Emerging Role of Nanomedicine in Cancer Theranostics: Targeted Drug Delivery, Mechanistic Insights, and Challenges in Clinical Translation

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Abstract
Nanotechnology has become an innovative platform in modern medicine in which it has become possible to gain unprecedented control over drug delivery, diagnostic imaging and oncologic therapy at molecular and cellular levels. Systems of nanoparticles have unique benefits as compared to traditional therapeutics including improved bioavailability, site selectivity, controlled release dynamics, and reduced systemic toxicity. These characteristics are especially crucial in the field of oncology where localization of tumor and real-time monitoring of therapeutic procedures continue to be important clinical issues. This review is a critical review of recent advances in nanotechnology-based drug delivery platforms, diagnostic imaging modalities and cancer theranostics with a focus on mechanistic insights, material design strategies and translational advances. It talks of key classes of nanocarriers, approaches to target specificity and multifunctional theranostic designs, as well as approved nanomedicines and current clinical trials. Notably, the review outlines the major limitations that had hindered clinical translation, such as, biological barriers, toxicity issues and regulatory challenges. Combining the current evidence and identifying the gaps, the manuscript provides a holistic vision of the role played by nanotechnology in the evolution of precision medicine and outlines the future directions in which the designing and production of clinically applicable nanotherapeutic and diagnostic tools can be developed.

Keywords: Cancer nanomedicine, Drug delivery systems, Diagnostic imaging, Nanotechnology, Theragnostic, Targeted therapy

1. Introduction

The intensive nanotechnological development has greatly redefined the scenario of modern medicine by enabling the creation and manipulation of materials at the nanoscale, which is usually less than 100nm[1]. At this scale, materials have special physicochemical behavior- e.g. increased surface reactivity, optical behavior which is tuneable and interaction with biological systems which can be controlled-behaviors which are not present in their bulk counterparts[2]. These properties have led to the development of nanomedicine which is an interdisciplinary science incorporating nanoscience, materials engineering, biology and clinical medicine to increase disease detection, tracking and treatment. Traditional therapeutic and diagnostic methods are often characterized by the severe drawbacks, such as low bioavailability, nonspecific biodistribution, systemic toxicity and insufficient real-time monitoring of treatment effects[3]. Such issues are acutely felt in the context of treatment of cancer where the inability to selectively target malignant cells will usually lead to adverse side effects characterized by dose limiting and inferior clinical performance. Nanotechnology-based systems help solve most of these limitations by providing the ability to deliver drugs specifically to the location of disease, have controlled release patterns, and integrate both diagnostics and therapeutic functions into a single device[4]. The nanoparticle-based drug delivery has become one of the most thoroughly researched uses of nanomedicine. Such nanocarriers as polymeric nanoparticles, liposomes, metallic nanoparticles, and hybrid systems can be used to encapsulate therapeutic agents and prevent their premature degradation, whereas targeting them in diseased regions is possible via surface functionalization[5]. These approaches will increase the therapeutic effectiveness and reduce off-target toxicity. These systems have been also used in oncology to capitalize on tumor specific characteristics in which case tumor vasculature and cellular metabolism is aberrant, which enhances the accumulation and retention of drug in tumor tissues[6]. At the same time, nanotechnology has made significant contributions to the field of diagnostic imaging by facilitating the creation of nanoscale contrast agents with

improved sensitivity, specificity and multi-modal imaging properties. Engineered nanoparticles that are used in magnetic resonance imaging, computed tomography, optical imaging, nuclear medicine offer a better visualisation of pathological processes at the early stages of disease[7]. The integration of both therapeutic and diagnostic capabilities into a single nanoplatform also referred to as theranostics is a significant milestone in the direction of personalized and precision medicine since it allows monitoring of drug distribution, therapeutic response, and disease progression in real time[8]. Although there has been a lot of improvement, the clinical translation of nanomedicine has not been much. Animal barriers are also biological, immunogenicity, long-term toxicity, manufacturability, and regulatory issues that remain a limitation to extensive clinical use[9]. In addition, new data has undermined conventional thinking including the predominance of the Enhanced permeation and retention (EPR) effect with a strong need to gain more mechanistic insight into nanoparticle-tumor interactions[10]. This review gives a dedicated and critical summary of nanotechnology-based drug delivery system, diagnostic imaging system and a theranostic system against cancer. The focus is based on the principles of material design, mechanism-based, clinical progress, and translational barriers. This paper will combine the latest developments with the existing problems to inform future research on the rational design of nanomedicine platforms with augmented clinical applicability and therapeutic efficacy.

2. Nanotechnology-Based Drug Delivery Systems

The development of nanotechnology drug delivery systems is proving to be some of the most impactful applications in nanomedicine with an explicit challenge to the long-term limitations that affect the conventional treatment plans; specifically, low solubility, low bioavailability, unspecific biodistribution and dose limiting toxicity[11]. Drug delivery platforms may be engineered to engage biological systems at both the cellular and molecular scales by fabricating materials at high nanoscale (usually 1 100 nm) to enable the modulation of pharmacokinetics and pharmacodynamics in a precise manner[12]. Nanocarriers work based on encapsulation, adsorption or conjugation of therapeutic agents and thus protect them in case of premature degradation and provide controlled transport of the therapeutic agents to the target tissues. Notably, nanoscale delivery systems can be configured to overcome biological barriers including enzymatic degradation, renal excretion, and cell membrane impermeability which most of the time compromise the clinical efficacy of standard preparations[13].

