving tumors are successfully rejected by the innate and adaptive immune response through various mechanisms (IFNγ, Perforin, TRAIL, IFNα/β, NKG2D) (Swann and Smyth, 2007). Then, some of the tumor cells that are not completely eliminated may enter the equilibrium phase when the immune system controls tumor outgrowth and tumor cells enter a dormant state or continue to evolve over a period of time (Dunn et al., 2004). In this phase, the constant interaction of tumor cells with the immune system over a period of time may edit the phenotype of the developing tumor into a less immunogenic state (Teng et al., 2008). Being in this state, the tumor cells are no longer susceptible to immune attack and this is where the tumor cells may escape from immune control and proliferate in an unrestricted manner, leading to clinically apparent tumors (Muenst et al., 2016). According to Mak et al., 2014, there are two forms of escape from immune control that are thought to be associated with all TMEs, regardless of which leukocytes respond to the malignancy. First is the abnormal property of the tumor vasculature comprised of capillaries that wind in and out of a tumor mass that hinder leukocyte extravasation into the tumor site. The second form of escape is from the elevated levels of plasma TGFβ that is established to promote malignant transformation of fibroblasts and stimulate angiogenesis within the tumor, termed as immunosuppression.

DEVELOPMENT OF APPROVED NANOMEDICINE

Over the years, the Food and Drug Administration (FDA) in the US and its equivalent in the EU, the European Medicines Agency (EMA), have certified a number of nanomedicine-based drugs for cancer diagnostic and therapeutic purposes, and many other formulations are currently being evaluated (Martinelli et al., 2019). Worldwide, nearly 250 formulations based on the nanotechnology platform have been approved for the market or are in various clinical stages for evaluation (Bremer-Hoffmann et al., 2018) (**Table 1**). The approval process for nanomedicine in humans regulated by the FDA is essentially the same as for any other regulated drug, device, or biologic (Eifler and Thaxton, 2011). According to the FDA, development of a drug and its approval is categorized into three major phases as outlined in **Figure 1**. Following discovery of the material, the pre-clinical phase of testing usually involves animal studies to demonstrate the efficacy, safety, and toxicity profile and to identify appropriate dose ranges (Tinkle et al., 2014). The FDA approval process is time consuming, labor intensive, and rigorous, hence it is estimated that it takes approximately 10–15 years to develop a new medicine (DiMasi et al., 2003). For nanomedicine, the important aspect regarding its R&D, highlighted by the FDA, is the comprehensive characterization of the nanomaterial considering its efficacy, toxicity, and physiochemical properties (Bobo et al., 2016). These findings are compiled into an Investigational New Drug (IND) application for FDA consideration. Upon approval of an IND, clinical trials, which are divided into three phases, are conducted to determine the safety and efficacy of the new nanomedicine. Since 2005, more than 30 new and abbreviated drug applications involving nanomaterials have been approved by the FDA (D'Mello et al., 2017). This is remarkable for a newly developing field. By comparison, for recombinant proteins and for antibody-based therapeutics, it took almost 2 decades of developments before the first drugs started to make it to the market (Reichert, 2003). More than 50 drug products containing nanomaterials are FDA approved for clinical use and more than a dozen of them have been approved in the last decade (Bobo et al., 2016; D'Mello et al., 2017).

EFFECT OF NANOMEDICINE TOWARDS IMMUNE RESPONSES

Previously, most cancer therapies were designed to directly killed/removed tumor cells either by pharmacological agents, surgery, or radiotherapy. Then it moved to targeted therapy when specific drugs with some molecular targets such as selective kinase inhibitors and monoclonal antibodies were developed (Falzone et al., 2018). While these therapies significantly improved quality of life as well as survival of cancer patients, variable efficacy and

TABLE 1 | Approved nanomedicine in cancer.

