Nanomedicine: Current Issues and Future Directions

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Abstract: Recognizing and promoting contributions relevant to public health is crucial as the range of nanotechnology's uses in medicine expands. Nanomedical advances promise to have far-reaching effects across the medical spectrum, revealing exciting new approaches to enhance health and lengthen life that can be quantified on both an individual and a societal scale. In the United States, for instance, cardiovascular disease and cancer account for over half of all deaths each year, yet there is promising evidence that improvements in nanomedicine can help cut these numbers. Nanomedicine's public health uses, like quicker and more portable diagnostics and more potent immunizations, could radically alter the state of global health. Innovators in fields as diverse as engineering, biology, medicine, and public health should work together to maximise the influence of their research on people's health. Therefore, there is a constant need to fill up the gaps in our understanding of the health and safety risks associated with exposure to manufactured nanomaterials. Nanomedicines will play an increasingly integral and revolutionary role in 21st century medicine and public health, driven by research that is both proactive and socially responsible.

Keywords: nanotechnology, medicine, epidemiology, policy, environmental health

1. Introduction

When discussing the application of nanotechnology to these medical endeavours, the term "nanomedicine" is commonly used. It's an emerging area with the potential to significantly impact health in the twenty-first century, on both an individual and societal level.Public health's goal is to promote, safeguard, and maintain populations' or groups' health, as opposed to clinical medicine's focus on the individual. For the maximum number of people to reap the advantages and avoid the risks associated with nanomedicine, it is essential to analyse and investigate its uses and effects from a public health perspective. (West & Halas, 2000). Applications of nanotechnology are appealing because of the distinctive properties and phenomena that result from their small scale. The scale for nanotechnology that is most frequently used is 1–100 nm. This level of material engineering enables the development of

cutting-edge medical treatments, such as the creation of nanoparticle-based medications with more precise cell targeting and fewer adverse effects for patients. Other improvements in medical equipment and instruments are being produced for use in less invasive surgical operations, which will result in quicker recovery times and a lower risk of postoperative infections or other consequences. These advancements will raise living standards, lengthen lifespans, and may even lower overall healthcare costs. In cardiology, neurology, and many other medical disciplines, research is currently being conducted on a global scale to develop nanotechnology applications (Etheridge et al., 2013). The use of carbon nanotubes in imaging modalities and nanoparticles in drug delivery systems are two such examples. Research that is motivated by scientists with a high understanding of the needs of public health is vital to successfully progress the subject and produce medical technology for use in real-world applications. Ongoing research is needed to fill knowledge gaps in the fate and transport of engineered nanoparticles in biological systems. The FDA has not created any clear regulations regarding the use of engineered nanomaterials in food, cosmetics, or other products that fall within their authority.(Hare et al., 2016)(S, Elger, Hunziker, & Shaw, 2015). However, the lack of data to predict and mitigate the health impacts of exposure to produced nanoparticles is raising concerns about the safety of this technology. More study is needed to determine the effects of manmade nanoparticles on the environment, human health, and safety. To properly promote nanotechnology, however, dialogue with stakeholders about possible dangers and advantages is essential. Regulatory bodies, public concern organisations, insurance companies, and others will present numerous obstacles to the integration of nanomedicine into standard clinical practise for a variety of reasons. To address these issues early on, collaboration amongst people with a stake in the advancement of nanomedicine should be encouraged. According to Mg, Krenn, Huebner, Wagner, and Resch ((Mg, Krenn, Huebner, Wagner, & Resch, 2015), However, growing concerns regarding potential health and safety hazards have been prompted by the scarcity of information available to predict and mitigate the effects of exposure to manmade nanomaterials. More study is required to accurately assess the environmental, health, and safety impacts of the life cycle of manufactured nanomaterials.

2. Public health

The field of nanomedicine will have far-reaching effects on public health. Disease prevention, increased longevity, and community-wide health and productivity are the goals of public health. Public sanitation, infectious disease control, and clinical preventive care, such as early screening and detection, are common examples of such population- or community-

level interventions. Public health, in this sense, is concerned with improving the health of an entire community rather than just certain demographics within it. The Association of Schools of Public Health classifies public health as consisting of the following five subfields:

• Epidemiology
• Biostatistics
• Health policy management
• Social and community behaviour
• Environmental health sciences.

The study of the causes and prevalence of disease is known as epidemiology. It makes sense in relation to biostatistics, which conducts quantitative analyses of the causes and distribution of disease. Using information from the fields of medicine and public health, legislation, regulations, and guidelines are produced for the public's health. Social and communal behaviour researches impacts on health outcomes at all levels, from the individual to the organisational (Mg et al., 2015; S et al., 2015). Environmental health is concerned with how people's health is impacted by their immediate surroundings, both physically and socially. A platform for analysing, comprehending, and predicting the effects of nanomedicine on population health is provided for public health professionals by the knowledge base developed through these core disciplines. Human history has been shaped by public health technological advancements. For instance, vaccines have been effective in completely eliminating or greatly reducing deadly infectious diseases all over the world. The creation and application of vaccines have been influenced by side effects and health risks. The hepatitis B vaccination is an example of how nanotechnology can be utilised to improve present medical practise and have a substantial impact on population health. Approximately two billion people are infected with the viral illness hepatitis B. Currently, a highly effective vaccination exists to prevent this disease, but it must be taken in three to four doses.