2.1. Nanoparticle-based drug carriers

Nanoparticles are colloidal systems based on organic, inorganic, or hybrid substances, where nominal size ranged between 10 and 200nm is used in biomedical applications. This dimensional size is largely viewed as ideal in terms of extended circulation, efficient uptake by cells and reduced clearance by the reticuloendothelial system[14]. The typical nanoparticle systems are polymeric nanoparticles, liposomes, solid lipid nanoparticles, metallic nanoparticles, and ceramic-based systems[15]. Polymeric nanoparticles and liposomes have demonstrated specific levels of success due to their biocompatibility, degradation profiles which can be controlled and their ability to deliver hydrophilic and hydrophobic drugs[16]. By providing additional functionality (e.g. imaging contrast enhancement and photothermal) to metallic nanoparticles, including gold and iron oxide, makes them interesting as a combined therapeutic and diagnostic agent. Physicochemical characteristics of nanoparticles, i.e. size, shape, surface charge, and composition are the decisive factors in determining biodistribution, cellular internalization, therapeutic performance[17].

2.2 Strategies of Targeted Drug Delivery

Delivery of drugs to their intended targets is a key aspect of nanomedicine, and it is hoped that in the future, it will be necessary to deliver therapeutic agents to specific diseased tissues to reduce exposure to normal cells. Strategies of targeting can be classified into passive and active strategies[18]. Passive targeting takes advantage of pathological alterations of abnormal vasculature and lymphatic drainage, especially in tumour tissues to improve nanoparticles engagements[19]. However, new findings demonstrate that passive accumulation is not always sufficient to achieve effective drug delivery, which proves the necessity of more sophisticated approaches. Active targeting involves surface functionalization of nanocarriers with ligands, such as antibodies, peptides, aptamers, or small molecules, that bind receptors that are over expressed on target cells[20]. This ligand-receptor interaction enhances receptor mediated endocytosis, which enhances intracellular drug delivery and therapeutic specificity. Despite its very high levels of precision, active targeting in clinical practice has been hampered by the lack of homogenous target expression and instability of ligands in physiological environments[21].

2.3 Controlled and Stimulus responsive Drug Release

The release of drugs at controlled rates is one of the distinguishing features of nanotechnology within the scope of delivery. Through fine control of nanoparticle composition, structure and surface properties, release kinetics can be controlled to sustain therapeutic concentrations during prolonged times[22]. This controlled release prevents excessive dose toxicity and decreases the number of frequent dosing which enhances patient compliance. State of the art nanocarriers is often targeted to react to some form of internal or external stimulus, including pH or redox gradients, enzymatic activity, temperature, light, or magnetic fields[23]. The stimuli -responsive systems are especially useful in cancer treatment, where the tumour microenvironment has significantly different properties compared to normal tissues. The ability of these so-called smart nanocarriers to target therapeutic efficacy at the site of action increases therapeutic effects and reduces side effects produced by the system[24]. The second action is to increase the Bioavailability of Drugs. Lack of solubility and natural instability

are a significant impediment in the process of developing many therapeutic agents particularly hydrophobic ones[25]. The nanotechnology solutions can attain this effective solution by increasing the surface area, the rate of dissolution, and stabilisation of drugs under the nanoscale carriers. Nanoparticles enhance solubility of poorly soluble drugs and facilitate better systemic distribution and absorption of these drugs in the biological fluids[26]. The increased bioavailability does not only increase the therapeutic effect, but also allows the reduction of dose, which reduces the adverse effect. The advantage has important applications in agents that have small therapeutic indices and long-term treatment courses[27].

2.4 Theranostics Drug Delivery System

A significant change in paradigm in precision medicine is the incorporation of therapeutic and diagnostic functionalities in a single nanoscale system, i. e. called theranostics. Simultaneous drug delivery and real-time imaging Theranostic nanocarriers provide the option of monitoring biodistribution, therapeutic response, and disease progression and allow clinicians to monitor it[28]. Nanoparticles can be designed to deliver therapeutic functionalities and at the same time can be used as contrast agents in imaging techniques like magnetic resonance imaging, computed tomography or optical imaging[29]. This two-fold feature favors individualized treatment plans through adaptive therapy that is informed by feedback in real time. The theranostic platforms, however, have not been translated into practice due to the challenge of translational complexity to design, regulatory passing and manufacturing at large scale[30].

2.5 Limitations in the Current and Translational Problems

In spite of the impressive potential of nanotechnology-based drug delivery systems as demonstrated in preclinical research, it has not been translated to clinical trials.[3] Among the main limitations are the lack of predictable behaviour *in vivo*, immune response, chronic toxicity and there are challenges of producing in-vitro in large scale. Further, the animal models and human physiology are not consistent, thus making it difficult to extrapolate clinical outcomes[31]. The challenges that require to be tackled include standardized characterization guidelines, better interpretation of the nano-bio interactions and better cooperation between the material scientists, biologists and clinicians. The next stage in nanomedicine development will rely on both the technological innovation and regulatory harmonization as well as strict clinical validation[32].