Type	Nano medicine	Nanomaterial	Active substance	Indication	Approval year	Advantage	Reference
Liposome	Doxil/Caelyx	PEGylated liposome	Doxorubicin	Ovarian cancer Multiple myeloma HIV-related kaposi sarcoma	2005 2008 1995	Improved delivery Decrease systemic toxicity Less cardiotoxic	Barenholz (2012), Tejada-Berges et al. (2014)
	DaunoXome	Liposome	Daunorubicin	HIV-related kaposi sarcoma	1996	Improved delivery Decrease systemic toxicity Less cardiotoxic	Pillai (2014)
	Myocet	Non-PEGylated liposome	Doxorubicin	Metastatic breast cancer	2002	Less cardiotoxic	Batist et al. (2005)
	Marqibo	Liposome	Vincristine sulfate	ALL	2012	Improved delivery Decrease systemic toxicity	Pillai and Ceballos-Coronel (2013)
	Mepact	Liposome	Mifamurtide	Bone sarcoma	2009	Improve OS	Hartmann et al. (2013)
	Onivyde	Liposome	Irinotecan	Pancreatic cancer	2015	Reduced AE	Havel et al. (2016)
	Vyxeos CPX-351	Liposome	Cytarabine Daunorubicin	AML	2017	Improve OS	Krauss et al. (2019)
	Depocyt	Liposome	Cytarabine	Lymphomatous malignant meningitis	1999	Improved delivery Decrease systemic toxicity	Patra et al. (2018)
Inorganic and metallic	NanoTherm	SPION	Aminosilane	Glioblastoma	2010	Less invasive ablation therapy Reduce risk of overtreatment	Massadeh and Al Aamery (2016)
Protein	Abraxane	Albumin	Paclitaxel	Breast cancer NSCLC Pancreatic cancer	2005 2012 2013	Increased solubility Reduced IR —	Gradishar et al. (2005), Fu et al. (2009)
	Ontak	Recombinant DNA-derived cytotoxic protein	IL-2 and diphtheria toxin	Cutaneous T cell lymphoma	1999	Targeted delivery	Ventola (2017)
	Oncaspar	PEGylated protein conjugate	L-asparaginase	Acute lymphoblastic leukemia	2006 2016	Improved stability of drug load	Brandenburg et al. (2020)
Polymer	SMANCS	Polymeric conjugate	Neocarzinostatin	Hepatocellular carcinoma	1994	Decrease toxicity	Maeda (2001)
	Genexol-PM	Polymeric micelle	Paclitaxel	NSCLC Breast cancer Ovarian cancer	2006	Controlled drug release Targeted delivery —	Guo et al. (2016)
	Eligard	Polymeric NPs	Leuprolide acetate	Advanced prostate cancer	2002	Controlled drug release Longer circulation time	Sartor (2003)

HIV—human immunodeficiency virus, SPION—superparamagnetic iron oxide nanoparticle, NSCLC—non-small cell lung cancer, AML—acute myeloid leukemia, ALL—acute lymphoid leukemia, PEG—polyethylene glycol, AE—adverse event, OS—overall survival, IR—immune response.

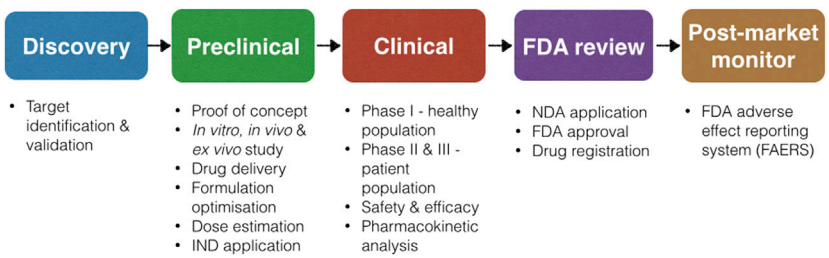

FIGURE 1 | Process of new drug development according to the FDA, adopted from (Lipsky and Sharp, 2001).

safety issues persistently limited the full capacity of cancer therapies. Nanomedicine offers these therapies a better targeting approach that would increase drug accumulation into a tumor without affecting other healthy cells, thus reducing systemic toxicities (Gao et al., 2019). Furthermore, nanomedicine is established to address several issues with current cancer therapies including the low response rate of free drugs as well as the emergence of drug resistance. Like the drug itself, introduction of NPs would induce a different interaction in the body, particularly with the immune system, either targeted or spontaneous.

Immunogenicity

Cancer chemotherapy is often immunosuppressive and drug resistance usually occurs after a short period of tumor shrinkage. Certain chemotherapeutic drugs such as doxorubicin have the potential to increase tumor immunogenicity through activation of immunogenic cell death (ICD). ICD is defined as the chronic exposure of damage-associated molecular patterns (DAMPs) in the TME, which provide long-lasting antitumor immunity (Zhou et al., 2019). Doxil is shown to increase the expression of CD80 on mature dendritic cells which activate an anti-tumor T cell response (Rios-Doria et al., 2015), improve macrophage immunostimulatory (M1) content in tumor tissue and efficacy of immune checkpoint blocking antibodies anti-CTLA-4/anti-PD-1 (Panagi et al., 2020), upregulate MHC-1 and Fas, and sensitize CTL killing and Fas-mediated death *in vitro* (Alagkiozidis et al., 2009). Meanwhile, Abraxane is taken up by macrophages *via* macropinocytosis which induces M1 cytokine expression and promotes nitric oxide synthase expression, thus increasing cytotoxicity towards tumor cells (Cullis et al., 2017). Furthermore, Abraxane is shown to enhance drug uptake and penetration into tumors *in vitro*, hence the superior efficacy in numerous cancer types compared to Taxol alone (Yuan et al., 2020).