Particularly in third-world nations, noncompliance with the dose schedule is a serious issue that can reduce or eliminate the vaccine's effectiveness. The vaccine can now be given in one dosage with the same efficiency because to advancements made by ongoing research and development (Hofmann-amtenbrink, Grainger, & Hofmann, 2015). One group is primarily looking into the efficiency of several PLGA microspheres for the single-dose administration of the hepatitis B vaccine. It is now possible to immunise a bigger population against an infectious illness that causes over 600,000 deaths a year thanks to this sort of hepatitis B preventive therapy. Regarding the treatment of chronic diseases, nanomedicine has the potential to have a substantial impact on global and local health. Cancer is the second biggest

cause of death in the United States, affecting an estimated 1.48 million individuals in 2009. Traditional cancer treatments, such as chemotherapy, surgery, and radiation therapy, are often nonspecific and harmful to both malignant and healthy cells, placing a burden on patients. The National Cancer Institute (NCI) established the Alliance for Nanotechnology in Cancer in 2004 after realising the immense potential of nanotechnology to improve cancer diagnosis and treatment.. This collaboration promotes the study and creation of more effective and unobtrusive nanotechnology-based cancer treatment and diagnosis options (Sandhiya, Dkhar, & Surendiran, 2009). Numerous medications and treatments that make use of nanotechnology are supported by the NCI throughout all stages of testing, including clinical trials. Current nano-enabled cancer treatments authorised by the FDA include Abraxane® for breast cancer treatment and Doxia® for ovarian cancer treatment. New technologies are being developed to combat additional key sources of morbidity and mortality in the United States, such as cancer, Alzheimer's disease, and heart disease. Regenerative medicine innovations utilising carbon nanotubes and nano biers, nanopatterned extracellular matrices, and dendritic nano polymers are a few examples. Nanomedicine can be utilised in a variety of ways to solve critical public health issues, as demonstrated by research efforts focusing on several extremely pervasive diseases. (Boulaiz et al., 2011).

3. Scope of analysis

There is still debate about what constitutes "nanotechnology" and "nanomedicine," and there is no agreed-upon classification. Nanomedicine is the use of nanoscale or nanostructured materials in medicine that have been created to have specific medical effects depending on their architectures, including structures having at least one distinctive dimension up to 300 nm.(Boulaiz et al., 2011; Chan, 2017), owing to the necessity of an operational definition for the objectives of this investigation. In nanomedicine, transitions in physiochemical properties and transitions in physiological interactions are two universal nanoscale phenomena. The National Nanotechnology Initiative (NNI), which concentrates on the former and where quantum effects are typically limited to structures on the range of a few nanometers to tens of nanometers, is one of the earliest definitions of nanotechnology that employs a 100 nm cutoff. Nevertheless, for some nanomaterials with distinguishing properties larger than 100 nm, such as the plasmon-resonance in gold nanoshells with a 150 nm diameter, which is now being examined in clinical trials for cancer heat therapy, a unique physiochemical behaviour can occur. In addition, a substantial amount of the advantages (and downsides) of nanomedicine are related to the physiological interactions that develop at the boundary between the molecular and microscopic dimensions. Liposomes with sizes between 150 and

200 nm remain in the bloodstream longer than those with diameters smaller than 70 nm, according to research. Using the increased permeability and retention (EPR) effect, many nanomedicine devices with feature sizes between 100 and 200 nm aim to passively target locations at the tissue level. However, particles as small as 400 nm have been demonstrated to extravasate and accumulate in tumours (albeit this is an extreme example).)(Lammers, 2018). Numerous factors influence the pathways for NP absorption and processing at the cellular level, but particle size plays a vital role. Macrophages may easily phagocytose polystyrene beads with a diameter of up to 200 nm, despite the fact that optimal cellular absorption of colloidal gold has been observed for sizes of approximately 50 nm. Consequently, despite the fact that a substantial fraction of nanomedicine employs features with widths at or below 100 nm, this cutoff excludes numerous applications. that have important implications for the field. In order to better capture the distinct physiological behaviour that is taking place at these sizes, we picked 300 nm. Additionally, it should be highlighted that all of this behaviour is quite material- and geometry-specific, with much of the prior discussion concentrating on spherical NPs because they are the most common in the literature. However, a lot of recently created microscale systems that improve vascular extravasation will still be covered by our concept. From basic science to a commercial medical product, an application will typically go through five developmental phases (Figure 1). We concentrated on identifying applications that are currently or about to begin clinical testing in human subjects, as well as goods that have already received FDA (or equivalent) approval in other countries, in order to depict and analyse the nanomedicine landscape. This doesn't include earlier-stage uses, including those in bench science or early animal testing. Many of the ground-breaking nanomedicine innovations predicted in the literature could take 20 or more years to reach the clinic. It is challenging to predict how these would ultimately be put into practise and what effect they might have. For instance, according to a poll conducted in 2006, "nanomachines" capable of theragnostic (combined therapy and diagnostics) in humans won't be available until 2025. Thus, the applications and products that are currently being tested on or utilised on humans are the subject of our study. For the foreseeable future, industry, regulation, and society will be most significantly impacted by these applications and products (Boulaiz et al., 2011; Bregoli et al., 2015).

4. Anti-cancer nanomedicines in pre-clinical and clinical development

Despite the fact that there is much overlap within categories, anti-cancer nanomedicines in clinical development can be generally classified into five basic types: liposomes, polymeric conjugates, polymeric nanoparticles, polymeric micelles, and others. As an important

therapeutic class distinct from the particulate nanomedicine systems discussed in this article, antibody-drug conjugates were believed to fall outside the scope of this study. (Chan, 2017; Farokhzad & Langer, 2006; Lammers, 2018). Table 1 summarises examples of anti-cancer nanomedicines that have been commercialised as well as those that are still in clinical development.