3. Nanotechnology Diagnostic Imaging

Early and accurate diagnosis is a basic requirement that can result in proper disease management, especially in the oncology field, where therapeutic results highly depend on the speed of detection and characterisation of tumours[33]. The traditional diagnostic imaging modalities, including the X-ray imaging, computed tomography (CT), magnetic resonance imaging (MRI), ultrasound, and nuclear medicine have significantly improved clinical practice[34]. However, most of these methods have reduced sensitivity in the early stages of the disease, poor specificity and fail to identify molecular level changes, which occur before morphological changes become visible. Nanotechnology has proved to be a strong tool against these shortcomings and has allowed the creation of more advanced contrast agents and multifunctional imaging probes that are better in performance[35]. The imaging agents based on nanoparticles come with a number of benefits compared to classical small-molecule contrast agents, such as, long circulatory lifetime, enhanced signal levels, accumulation of tissue at the target site, and decreased systemic toxicity. Their tunable physicochemical characteristics, including size, surface chemistry, and composition, allow their specific optimisation to specific imaging modalities and clinical indications[36].

3.1 Nanoparticles as Imaging Contrast Agents

The use of nanoparticles as contrast-enhancing agents on numerous imaging platforms has been thoroughly explored. Having high surface area-to-volume ratio, they can be easily loaded with imaging moieties, and surface modification can be used to target them selectively to pathological bodies. In X-ray and CT, nanoparticles with high atomic number like gold nanoparticles have been found to yield better X-ray attenuation as opposed to the traditional iodine-based agents[37]. Gold nanoparticles have favourable biocompatibility properties and can be designed to mitigate metal related toxicity by encapsulating dense cores in inert shells[38]. Their selective concentration in tumours also increases the image contrast with the least amount of exposure to normal tissues. In the case of MRI, superparamagnetic iron-oxide nanoparticles, and other magnetic nanomaterials have been created to enhance the sensitivity of MRI and its spatial resolution[39]. These agents relax better in comparison to the traditional gadolinium-based contrast agents, which are safe substitutes with fewer chances of nephrotoxicity. Moreover, floating of nanoparticles and surface functionalisation allow control of magnetic characteristics to improve imaging[40].

3.2 Optical and Fluorescence-Based Imaging

Optical and Fluorescence-Based Imaging Visualization of the protein samples may be conducted using fluorescence or optical microscopy to determine the presence of any protein aggregates in the samples[41]. Fluorescence and bioluminescence imaging are optical imaging methods that offer high sensitivity and real time images and visualisation of cellular and molecular processes in biological systems. Nanotechnology has significantly increased the performance of optical imaging to come up with nanoparticles with superior photostability, bright emission properties, and multifunctional properties[42]. Optical imaging has been widely tested with quantum dots, fluorescent silica nanoparticles and dye-loaded polymeric nanocarriers. These nanostructures address some of the major shortcomings of traditional fluorophores including photobleaching and poor brightness[43]. Further generation techniques like multiphoton fluorescence lifetime imaging tomography help to increase imaging depth, resolution and reduce photodamage and radiation dose. Although these have

these benefits, optical imaging modalities have a limitation of limited tissue penetration, limiting the clinical applications of these modalities only to the superficial tissues or intraoperative imaging[44]. In future studies, there exists a need to combine optical imaging to other modalities to surmount these limitations. Nuclear Imaging and Multimodal Platforms.

3.3 Nuclear Imaging and Multimodal Platforms

The nuclear imaging methods, such as positron emission tomography (PET) and single-photon emission computed tomography (SPECT), are some of the most sensitive diagnostic methods, which can be used to detect molecular and metabolic alterations in vivo[45]. Nanotechnology has made possible the creation of radiolabelled nanoparticles which provide an increase in signal stability, increase in circulatory residence, and increase in targeting accuracy. Radiolabelled nanocarriers can be designed to selectively localize to diseased tissues and at the same time act as a carrier of therapeutic agent, thus establishing the basis of theranostic uses[46]. Besides, nuclear imaging with complementary modalities: e.g. MRI or optical imaging could be made within one nanoparticle platform, thus enabling the study of disease progression in both spatial and time dimensions to be comprehensively visualised. The combination of the advantages of imaging modalities offers synergistic diagnostic data through multimodal imaging probes[47]. These facilities enable accurate localisation, increased sensitivity, and cross-validation of imaging data, and this is especially important in complicated diseases like cancer[40].

3.4 Applications of *In Vivo* and *In Situ* Diagnostics

Nanotechnology has also been used in vivo and in-situ diagnostic plans, in order to be able to monitor disease conditions by minimal invasion. Capsule endoscopy and implantable diagnostic systems have been integrated with nanoscale sensors and image agents to identify biochemical, pH changes, pathogenic, and inflammatory responses of the gastrointestinal tract and other internal devices[48]. These systems provide real time visualisation and molecular level diagnostics without having to do invasive surgery. The current processes are expected to lead to the future incorporation of diagnostic and therapeutic services in such platforms, hence allowing the provision of localized treatments and persistent monitoring of diseases[49].