Mepact is a liposome conjugated to a synthetic analog of a bacterial cell wall component and is used as an adjuvant in standard chemotherapy. This potent, non-specific immunomodulator mediates the activation of monocytes and macrophages, thus modulating the balance of immune responses such as increased circulating TNF and IL-6 (Punzo et al., 2020). Not only that, Mepact is demonstrated to be a possible anti-resorption agent by reducing pro-osteoporotic markers, thus explaining the improved overall survival from osteosarcoma (Ando et al., 2011; Bellini et al., 2017). Oncaspar, a PEGylated form of native *Escheria coli*-asparaginase is indicated for treatment of acute lymphoblastic leukemia. The PEGylation showed diminished asparaginase immunogenicity without affecting its enzymatic properties (Heo et al., 2019). Reduction of Oncaspar's immunogenicity is portrayed by the decrease of neutralizing antibodies that may induce hypersensitivity and/or loss of enzyme activity. Ontak is an engineered fusion protein of IL-2 and diphtheria toxin that targets the IL-2 receptor, such as CD25 on tumor-infiltrating cells regulatory T cells (Tregs), the internalization releases diphtheria toxin, causing apoptosis (Foss, 2006). The effect of Ontak on immunosuppressive Tregs further enhances anticancer immune responses. Furthermore, CD25 that can be targeted by the IL-2 fusion protein on Ontak is also present on lymphoid tumor cells and dendritic cells effector T cells, making this recombinant protein a great pharmacological intervention strategy (Lutz et al., 2014). However, due to production issues related to bacterial immunotoxin, Ontak was discontinued in 2014 although currently there are several Ontak-like formulations under development that use other bacterial expression systems (Shafiee et al., 2019).

TME Normalization

The tumor microenvironment (TME) consists of a complex ecosystem with blood vessels, immune cells, fibroblast, extracellular matrix, cytokines, and hormones that promote the growth of cancer. So, the normalization of the TME to a normal tissue environment may inhibit the growth of cancer and improve cancer therapeutics including checkpoint blockers and TNFR agonists. In *in vitro* studies, nanoparticles such as gold have been demonstrated to facilitate TME normalization, increase blood perfusion, and reduce hypoxia (Li et al., 2016; Li et al., 2017; Xiao et al., 2017). Instead of playing a role in TME normalization directly, the efficacy of nanomedicine is enhanced when adjuvanted with several approaches of TME normalization including anti-inflammatory agents, immune checkpoint blockade, and stromal and tumor vessel normalization (Zheng and Gao, 2019). Furthermore, studies showed that TME normalization improves the delivery of nanomedicine in a size-dependent manner (Chauhan et al., 2012). Delivery of Doxil, with a diameter of ~100 nm is hindered upon normalization of blood vessels by the VEGFR-2 blocker while enhanced delivery of the smaller diameter Abraxane was demonstrated, hence greater accumulation within the TME. Meanwhile, Onivyde, liposomal irinotecan, is shown to enhance accumulation of active metabolites within the TME, thus improving its antitumor activity with minimal systemic toxicity (Zhang, 2016). Another issue in pharmacological intervention in cancer that needs to be addressed is their defective vasculature. Due to this, macromolecules such as drugs could not be retained in tumor cells and leak out into interstitial space, limiting its efficacy. Nanoparticles, due to their physiochemical properties, could be utilized to address this issue using the principle of enhanced permeability and retention (EPR) (Maeda, 2017). SMANCS, a conjugate of a hydrophobic polymer with antitumor Neocarzinostin is the first nanomedicine using this EPR principle, was developed to selectively deliver drugs to solid tumors and prolong intratumoral concentration of the drug (Maeda, 2012).