Table1: Some Examples of anti-cancer nanomedicines in clinical trials

Drug	**Product Name**	**Indication**	**Clinical trial phase**
Doxorubicin	Myocet™/ Teva UK	Breast cancer	Approved
	Doxil™/ Janssen	Ovarian cancer	Approved
	ThermoDox™/ Celsion	Primary hepatocellular carcinoma	Phase III
	2B3-101/ 2-BBB Medicines BV	Brain metastases Glioma	Phase II
Vincristine	Marqibo™/ Spectrum Pharmaceuticals	Acute lymphoblastic leukaemia	Approved
Paclitaxel	LEP—ETU/ Insys	Breast cancer	Phase II
	EndoTAG-1/ MediGene	Breast cancer	Phase II
Camptothecin	CRLX101 (Cyclodextrin adamantane)/ Cerulean	Renal cancer Small cell lung cancer Ovarian cancer	Phase II
Asparaginase	Oncaspar™ (PEG)/ Baxalta	Acute lymphoblastic leukaemia	Approved
Paclitaxel	Opaxio™ (Polyglycerol adipate)/ CTI Biopharma	Ovarian cancer Non-small cell lung cancer (women)	Phase III Phase II
Docetaxel + Prostate-Specific Membrane Antigen (PSMA)	BIND- 014 (Accurin™) / BIND Therapeutics	Cholangiocarcinoma Cervical cancer Bladder cancer Head and neck cancer Non-small cell lung cancer subtypes	Phase II

A small fraction of licenced anti-cancer nanomedicines (such as BIND-014 from BIND Therapeutics and MM-302 from Merrimack Pharmaceuticals) aim to alter the nanomedicines'

behaviour immediately by ligand-mediated targeting. Typically, EPR-based treatments aim to modify the drug's pharmacokinetics and biodistribution in order to improve its efficacy and tolerability. To provide prolonged exposure to therapeutic levels of medication at the target, they can minimise the peak free drug concentration (Coax) while frequently expanding the area under the plasma and tumour concentration curves. Several nanomedicines, such as CRLX101 (Cerulean) and AZD2811 nanoparticle (AstraZeneca), have permitted new innovative treatment techniques or conferred a significantly improved therapeutic index to an existing drug by achieving the proper target and exposure. In preclinical studies, the Aurora-B kinase inhibitor employed in the AZD2811 nanoparticle was innovatively encapsulated to decrease dose-limiting bone marrow toxicity.(Bregoli et al., 2015; Pautler & Brenner, 2022; Webster & Webster, 2022). The capacity to construct a drug without employing harmful dose-limiting excipients found in currently marketed formulations is one of some nanomedicines' key advantages. This frequently improves tolerability and makes it possible to administer more medications to patients. For instance, because Abraxane™ (Celgene) and the polymeric micelle formulation Genero-PM™ (Samyang Biopharmaceuticals) do not require the use of Cremophor™, which is required to produce Taxol™, greater dosages of paclitaxel can be given to patients. Even though they are not frequently the main focus of nanomedicine research programmes, these solubilization benefits can be very cost-efficient. Additionally, by achieving the proper safety "profile," this strategy can significantly impact the patients' experiences and the clinical results because it allows for an increase in the maximum tolerated dose of the active ingredient while avoiding the tolerability issues brought on by solubilizing surfactants (Duncan & Gaspar, 2011; Emerich & Thanos, 2003).

If their efficacy is not enhanced, the rising cost of nanomedicine systems may prevent them from becoming a widespread treatment choice.Engaging physicians and other healthcare professionals is crucial for this new generation of therapies in order to show (what they see as) real clinical distinction. The discipline of nanomedicine has invested a lot of time and energy into gaining understanding of the benefits and drawbacks of various nanomedicine systems from a technological and biopharmaceutical perspective. Numerous unique nanomedicines have enhanced the stability, solubility, pharmacokinetics/biodistribution, toxicity, and/or effectiveness of cytotoxic and other types of payload. The nanomedicine's biodistribution and clearance are substantially influenced by the nanomedicine's size, charge, shape, kind of surface modification, and biocompatibility. Stealth nanomedicines with prolonged circulation lengths are capable of accumulating significantly at sites of leaky vasculature, as shown in preclinical models and humans. This size impact has also been

associated with enhanced efficacy in preclinical models, where smaller (sub-100 nm) nanomedicine systems and lower molecular weight macromolecules extravasate more and/or penetrate further from the vasculature than bigger systems. Nevertheless, it is too soon to generalise this size-dependency, which is comparable to tumor- and nanomedicine-dependency.(Park, 2019). The ability of a nanomedicine to control the pace of drug release can have a substantial effect on the safety and efficacy of a treatment. By altering diffusion via a polymer matrix or utilising chemical conjugation linkers with different rates of in vivo breakdown (such as hydrolysis), it is possible to tailor drug release to exploit the therapeutic window. (Flühmann, Ntai, Brorchard, Simoens, & Mühlebach, 2018; Sahoo, Parveen, & Panda, 2007). Once the relationship between sickness biology and nanomedicine behaviour is more understood, it will be feasible to adjust the characteristics of the delivery system based on data. This article elaborates on concentrating nanomedicine development in order to match a delivery system, tumour, and drug to a specific clinical line of sight.