3.5 Project Problems and Safety

Nevertheless, the clinical translation of imaging agents based on nanoparticles has experienced several challenges even with the tremendous progress. Possible toxicity due to long-term accumulation of nanoparticles, lack of biodegradability and immune system interactions are critical issues[50]. Furthermore, the characterisation of nanoparticles is a complex regulatory approval due to the necessity to use standardised characterisation protocols. To facilitate clinical adoption, there is the need to balance imaging performance with safety and scalability[51]. The biocompatible materials, reproducible synthesis protocols and stringent validation in vivo should be the focus of future research to warrant the safe and effective application of nanotechnology-facilitated diagnostic imaging[51].

4. Cancer Nanomedicine

Cancer nanomedicine is one of the most developed and clinically investigated fields of nanotechnology-based healthcare[52]. The major goal of this field is to make cancer diagnosis and treatment more accurate, effective and safer through the unique physicochemical characteristics of nanoparticles. The traditional methods like chemotherapy and radiotherapy are often not selective hence causing systemic toxicity and low therapeutic index[53]. Nanotechnology-based solutions have potential solutions in the form of targeted drug delivery, controlled delivery, and the combination of diagnostic and therapeutic capabilities on one platform[21].

4.1 Principles of Nanoparticle-Mediated Tumor Targeting

Early cancer nanomedicine was driven largely by the notion of the so-called enhanced permeation and retention (EPR) effect of preferential accumulation of macromolecules and nanoparticles in tumour tissues due to leaky vasculature and disrupted lymphatic drainage. The effect of this phenomenon was a theoretical basis of passive targeting strategies and the design of many drug delivery systems based on nanoparticles[54]. Nevertheless, cumulative experimental and clinical data has demonstrated considerable heterogeneity of the EPR effect between tumour types, disease stages, and populations of patients. According to recent research, active transportation processes such as transcytosis through endothelial cells may be more predominant in the processes of nanoparticle tumour penetration than previously thought[55]. These results demonstrate the shortcomings of using passive targeting only and emphasise the need to implement more complex design approaches that consider the complexity of the tumour micro-environment. A perfect cancer nanocarrier must have long circulation, low off-target effects, effective tumour cell penetration and regulated release of therapeutic agents into cells. This is one of the key challenges of nanomedicine research to achieve this balance[56].

4.2 Nano-based Carrier Systems to treat cancer

Numerous types of nanocarrier platforms have been created with respect to treatment of cancer and they include: liposomes, polymeric nanoparticles, dendrimers, metallic nanoparticles, and hybrid nanostructures[21]. Of these, liposomal formulations have had the most successful clinical experiences due to their biocompatibility and their ability to entrap chemotherapeutic agents without excessive toxicity in the system[57]. An example of how nanoparticle encapsulation can reduce dose-limiting toxicities, especially cardiotoxicity is the use of clinically approved nanomedicines, including liposomal doxorubicin. More sophisticated derivations have also optimised the ratios and release kinetics of the drugs to

enhance therapeutic effects. The passage of the combination nanomedicines in haematological malignancies represents the capability of nanotechnology to intensify the combination drug interactions and drug efficacy[58]. Other benefits of polymeric and inorganic nanocarriers are structural versatility and multifunctionality. Photothermal and photodynamic therapies are made possible through the use of metallic nanoparticles, including systems containing gold, and therefore provide the benefit of non-invasive treatment alternative to conventional chemotherapy. However, issues with long-term accretion and toxicity remain to limit clinical transfer of some inorganic platforms[59].

4.3 Nanotechnology in Cancer Chemotherapy

In nanotechnology, the delivery of chemotherapeutic agents has been greatly enhanced in terms of solubility, stability, and tumour selectivity. Chemotherapy using nanocarrier is expected to enhance the concentration of drugs at the tumour sites with minimum exposure to normal tissues[60]. The sustained therapeutic levels are also provided by controlled release mechanisms, which decrease the number of administration and enhance patient compliance. Although these are the benefits, nanocarrier-based chemotherapy is challenged by distribution of drugs that is not homogenous in tumours and difficulty in penetrating the dense tissues of the tumours[61]. To overcome these barriers, it needs superior carrier designs that will be able to react to the tumour-specific stimuli and react to the dynamic tumour micro-environment.

4.4 Nanomedicine Assisted Immunotherapy and Gene Therapy

Immunotherapy has become an effective way of treating cancer, but the inefficiency of delivery of immunomodulatory agents and adverse effects related to immunity limits its effectiveness. Immunotherapy with the help of nanotechnology aims at overcoming these shortcomings by allowing the delivery of immune checkpoint inhibitors, cytokines, vaccines, and nucleic acids in a targeted manner[62]. Nanoparticles help to deliver immunotherapeutic agents to immune cells or tumour locations and thus, increase immune activation whilst decreasing systemic toxicity. Specifically, delivery of antibodies against immune checkpoints with nanoparticles has been shown to have better pharmacokinetics and tumour localisation[63]. Nanotechnology-based delivery systems have also been useful in gene therapy methods, such as RNA interference, and CRISPR/Cas9-based genome editing. Nanocarriers ensure the optimal protection of nucleic acids against enzymatic destruction and ensure an increase in cellular uptake, thus overcoming the major challenges of low transfection efficiency and poor stability[64]. Nanocarriers made of lipids and hybrid nanocarriers have demonstrated valuable promise in preclinical cancer models, outlining their potential to be used in the future.