Tolerability

Chemotherapy is known to induce several side effects such as myelosuppression, cardiotoxicity, and even skin toxicity which is a dose-limiting factor that often limits drug efficacy. Since chemotherapy suppresses the hematopoietic system and impairs its protective mechanism, neutropenia is one of the serious adverse events associated with the risk of life-threatening infections. Doxil is reported to be much less toxic to the immune system than free doxorubicin with comparable efficacy (O'Brien et al., 2004). In a systematic review, Abraxane is demonstrated to induce a higher number of hematological toxic effects (neutropenia, leucopenia, increased alanine aminotransferase and aspartate aminotransferase) and frequent

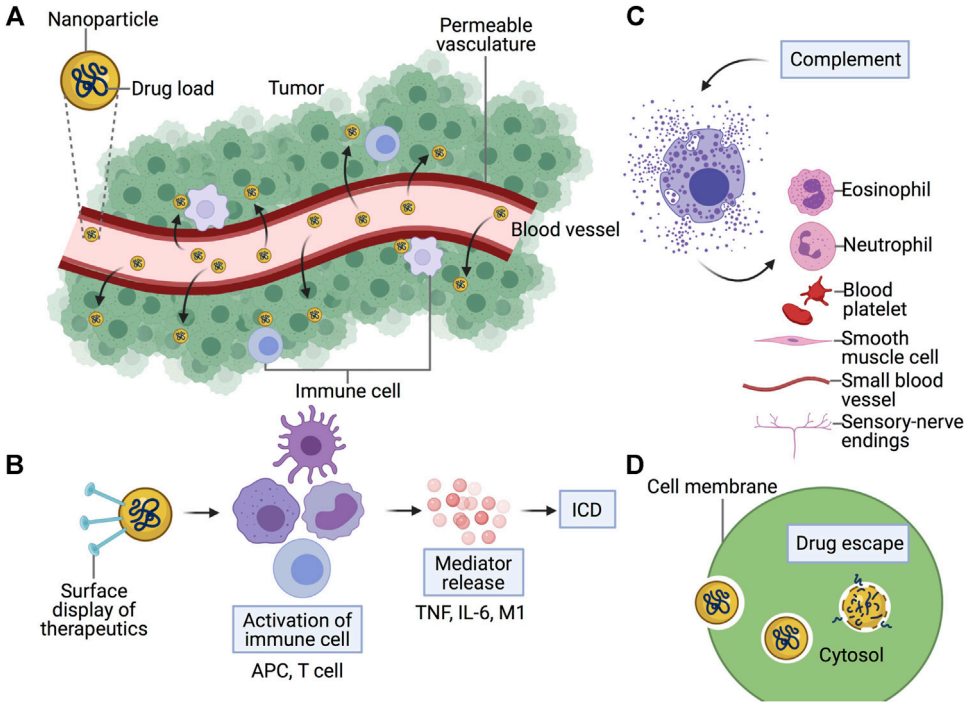

FIGURE 2 | Immune responses of cancer nanomedicine. Combination of nanoparticles with cancer drugs induce a different effect towards immune responses compared to free drugs in terms of **(A)** Normalization of the tumor microenvironment, **(B)** Immunogenicity, **(C)** Hypersensitivity, and **(D)** Tolerability. **(A)** Due to permeable vasculature in the tumor microenvironment, nanomedicine is designed with an enhanced permeability and retention (EPR) effect to enhance the effect of the drug. **(B)** Upon introduction of nanomedicine, immune cells such as antigen-presenting cells (APC) and T cells promote the release of mediators and induce immunogenic cell death (ICD) pathways. **(D)** Nanomedicine is demonstrated to increase the tolerability of drugs due to targeted release into tumor cells. **(C)** However, nanomedicine could provoke the immune response to release complements responsible for hypersensitivity reactions. Created with BioRender.com.

non-hematological toxic effects (peripheral sensory neuropathy) compared to the free drug-paclitaxel group (Zong et al., 2017). Abraxane is also reported to cause drug-induced immune hemolytic anemia, a rare but fatal adverse event that affects only one patient in a one million population (Thomas and Shillingburg, 2015). Marqibo is designed to overcome the dosing and pharmacokinetic limitation of Vincristine. Marqibo is demonstrated to increase the circulation time with targeted and intense delivery of Vincristine without augmented toxicities including hematologic toxicity (Deitcher et al., 2014). Most common adverse events for Onivyde and Vyxeos are neutropenia, abdominal pain, and diarrhea that are considered manageable, except for prolonged severe neutropenia in patients receiving Vyxeos (Zhang, 2016; Tzogani et al., 2020). Cardiotoxicity is another toxicity induced by chemotherapeutic drugs including nanomedicine. Doxil and Daunoxome are both demonstrated to reduce the rate of cardiotoxicity compared to their free drugs, Doxorubicin and Daunorubicin, which are significantly limited by dose-dependent cardiotoxicity (O'Brien et al., 2004; Fassas and Anagnostopoulos, 2009). Palmar-plantar erythrodysesthesia or hand-foot syndrome is a type of skin toxicity that could develop from some cancer treatments. This type of skin toxicity is demonstrated to often occur in patients receiving PEGylated liposomal doxorubicin such as Doxil (Huang et al., 2018; Ni et al., 2020). Polymer-based nanomedicine including Genexol and Eligard are demonstrated to show good safety profiles in terms of the absence of increased toxicities and occurrence of adverse events (Sartor, 2003; Kim et al., 2004).