5. Perceived difficulties within the nanomedicine field

It's crucial to understand why anti-cancer drugs fail so frequently in clinical trials if you want to increase your chances of success. The cause of failure for a few nanomedicines has been looked at. Phase III clinical trials evaluating the paclitaxel polyglutamic acid conjugate OpaxioTM for the treatment of incurable lung cancer were conducted. However, OpaxioTM treatment only had a positive effect on female survival; It had no influence on the survival of males. Since the clinical experiment, a link has been shown between oestrogen levels and cathepsin B activity.(Sahoo et al., 2007), which is important because OpaxioTM depends on cathepsin B-mediated activation. As a result, women with oestrogen levels above a set threshold were only allowed to participate in subsequent clinical investigations with OpaxioTM. OpaxioTM has created a sound plan to deal with the problem moving forward, but for the majority of nanomedicines that are unsuccessful in the clinic, the cause of the underwhelming efficacy or elevated toxicity is unknown. Furthermore, Complex biological variables likely contribute to the inadequate clinical translation. In addition, persons with advanced, metastatic cancer and co-morbidities who have received significant pre-treatment frequently participate in early-stage clinical studies. Many of these features are difficult to predict from pre-clinical testing alone; interaction with clinicians is vital. It is believed that the success rate of nanomedicines is limited, similar to that of early antibody treatments. Nanomedicines and other cures take time to reach the market. It is possible that their clinical efficacy is insufficient to warrant accelerated development, or that technical or financial challenges in scale-up or production can cause delays (or call for further investment).

Inadequate understanding of disease heterogeneity in the patient population, inability to fine-tune the system based on the disease biology or stage of the target patients, and inability to establish a foundation of evidence in support of a particular end clinical application may be the most significant reasons for failure.(Lammers & Ferrari, 2020; Sahoo et al., 2007).

This circumstance ought to motivate us to improve the planning and execution of our projects. Focusing on how nanomedicine therapies are tested in clinical settings is crucial if we are to fully benefit from the considerable breakthroughs in nanomedicine engineering. The clinical results will be improved by investing in translational science, as it has been for other classes of cancer treatments. Nanomedicines will become widely recognised as a reliable and practical medication development option after they have proven to have better clinical performance. As was said above, traditional nanomedicine research initiatives have been designed to modify a delivery system's physical and chemical properties (loading, chemistry, size, charge, and surface modification) in order to manage its in vivo behaviour. Understanding the characteristics of patient malignancies that pose particular difficulties for nanomedicines to work at their best has been mostly absent. The task of identifying the relationships between patient biology and nanomedicine behaviour has received considerably less scientific attention. Despite the fact that the current emphasis of nanomedicine is focused on the enticing, but frequently unproven, premise of a positive correlation between EPR and efficacy, a greater emphasis on four critical areas will improve the clinical translation of nanomedicine initiatives.(Fig. 1):

1. creating an understanding of how tumour pathophysiology interacts with the behaviour of nanomedicines in tumours in order to optimise tumour accumulation, intra-tumoral distribution, and retention of different nanomedicines;
2. Developing and employing more clinically relevant animal models to optimise the characteristics and dosage regimens of nanomedicine.
3. Change from formulation-driven research to disease-driven rational development.
4. Patients who are likely to respond to nanomedicine-based therapies are selected beforehand.

Utilizing the 5Rs framework's principles and implementing these enhancements in nanomedicine science will provide a more precise and better-translatable approach to nanomedicine development that is patient-centered and disease-driven.

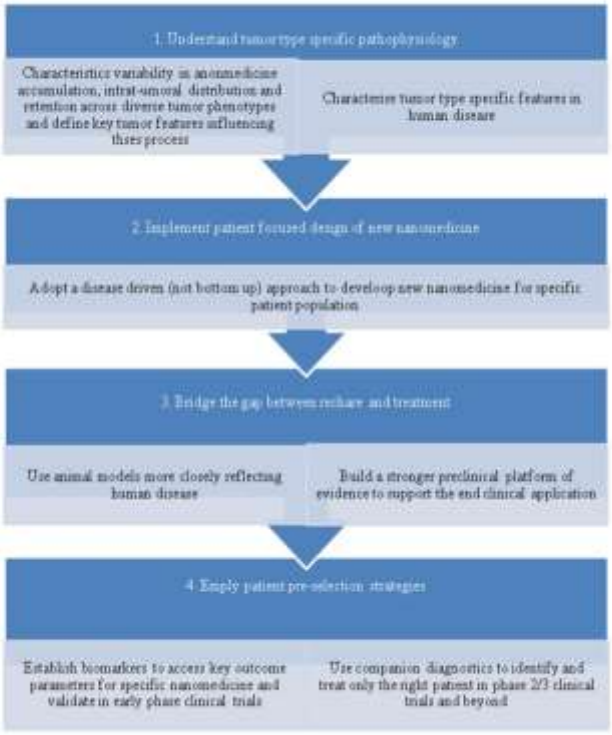

Figure1: The successful clinical translation of nanomedicine

These four areas are essential for boosting the clinical translation of nanomedicines, but the selection of financing priorities is equally significant. This will depend on the unique challenges that each nanomedicine experiences during its development. In the development of nanomedicine, innovative delivery methods with existing drugs and established delivery systems with innovative payloads are two common scenarios. The development of a novel nanomedicine employing a well-defined delivery strategy will be aided by the selection of suitable patients. Here, it is believed that the factors affecting the efficacy of the free drug (concentration versus exposure length) as well as the in vivo behaviour and critical delivery system quality factors affecting in vivo performance are previously known. In contrast, while evaluating a novel delivery system, expenditures should be focused on collecting understanding of the delivery system's behaviour across a number of cancer models in order to assist select the most relevant therapy populations.(Jr, 2005). When beginning the development of a novel drug with a novel delivery route, incorporating patient-driven design and generating robust pre-clinical evidence will be the most advantageous areas to focus on.