4.5 Resistance, Safety and Translational Barriers

The resistance to nanomedicine-based therapies is an issue despite the promising breakthroughs being encouraged. Mechanisms of tumour adaptation including changes in uptake pathways and micro-environmental alterations have the potential to decrease the efficacy of nanoparticles with time[65]. Furthermore, differences between laboratory findings and the human tumours in preclinical models of those same tumours complicate the issue of translating laboratory results into clinical success. Regulatory issues are a major challenge of safety, such as immunogenicity, off-target, and long-term toxicity[66]. Nanoparticles are also complex in their formulations, which makes them harder to produce in large quantities and to be checked in quality. The solution to these problems will entail standardised assessment schemes, enhanced predictive analytics and early incorporation of clinical factors in the design of nanomedicine[67].

4.6 Future Perspectives in Cancer Nanomedicine

The future of cancer nanomedicine is in rational development of multifunctional platforms, which combine targeting, therapy, and real-time monitoring. Individual nanomedicine strategies considering tumour heterogeneity and patient-specific aspects are likely to improve treatment effectiveness and clinical outcomes[52]. The development of new materials, tumour biology and computational modelling will be essential to the development of new nanocarriers in the next generation. Finally, the translation of cancer nanomedicine into clinical practice is bound to be successful due to interdisciplinary teamwork, stringent clinical testing, and compliance with regulatory standards[68].

5. Difficulties, Toxicity and Regulatory Obstacles of Nanomedicine

Although there has been a significant progress in the creation of nanotechnology-based drug delivery vehicles, diagnostic imaging agents, and cancer nanomedicine vehicles, they are still not translated into clinical practice[69]. This gap between the promising results in preclinical studies and a successful clinical trial is an indicator of a complicated combination of biological, technological, and regulatory barriers that should be overcome to achieve the full potential of nanomedicine[70].

5.1 Biological Barriers and *in Vivo* Complexity

The major challenge to nanomedicine is the unreliability of nanoparticles in the complexity of biological systems. After the systemic delivery, nanoparticles face numerous physiological obstacles, such as the formation of protein corona, immune response, and non-specific uptake by the reticuloendothelial system[71]. These interactions can significantly change the size of nanoparticles, surface properties, biodistribution and therapeutic activity. The heterogeneity of the tumor also makes nanoparticle delivery more complicated, as the differences in vascular density, interstitial pressure and cellular composition may affect nanoparticle penetration and retention[72]. These are some of the reasons behind inconsistent results in therapeutic interventions, and the shortcomings of reduced preclinical models, which cannot reflect the complexity of human disease[73].

5.2 Long-term Safety and Toxicity

One of the main issues of clinical translation of nanomedicine is safety. Despite the fact that numerous nanocarriers are made of biocompatible materials, their nano-scale size predisposes them to interact with biological systems and induce unknown side effects in toxicology[74]. The risks involved include oxidative stress, inflammation, genotoxicity and interference with normal cell functions. The chronic toxicity is raised due to the long-term deposition of non-biodegradable nanoparticles in the organs like liver, spleen and kidneys[75]. Nanoparticles made of metals and inorganics, specifically, require thorough consideration of the clearance mechanisms and long-term outcome in the body. Detailed toxicological evaluations such as the chronic exposure studies and post treatment follow-ups are essential but underrepresented in most preclinical studies[76].

5.3 manufacturing, Reproducibility and Scalability

Much sophistication of manufacturing nanoparticles makes it difficult to produce large quantities of nanoparticles and translate to clinics. Many nanomedicine systems rely on multistep fabrication which is challenging to reproducibly generate in batch-to-batch production[77]. Differences in size, surface chemistry and drug loading may produce significant differences in the performance of biological systems making them difficult to control and obtain regulatory approval. Scalability is also a crucial bottleneck particularly with multifunctional and hybrid nanocarriers[78]. Moving the synthesis process out of the lab to create products at large scale will require strong, standardized production procedures that can be reproducible, steady, and economical. Without such frameworks, even high-performing nanomedicine platforms can end up being stuck at the stage of developing a prototype[79].

5.4 Clinical and Regulatory Translation Problems

Nanoscale therapeutics and diagnostics lack the guidelines to ensure regulatory approval of nanomedicine products. There is a tendency of nanomedicines to have properties, which do not readily fit into the current regulatory frameworks of a drug, biologic, or medical device, creating ambiguity in the evaluation routes[71]. Besides, because of the multifunctionality of many nanomedicine platforms, especially theranostic systems, they present a special regulatory challenge because both therapeutic and diagnostic subunits should be evaluated simultaneously[80]. Standardized characterization procedures, approved biomarkers and standardized regulatory procedures are much needed to foster uniform assessment and authorization. Clinical trial design also presents some new challenges, which include stratification of patients, selection of endpoint and long-term safety[81]. The variability of patient groups and disease conditions requires individualized methods, which may be incompatible with the traditional clinical trial methods.