Infusion-Related Reaction

Hypersensitivity upon administration of a variety of drugs is common, including nanomedicine formulation. Doxil is reported to cause hypersensitivity, which is a non IgE-mediated allergy caused by activation of a complement referred to as complement activation-related pseudo allergy (CARPA) (Chanan-Khan et al., 2003). The mechanism of CARPA upon administration of Doxil is partly associated with some pre-existing anti-PEG antibodies (Neun et al., 2018). Since solvent-based taxane administration such as paclitaxel induces a high rate of hypersensitivity, albumin-bound paclitaxel, Abraxane, represents a valid treatment option as fewer hypersensitivity reactions towards Abraxane compared to free paclitaxel have been reported (Zong et al., 2017; Parisi et al., 2019). Unlike PEG, the absence of cross-reactivity between a previous history of hypersensitivity towards taxanes and Abraxane indicate the advantageous safety profile of this nanomedicine (Pellegrino et al., 2017). However, another approach of PEGylation of *E. coli* asparaginase in Oncaspar successfully reduced immunogenicity of the enzyme, which subsequently reduced the occurrence of hypersensitivity (Heo et al., 2019). As an immunomodulator, Mepact could activate immune responses

TABLE 2 | Advantages and challenges of nanoparticles to be translated into nanomedicine.

Advantages	Challenges
• As a non-invasive therapeutic vehicle or agent or device for theranostic application on human diseases Poirot-Mazeres (2011)	• Less value was given to toxicity and safety of the patients Seigneuric et al. (2010)
• A smaller size of NPs helps in boosting the theranostic purpose in terms of increasing the drug dissolution rate, saturation solubility, and intracellular uptake of drugs in the human body Bawa (2011), Galvin (2012)	• Theranostic NPs can present unexpected toxic effects compared to usefulness Seigneuric et al. (2010)
• Enhancing bioavailability of drugs at specific sites in the right proportion for a prolonged period of time Galvin (2012)	• Induction of oxidative stress and formation of free radicals lead to further damage of lipids, proteins, DNA, and other biological components through oxidation Bhaskar et al. (2010)
• Targeting only the diseased cells without affecting normal healthy cells Sajja et al. (2009)	• Accumulation, storage, and slow clearance of NPs from the body will lead to toxicity of the organs such as liver and spleen Seigneuric et al. (2010), Galvin (2012)

with a standby effect, thus causing a hypersensitivity reaction such as pericardial effusion (Şimşek et al., 2020). The mechanism of this reaction might be due to both the active and inactive ingredients of Mepact that target immune cells in the lungs (Anderson et al., 2010). The most common related effects for Mepact are chills, fever, and headache in the initial dose and delayed fatigue in the subsequent doses (Jimmy et al., 2017).

In conclusion, incorporation of NPs with cancer drugs induce a different effect towards host immune responses compared to free drugs, either intended or spontaneous. Its immunogenicity, normalization of the TME, tolerability, and other infusion-related reactions could be due to NPs' own physiochemical characteristics or interaction between the drugs (**Figure 2**).

CHALLENGES FOR CLINICAL USE

Although involvement of NPs in human clinical settings increased a decade ago, extensive research to improve biocompatibility and efficacy of NPs is still needed. Despite several challenges that need to be addressed in the application of NPs as a nanomedicine, its advantages outweigh those challenges, making NPs a highly potential tool (**Table 2**).

Despite the abundance of encouraging experimental data on NPs for medical purposes, only a few reach clinical use. This statement is supported by Greish *et al.*, who explored more than 20,000 scientific papers published on nanomedicine, and found of these, only 15 nanoparticle-based anti-cancer drugs had reached the market as of 2017. It is clear that the number of publications claiming to have found new, effective, and safe anticancer formulations, compared to the number of compounds that actually reached the clinic, is remarkably small (Greish et al., 2018). In their review, Greish *et al.* discuss different biological aspects that hinder the clinical progression of cancer nanomedicine, which include misconception of EPR phenomenon, overlooking the acquired pharmacokinetics and clearance of nanomedicine through reticuloendothelial system, and accelerated blood clearance. The limitations of animal models and heterogeneity of human tumors further restricted the clinical application of formulated nanomedicines.