6. Developing nanomedicines in accordance with "industry-style" principles to improve clinical translation

Pre-clinical experimentation has been effectively utilised to provide proof-of-concept and drive the optimisation of new nanomedicine technologies, but it is essential to recognise its limitations and retain objectivity regarding its significance for future development. Early preclinical testing should largely focus on identifying the therapeutic potential and any potential clinical issues, as well as selecting formulations that are safe, effective, and exhibit

the required pharmacokinetic and biodistribution characteristics. In the past, anti-cancer nanomedicine research followed the conventional formulation-driven methodology: novel nanomedicines were created and evaluated using in vivo pharmacokinetics/biodistribution studies, anti-tumor experiments in xenograft models susceptible to the payload, and in vitro cytotoxicity assays. This paradigm has not produced the data required to shed insight on the critical difficulties preventing the successful translation of nanomedicines into the clinic. Instead, scientists should be able to determine whether or not to invest early in the development process, prior to spending a substantial amount of money on clinical studies. (Koo et al., 2005). This section focuses on the goal of disease-driven design and creating pre-clinical project data that more consistently disclose clinically relevant therapeutic results, to be implemented in the treatment of the right patients. This section acknowledges the need to enhance the present nanomedicine development process.

6.1 Adopting a systematic strategy for nanomedicine initiatives

No single nanomedicine can effectively and adequately cure every type of tumour. Thanks to the range of nanomedicine systems that are currently available, big pharma can adopt a disease-driven development strategy and abandon formulation-driven (bottom-up) techniques. Developing a clinical line of sight early on in the project is critical, as is recognising the specific issues with the existing standard of care, such as a high incidence of normal organ toxicity or an incorrect pharmacokinetic profile. Rather of establishing a delivery system and then trying to match it with an existing clinical issue, it is more likely that a nanomedicine will be successful if it is designed to address a specific cancer's well-defined problem. To enable the data-driven selection of nanomedicine systems that are best suitable for specific disease types, it is essential to consider the interplay between the different pathophysiology of the disease and the patient and the physicochemical properties of distinct nanomedicines. In addition, this necessitates that the clinic generate more specific data that can be used to improve development plans. Therefore, in order to generate clinically effective and transferrable nanomedicines, it is necessary to employ logical selection criteria. (Hare et al., 2016; Sandhiya et al., 2009). A disease-driven approach to drug development focuses on coordinating a pharmaceutical, delivery method, and target patient population in order to optimise therapeutic activity (Fig. 2). Certain drugs are effective against human cancers, for example. The physicochemical features of various nanomedicine systems affect their suitability for delivering specific pharmaceuticals and any off-target consequences that may result from the "dosage" of the delivery system required to achieve therapeutically active drug concentrations in patients. In addition, the cancer characteristics of the target patient

population will influence the levels of carrier accumulation and retention that can be anticipated, which will determine whether the system can achieve the drug release rate required to deliver the medication to the tumour at therapeutic levels/exposures. The off-target buildup of the carrier will decide if the drug achieves an acceptable safety profile when administered in conjunction with traditional standard-of-care regimens for the malignancy of interest. Although challenging, taking into account these patient- and disease-specific aspects throughout the design phase could result in more transferrable nanomedicines. (Bregoli et al., 2015; Farokhzad & Langer, 2006).

However, it would be impracticable to create customised nanomedicines for every patient. Using a structured framework, the goal is to tailor the development of a nanomedicine to a specific patient population. A thorough understanding of cancer genetics has led to a patient-centered approach to the development of drugs that target specific genetic causes. Initial investment is required to gain a comprehensive understanding of the needs outlined in Figure 2 in order to move forward with patient-driven nanomedicine development. This understanding, despite its complexity, will facilitate the potential to achieve focused, accelerated, and translational development with a clinical perspective. After establishing a clinical line of sight, the genetic profile and intrinsic sensitivity of the target patient group are taken into consideration. These consist of:

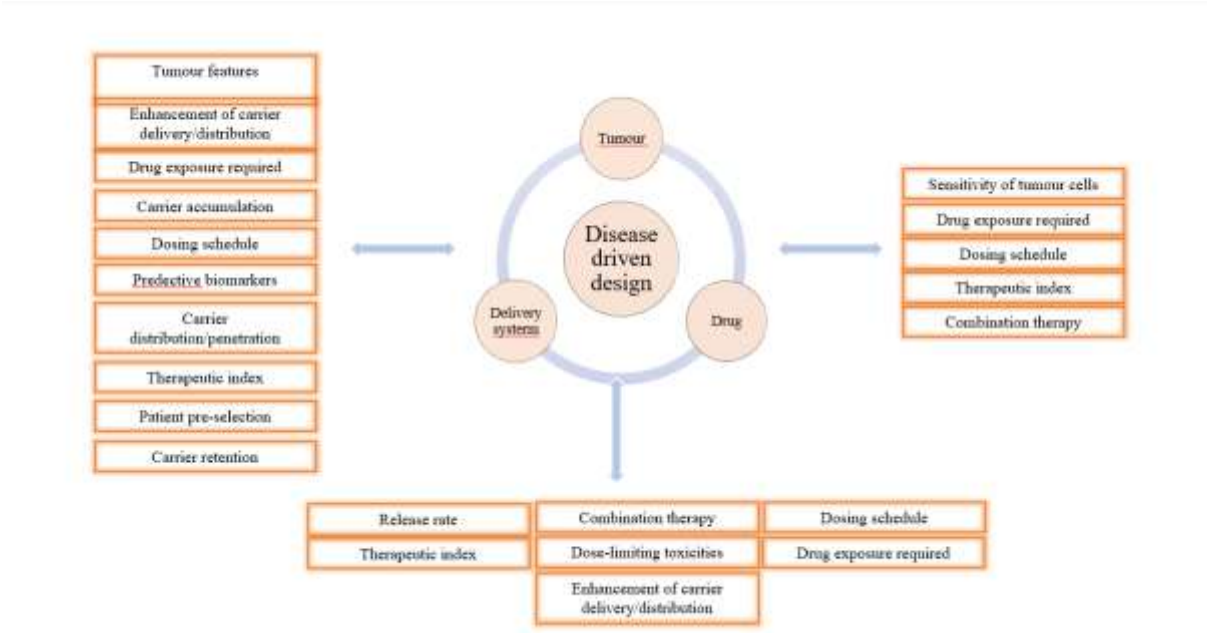

Figure2: Considerations when selecting the delivery mechanism, medication, and patient population for disease-driven design and development of novel anticancer nanomedicine

Choosing the appropriate models for testing, determining the optimal drug release rate (to achieve the desired high maximum concentration, increased area under the curve, and improved therapeutic index, etc.), optimising the dosing schedule, and gaining knowledge of combination therapy are all steps in the drug selection procedure.A series of targeted tests are needed to develop the nanomedicine and progressively address clinically pertinent queries concerning the lead candidate in order to create this clinically interpretable data set (Lammers, 2018). Given that in vivo research employing realistic models is significantly more expensive, it is essential to carefully evaluate the worth of the obtained data sets. The testing of models and nanomedicines that represent the extremes of many parameters (such as cancer phenotype or medication release rate) can provide more comprehensive knowledge and enable the application of complementary in silico modelling techniques to reduce overall cost.

6.1.1 Utilizing disease-driven design to attain the "appropriate effectiveness"

Understanding how biology affects the behaviour of nanomedicine is the foundation of disease-driven design, which helps choose a carrier that can take advantage of the pathophysiology. diverse tumours and diseases have diverse tumour microenvironments, which poses specific challenges for nanomedicine-based treatment. While some delivery systems can get over these challenges, others may have issues. In order to create the best nanomedicine to take advantage of the pathophysiology, disease-driven design takes the target patient population into account from the beginning (Hofmann-amtenbrink et al., 2015).

In highly stromal phenotypes, combining nanomedicines with treatments designed to modify the cancer microenvironment may be able to overcome the physiological limitations that some nanomedicines have on their ability to cure disease.(Farley, 2020). Combination approaches with hyaluronidase, collagen degradation or regulation of its synthesis or cross-linking, and vascular normalisation are all potential benefits of nano medical treatments. When present, the tumour cells in renal malignancies and certain other highly vascularized tumours are near to the blood vessels. However, the retention of the carrier may be decreased or confined to the tumor's periphery.

To get the desired exposure, it may be necessary to use a nanomedicine with a fast enough drug release rate to make the payload bioavailable before the delivery system is eliminated from the tumour. For cancer types in which prolonged retention of the delivery system is unlikely, slow-release nanomedicines may not be the ideal solution. Alternately, by including a specific ligand within the carrier, it may be possible to improve retention and circumvent this issue. Utilizing the mononuclear phagocytic system and investigating immune oncology

treatments or combinations are now realistic options for macrophage-rich malignancies. These examples illustrate the potential advantages of tailoring a nanomedicine to the biology of a certain patient population.

6.1.2 Utilizing patient-centered design to achieve "appropriate safety"

Evaluating the efficiency of nanomedicines is just as crucial as comprehending their off-target consequences.All tissues that have characteristics, such fenestrated vasculature, that allow the accumulation of the delivery system, such as nanomedicines, will exhibit these traits. To boost effectiveness, it is therefore equally important to define the characteristics governing the tissue localization of various delivery methods, particularly within the reticuloendothelial system. A new article by Kirtan et al. demonstrates how a predictive model of size-related carrier accumulation can help us build experimental hypotheses to test and obtain a more comprehensive understanding of the behaviour of nanomedicine. The model in this research shows that the EPR effect is not always the primary factor influencing the efficacy of nanomedicines and suggests that the characteristics of the tumour, specifically its pore size, determine the size of the delivery system. Additionally, the relative clearance from tumour versus normal tissues and the release rate of the medication from the delivery system regulate the levels of the drug in various target and off-target organs (Kirtane, Siegel, & Panyam, 2014). The creation of AstraZeneca's AZD2811, an Aurora-B kinase inhibitor administered by a BIND Therapeutics AccurintTM polymeric nanoparticle, exemplifies the necessity of comprehending therapeutic index. During preclinical study, the drug release rate from the nanoparticle was used to reduce bone marrow toxicity caused by therapeutic drug exposure.(Hofmann-amtenbrink et al., 2015). By adding diverse cancer types and normal tissues into core models of nanomedicine behaviour, decision-making pertaining to the development of nanomedicine-based therapeutics will be significantly facilitated. By defining these features across the nanomedicine toolbox, it is possible to match a delivery system with a suitable distribution profile to the toxicity profile of a particular drug in an appropriate disease scenario. This is especially important when creating a nanomedicine to address a recognised problem, such as the limitation of a patient's cumulative dose due to doxorubicin-induced cardiotoxicity. Doxorubicin is delivered in a liposomal formulation, which eliminates or substantially lowers cardiac exposure and permits patients to receive higher lifetime doses. In addition, well-tolerated nanomedicines such as DoxiaTM may be useful in combination regimens to promote tolerance or allowing the delivery of higher dosages of the combination partners.(Boulaiz et al., 2011; Sandhiya et al., 2009). Due to changes in pharmacokinetics

and biodistribution, the off-target toxicities of nanomedicines may be distinct from those of the parent medication.