5.5 The measures that can be taken to defeat the transnational barriers

The translationational issues of nanomedicine require a multi-disciplinary solution incorporating materials science, biology, clinical studies and regulatory knowledge. Downstream barriers to translation can be prevented through early integration of safety and scalability-related aspects in the design of nanocarriers[30]. More human physiology-faithful in vitro and in vivo models are under development, including organ-on-a-chip models and patient-derived xenografts, and could increase the predictive potential of preclinical models[82]. Moreover, the academia, industry, and regulatory agencies should work closely to implement standardized procedures and expedite clinical integration.

6. Conclusion

The concept of nanotechnology has radically changed the approach to drug delivery, diagnostic imaging and oncological therapy by allowing a precise control of material properties and biological interactions at the nanoscale level. Advocacy of advanced nanocarriers has enhanced therapeutic bioavailability, enhanced tumour targeting, controlled and stimulus-responsive drug delivery, and increased the integration of diagnostic and therapeutic systems in coordinated theranostic systems. These developments, combined with each other, demonstrate a significant potential of nanomedicine in the domains of improved precision oncology and personalized cancer treatment. However, clinical translation of nanotechnological based systems is limited. There are long standing safety issues of prolonged concern, immunological interactions, complexity of biology, tumour heterogeneity and scalable manufacturability and reproducible barriers that impede wider clinical use. In particular, its over-reliance on simplified paradigms of targeting and conventional preclinical models have created a gap between the promotion of laboratory results and the relatively small clinical effects. These weaknesses drive the need to focus on more predictive assessment models and, finally, a more mechanistic understanding of nano-biological interactions in human illness. The future development of nanomedicine will be based on the rational design of lean, stable, and patient-directed nanocarriers that focus on safety, scalability, and reproducibility along with therapeutic effectiveness. Individualized nanomedicine plans that capture patient and tumour classified characteristics and complex imaging and real-time tracking are expected to improve accuracy of treatment and clinical performance. In addition, the integration of the emergent technologies such as artificial intelligence, patient stratification based on biomarkers, and sophisticated in-vitro models will be critical in shaping the direction of the development of next-generation nanomedicine. Finally, to achieve the successful adoption of nanotechnology in everyday clinical practice, interdisciplinary cooperation between materials scientists, biologists, clinicians, and regulatory agencies is required to last. Nanomedicine can go beyond the proof-of-concept research and demonstrate real benefits to cancer patients, by aligning technological innovation with clinical imperative and regulatory requirements.

Declarations
Ethics and consent to participate
Not applicable

Consent to Publish
Not Applicable

Competing Interests
The authors declare no competing interests.

Availability of data and materials
The data that support the findings of this study are available from the corresponding author upon reasonable request.

Submission declaration and verification
The authors declare that the article has not been published previously or under the consideration for publication elsewhere.

Declaration of Competing Interest
All authors declare no competing interests

Conflict of Interest
The authors declare that they have no conflict of interest.

Table 1 Comparison of Nanocarrier Systems for Drug Delivery, Imaging, and Cancer Therapy

Nanocarrier Type	Primary Applications	Key Advantages	Major Limitations	Clinical / Translational Status	References
Liposomes	Chemotherapy, drug delivery, imaging	Reduced systemic toxicity, high biocompatibility, and the capacity to encapsulate both hydrophilic and hydrophobic medications	Batch variability, quick clearing without surface modification, and limited stability	Several FDA-approved formulations	[57]
Polymeric Nanoparticles	Drug delivery, gene therapy, controlled release	Controlled release profiles, adaptable surface functionalisation, and adjustable degradation	Possible toxicity of polymers, complicated manufacture, and difficulties with scaling up	Numerous preclinical and initial clinical investigations	[16]
Solid Lipid Nanoparticles	Oral and parenteral drug delivery	Better medication stability, regulated release, and favourable biocompatibility	Polymorphic transitions and limited drug loading capacity	Certain clinical and preclinical assessments	[83]
Dendrimers	Gene delivery, targeted therapy	Multivalent surface, high payload capacity, and precise molecular architecture	High levels of cytotoxicity and costly synthesis	Mostly preclinical	[21]
Metallic Nanoparticles (e.g., gold, iron oxide)	Imaging, photothermal therapy, theranostics	Special optical/magnetic characteristics, improved imaging, and versatility	Potential toxicity, low biodegradability, and long-term accumulation	Approved imaging agents; mostly preclinical therapy	[63]
Ceramic Nanoparticles (e.g., silica, calcium phosphate)	Drug delivery, imaging, bone regeneration	Excellent drug loading, adjustable porosity, and high mechanical stability	Inflammatory reactions and poor biodegradability	Preclinical	[27]
Hybrid Nanoparticles	Theranostics, combination therapy	Combined benefits of various materials and platforms with multiple uses	Regulatory obstacles and complicated manufacturing	Early-stage translational research	[36]
Stimuli-Responsive Nanocarriers	Targeted cancer therapy, controlled release	Reduced off-target toxicity and site-specific medication release	Variability in the environment and complexity of the design	Mostly preclinical	[55]

Table 2 Comparative Overview of Nanocarrier Systems Used in Cancer Drug Delivery and Theranostics: Mechanisms, Advantages, Limitations, and Translational Status