Safety is the most important aspect in the development of new drugs. Although the size of nanoparticles represents their strength, for some nanomedicines it has also brought some shortcomings. The small size of NPs cause some of these particles to accumulate in the spleen and liver, which is a major safety concern in patients (Resnik and Tinkle, 2007). In some cases, the injected doses of nanosized molecules are cleared by reticuloendothelial system cells with a minimal percentage of the drug dose reaching the tumors which lowers the efficacy of the treatment.

Even when some studies reach clinical validation, logistics issues including mass production, consistency, and reproducibility of complex nanomedicine systems are the main hurdles. Furthermore, the controlled and scale-up manufacture of each component, batch-to-batch reproducibility, and stability of designed nanomedicines are essential for approval by the regulatory authorities (Greish et al., 2018). Not only that, regulation and standards for nanomedicine by regulatory bodies are severely lacking and could be geographically differed as one nanomedicine is approved in one country but not in others (Zhang et al., 2020). Due to these challenges (**Figure 3**), hundreds of nanomedicine formulations have failed in different phases of clinical trials, or even worse, some are withdrawn from the market even after its approval.

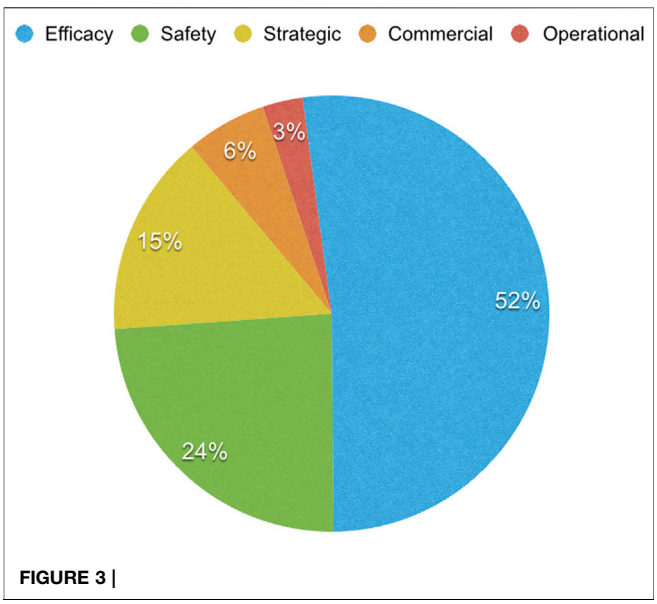

FIGURE 3 |

To overcome these issues, several solutions can be proposed. In order to address the biological challenges of nanomedicine in cancer that is a heterogenous disease, thorough designation of nanomedicine and identification of the right animal models and patients in preclinical investigations should be in mind when designing a new drug entity. Good laboratory practice (GLP) is a standard to ensure the safety and quality of new therapeutics during clinical transition by many countries. However, GLP for nanomedicine has not been made available yet, hence it is imperative to formulate GLP for nanomedicine to enhance its success rate in the market (Zhang et al., 2020). In addressing logistic issues, careful examination of the cost-benefit analysis should be done during the early stage of nanomedicine development.

CONCLUSION

Despite challenges, the latest technologies and advantages of nanoparticles continue to encourage research communities to develop new, better nanomedicines. It is recognized as a proven strategy to alleviate the side effects of cancer therapies and enhance their efficacies. Nevertheless, development of nanomedicine should always accentuate their interactions with host immune responses, as in cancer, it's tangibly interlinked between one another. Although there are several aversions to nanomedicine due to the induction of unwanted hypersensitivity, available findings suggested that targeted approach of nanomedicine provides a favorable effect in the immune system, from its immunogenicity and interaction in the TME to its tolerability. With this understanding of the interaction of nanomedicine with the immune system, the future of nanomedicine is promising as long as the shift to improve the clinical impact of nanomedicine moves alongside it.

AUTHOR CONTRIBUTIONS

SA, RI, WW, and KP wrote this paper. RM, JB, MP, JJ, and JL supervised this work and revised the manuscript. RM acquired funding for this work. All authors contributed to the paper and approved the submitted version.

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