6.2 Building a stronger evidentiary base to justify project advancement

Typically, throughout the development of nanomedicine, the primary focus is on tumour accumulation based on the EPR effect. Although the accumulation of nanomedicines is low or highly variable in some cancer types, changing the pharmacokinetics of the drug in peripheral plasma may still have therapeutic value. In order to evaluate the efficacy of nanomedicines, preclinical research must create data sets describing four behavioural features. (Hare et al., 2016). These characteristics include tumoral accumulation, intra-tumoral distribution, tumoral retention of the system, and the added contribution of the nanomedicine's peripheral pharmacokinetics (or circulation). For each malignancy, it is anticipated that each of these qualities will independently contribute to the potential efficacy; nevertheless, the dominant attribute can influence the preferred administration strategy and release kinetics. The following should be considered by informative and translatable data sets::

- Identify intra-tumoral carrier retention, drug release rates, and drug metabolism throughout time;
- Differentiate between bioavailable/released drug and total drug concentrations in the tumour, plasma, and other vital organs (e.g., liver, etc.);
- elucidate the intratumoral distribution of therapeutically active amounts of bioavailable drug and drug metabolites;
- Determine how repeat dose affects the plasma, off-target tissue, and tumour pharmacokinetics of the nanomedicine;
- assess therapy efficacy in cancers with decreased EPR content;
- determine the therapeutic value of extravasation against simple accumulation/residence in the tumour vasculature versus medication pharmacokinetic modification;
- determine the degree of therapeutic advantage conferred by extravasation versus simple accumulation/residence in the tumour vasculature versus change of the drug's pharmacokinetics;
- maintain clear focus on the final clinical application of the nanomedicine (such as conjunction with standard of care); analyse its effectiveness in this setting to determine an acceptable dose and administration schedule.

To further comprehend how a payload eventually has a therapeutic impact, we must consider the payload's release, trafficking, and target engagement. In addition, it is necessary to invest in the development and enhancement of essential analytical procedures, as many of the aforementioned parameters depend on the ability to differentiate between the concentrations of bioavailable and bound/encapsulated medication in the body. These intricate data sets may only be accessible through more strategic alliances. Once used, the data packages that can be created throughout the development of nanomedicines will be far more discriminatory and informative when selecting lead candidates and progressing towards the clinic. Maintaining a strong focus on the final clinical application and having a comprehensive grasp of the therapeutic margin of novel nanomedicines is likely to have a substantial effect on translation.

6.3 Improving the translation of nanomedicine by employing more clinically relevant models

Pre-clinical nanomedicine development projects often rely on insensitive subcutaneously implanted cell line-derived xenograft models, which have limitations in translatability to the clinic (Gabizon & Martin, 1997). These models often present pathologies that do not resemble the complexity and heterogeneity of clinical tumors. EPR-based efficacy should occur across all human tumors, and the drug delivery field is based on this belief. Pre-clinical testing in poorly representative models is a significant obstacle for translating nanomedicine research. To better represent the target patient tumor population, it is essential to generate data sets in diverse models that represent aspects of the target clinical tumor population.

Aligning drug and delivery system activity with the genetic profile of the target patient population and the suitability of the delivery system in specific tumor pathophysiology often requires multiple pre-clinical models. Identifying potential limitations early can inform stop decisions or constrain patient types in early trials. Establishing the therapeutic index with agents the nanomedicine will be combined with in the clinic can inform the likelihood of success in early clinical trials. Early decision-making is crucial for cost-effective development of nanomedicines and other anti-cancer therapeutics (Gabizon & Martin, 1997).

6.3.1 The benefits of using more clinically relevant models

The form, complexity, and variety of clinical cancers are accurately reflected in patient-derived tumour explant (PDX) models and genetically engineered mouse models (GEMMs). Although difficult to generate and maintain due to their sluggish growth rate and need for live passage, these models have the ability to evaluate the efficacy of nanomedicine in specific organs. Although they are not immediately predictive of the clinic, they enable the evaluation

of nanomedicine performance and provide insight into potential dangers. Using these models, researchers have developed fresh perspectives on nanomedicines, and GEMMs, in which the tumour develops in situ, can provide additional information. Realizing analyses of nanomedicine accumulation, intra-tumoral distribution, and retention will be useful for providing evidence for the efficacy of different nanomedicines across distinct tumour types as more therapeutically relevant and diverse models become accessible. (Kalra et al., 2014).

In clinical tumours and PDX models, the mature vasculature is less permeable than in xenografts, which develop over days and have features less affected by tumour cell proliferation.(Song et al., 2014). To gain a more realistic grasp of the probable outcomes in various human disease segments, it is required to evaluate many models with diverse vascular distributions and tumour-to-tumour variance.

6.3.2 With more therapeutically relevant models, greater variation is conceivable.

In a group of tumours with the same intrinsic sensitivity, the architecture of the tumour has a substantial effect on the efficacy of nanomedicine treatment. This emphasises the significance of creating biomarkers and imaging techniques that enable pre-selection strategies for patients. Enhanced vascular permeability and the presence of the enzyme that creates the active drug SN-38 were discovered to influence the accumulation of active drug in the tumour, which in turn affected the therapeutic efficacy.(Delgado, Martin, Hare, Yates, & Barry, 2015). Xenografts produced from tumour cells retained more active SN-38 than tumour cell explants. Exploring more diverse models can give useful insights into the potential of liposomal irinotecan and aid in the concentration of development and population-specific methods. The variety of models utilised in the study by Kalra et al. provides a deeper understanding of the potential of liposomal irinotecan and a data platform for concentrating development and population-specific methods.(Kirtane et al., 2014).