Nanocarrier Type	Composition	Targeting Mechanism	Imaging Capability	Therapeutic Application	Advantages	Major Limitations	Clinical/Translational Status
Liposomes	Phospholipid bilayer vesicles	Passive (EPR), ligand-conjugated active targeting	MRI, fluorescence (when labelled)	Chemotherapy delivery	Biocompatible, FDA-approved examples available	Stability issues, rapid clearance	Several approved (e.g., liposomal doxorubicin)
Polymeric Nanoparticles	PLGA, PEG, chitosan	Receptor-mediated targeting	Fluorescent tagging possible	Controlled drug release	Tunable release kinetics	Scale-up challenges	Some in clinical trials
Dendrimers	Branched polymers	Surface ligand functionalization	MRI, optical imaging	Gene & drug delivery	High loading capacity	Potential cytotoxicity	Mostly preclinical
Gold Nanoparticles	Metallic core	Surface antibody/peptide targeting	CT, photoacoustic imaging	Photothermal therapy	Easy surface modification	Long-term accumulation concerns	Early clinical evaluation
Magnetic Nanoparticles	Iron oxide	Magnetic targeting + ligand	MRI contrast	Hyperthermia + drug delivery	Dual diagnostic-therapeutic role	Aggregation, toxicity concerns	Some FDA-approved for imaging
Silica Nanoparticles	Mesoporous silica	Functionalized targeting ligands	Fluorescent, multimodal	Drug loading + imaging	High drug loading	Biodegradability issues	Preclinical stage

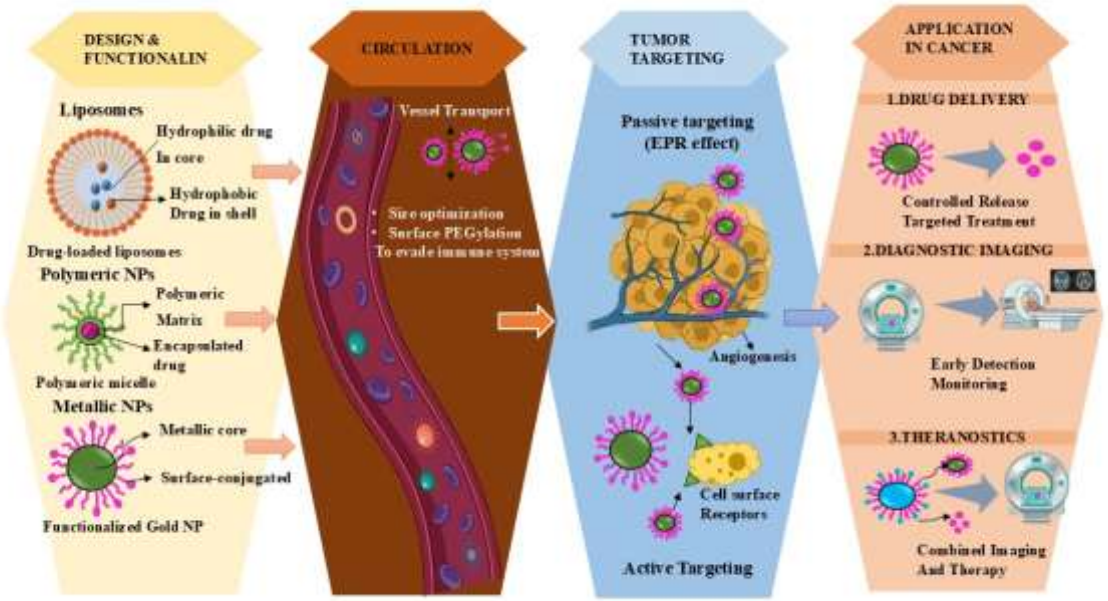

Figure 1 Overview of Nanotechnology in Cancer Nanomedicine

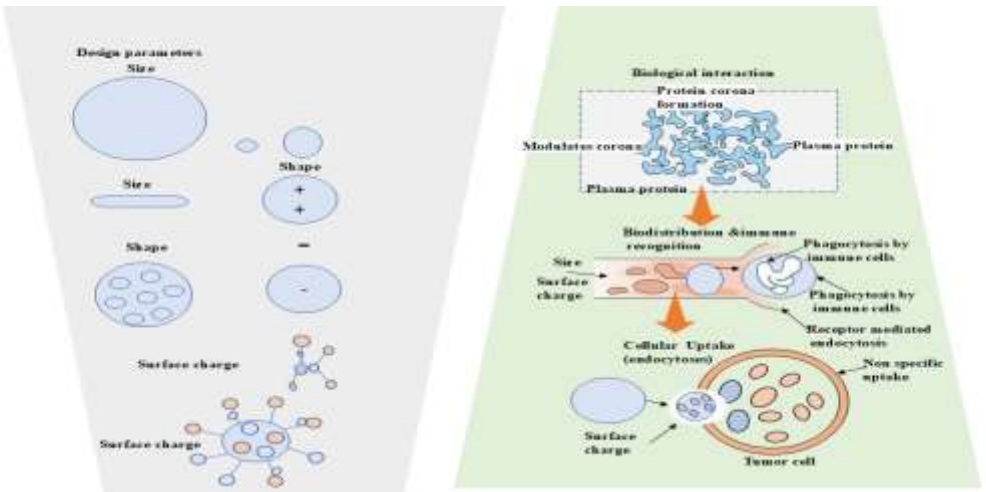

Figure 2 Nanocarrier Design Parameters and Biological Interactions

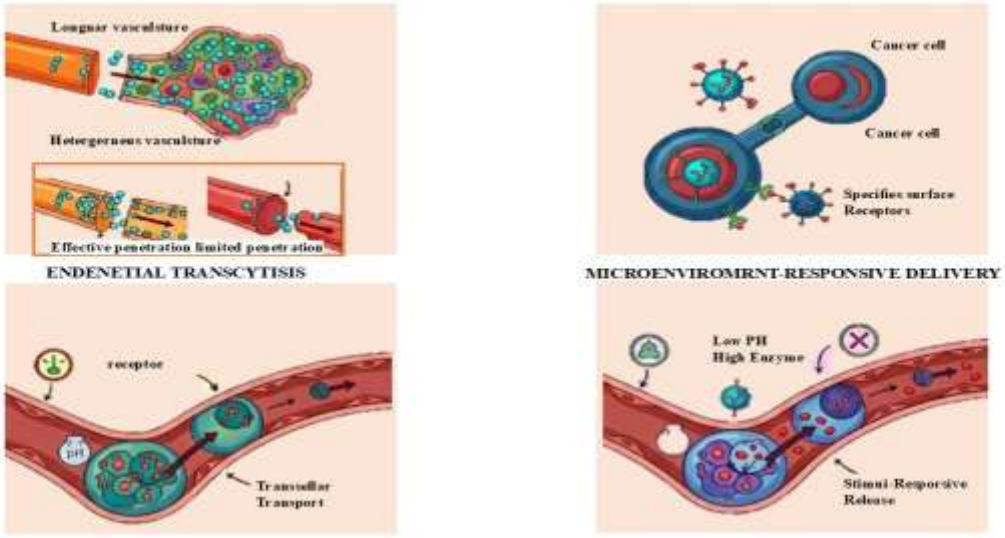

Figure 3 Targeting Mechanisms in Cancer Nanomedicine

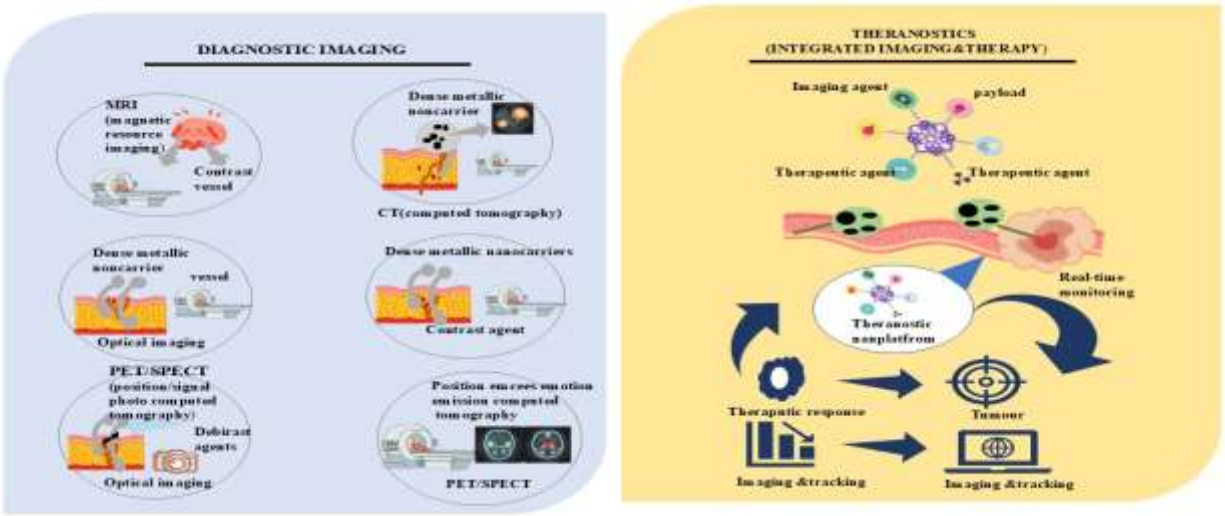

Figure 4 Nanotechnology-Enabled Diagnostic Imaging and Theranostics

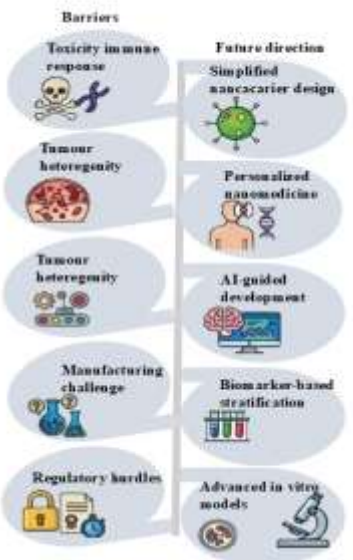

Figure 5 Translational Barriers and Future Directions

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