7. Pharma perspective

Oncology projects confront obstacles such as inadequate pre-clinical testing, a disparity between animal models and human patients, and success determinants. To enhance translation and gain greater investments, project teams must describe tumour type, stage, dose, and dosing regimen, as well as prospective medications that may be coupled with the novel agent. Answering these concerns is essential for translating oncology medicines and attracting further funding. To make a project appealing for pharmaceutical development, it must have the possibility to test targeted hypotheses and make success determinations with low initial investment. When there is confidence in the 5Rs (right target/efficacy, right

tissue/exposure, right safety, right patients, and right commercial potential), projects move forward.(Cook, Brown, Alexander, March, & Morgan, 2014).

7.1 The price of victory and defeat

The likelihood of a small molecule medicine advancing from pre-clinical proof of concept to commercial launch is approximately 6%. When investing in nanomedicines and other therapeutic classes, such as antibodies, peptides, and DNA/RNA-based agents, the sector encounters obstacles. Complex formulations, a lack of understanding of the association between quality qualities and efficacy, changing regulatory attitudes, technical hurdles in manufacturing and scaling up, maturation of analytical methods, and high costs are obstacles for these medications. The cost-benefit ratio of nanotherapeutics should not be discounted due to the disproportionately high development expenses. Instead, it may be more sensible to produce active pharmaceutical compounds that are compatible with nanomedicine.

Synthetic chemists can incorporate certain characteristics into the design of innovative tiny molecules in order to generate nanomedicine-compatible medications. However, the cost of moving a nanomedicine prototype into the clinic and beyond might be prohibitive for smaller biotech firms and academic laboratories. Due to increased technical sophistication, the risk associated with a novel medicine may be regarded as being lower by large pharmaceutical corporations.(Cook et al., 2014). Consequently, the pre-clinical data sets supporting nanomedicine treatments must be more robust than those supporting traditional drug therapeutics, which have more standard formulations, specified patient groups, and fewer treatment hurdles.

7.2 Collaborations are crucial to the development of nanomedicines in the future.

Nanotherapeutics development is a multidisciplinary activity integrating biology, chemistry, nanotechnology, and medicine. Early on in preclinical research, it is essential to build cooperation between giant pharma, smaller enterprises, and academia in order to generate translatable therapies. To develop data sets and insights relating the physicochemical features of nanomedicine systems to their biological consequences, effective cooperation between academia, industry, consortia, and cancer research hospitals are crucial. The Nanotechnology Characterisation Laboratory (NCL) was founded in 2004 by the National Cancer Institute, the National Institute of Standards and Technology, and the Food and Drug Administration. Its mission is to enable the preclinical characterization of nanomaterial-based drug delivery devices, to construct and standardise an analytical cascade for nanomaterial characterization, and to facilitate the clinical development and regulatory evaluation of nanomaterials for cancer clinical trials. The European Nanomedicine Characterisation Laboratory (EU-NCL)

was founded in 2015 with the same goals as the Clothier consortium.(Hare et al., 2016; Hofmann-amtenbrink et al., 2015).

8. Future opportunities and concluding remarks

Nanomedicines are increasingly being developed for cytotoxic applications, with future potential centred on the delivery of next-generation medications such as molecularly targeted agents, toxin-like agents, DNA/RNA-based therapies, and peptides. These medications confront obstacles including off-target accumulation, transmembrane passage, synergistic drug ratios, and restricted therapeutic windows. Alnylam Pharmaceuticals, Calando Pharmaceuticals, Avidity Nanomedicines, Merck, and Arrowhead Research Corporation are investing in cost-effective delivery of nucleic acid-based pharmaceuticals in order to make these treatments commercially feasible. Despite the fact that formulation-driven development has not yielded the anticipated patient advantages, nanomedicines have the potential to enter the mainstream of cancer therapies, including both conventional and novel drugs. To make nanomedicines cost-effective, one can employ focused design and a decision-making framework such as the 5Rs.

Without patient pre-selection methods, reaching the optimal cost-effectiveness for nanomedicine therapies remains problematic. The next wave of nanomedicines will be able to overcome the challenges encountered in present clinical trials as a result of a coordinated effort by the nanomedicine community to embrace new clinically focused methods of operation. Investing in the research underlying nanomedicine's core principles could have a substantial impact on the development of effective nanomedicine therapy for patients.

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Key terms:

Therapeutic Window: The therapeutic window (or pharmaceutical window) of a drug is the range of drug dosages which can treat disease effectively without having toxic effects.

Nanomedicines: Nanomedicine is defined as the development of nanoscale (1–100nm) or nanostructured objects/nano-robots/skin patches and their use in medicine for diagnostic and therapeutic purposes based on the use of their structure, which has unique medical effects.

Nanotechnology: Nanotechnology is the manipulation of matter on a near-atomic scale to produce new structures, materials and devices.

Human health: it is the ability of individuals or communities to adapt and self-manage when facing physical, mental or social challenges.

Potential health: It represents an imagined, possible observation of aspects of a current or future health state.

Public health: The science and art of preventing disease, prolonging life and promoting health

and efficiency through organized community effort.

Epidemiology: It is the study of distribution and determinants of health-related states among specified populations and the application of that study to the control of health problems

Heterogeneity: It signifies diversity.