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REVIEW

Nanotherapeutics to cure inflammation-induced cancer

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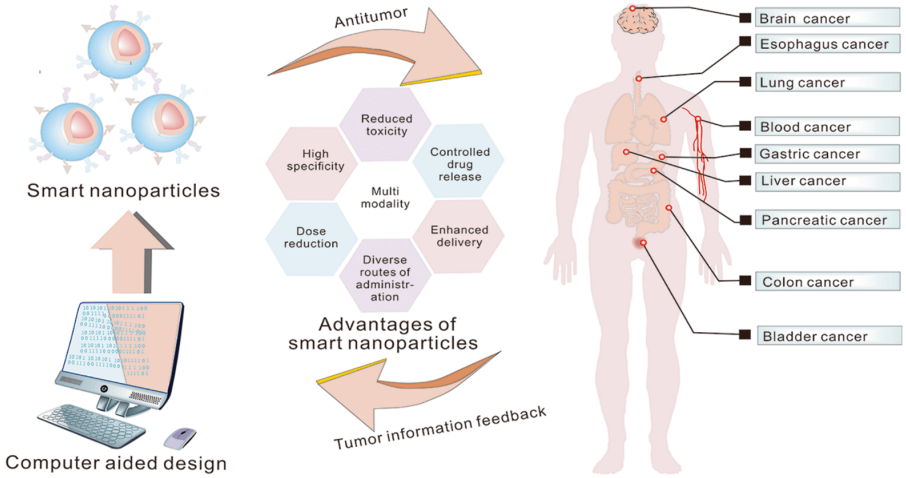
Abstract: Aims: Nanotherapeutics are being explored as a potential solution to treat inflammation-induced cancer. Nanotherapeutics enhance innate immune cells' immunity, enabling them to fight tumors effectively. These cells secrete specific chemicals like cytokines, allowing them to replicate quickly and respond to future threats, making them suitable for immunotherapy. **Methods**: Nanotechnology can significantly improve human health by enhancing infection detection, prevention, and treatment. Nanomedicines, composed of restorative and imaging compounds in submicrometer-sized materials, aim to deliver effective treatments and limit inflammation in healthy body areas. Combining nanotechnology and clinical sciences, nanoparticles are suitable for gene therapy and have been developed for treating various diseases, including cancer, cardiovascular, diabetes, pulmonary, and inflammatory diseases. **Results**: Neutrophils and their offspring, including films and extracellular vehicles, are crucial drug transporters for enhanced growth therapy. Tumor microenvironment inputs can modify tumor-associated neutrophils (TANs), which are essential for tumor growth and healing. Human tumor intratumor heterogeneity is crucial for tumor growth and healing. Nanomedicines have shown potential in targeted delivery, toxicity reduction, and therapeutic effectiveness enhancement. However, clinical relevance and efficacy remain inadequate due to a lack of understanding of the interaction between nanomaterials, nanomedicine, and biology. The diverse biological milieu impacts the dynamic bioidentity of nanoformulations, and their interactions can modify therapeutic function or cellular absorption. **Conclusion**: Nanotechnology holds great promise for improving human health by detecting, preventing, and treating infections. Nanomedicines, a fusion of clinical sciences and nanotechnology, use submicrometer-sized transporter materials for therapy delivery and reducing contamination. Nanoparticles' small size and high surface-to-volume ratio can benefit gene therapy. Research has led to a wide range of nanomedicine products globally.

Keywords: nanotherapeutics, inflammation-induced cancer, nanomedicines, nano-bio interactions



Graphical Abstract

Figure 1 Diagrammatic representation of intelligent nanoparticles in cancer therapy. Reprinted (adapted) with permission from Sun et al. (2023) [1]. Copyright (2023) Springer Nature Limited.

1 Introduction

Nature nanotechnology reports game-changer remedies and that are nanotherapeutics, which can tackle inflammation without creating any perturbation in the normal routine of healthy immune cells, can replace existing therapeutics [2]. Nanoparticles and multifunctional nanomaterials displayed enormous potential because of their physical and chemical features, for example, extremely small size at a scale of ten and a thousand times smaller than a pathogen. The nanotherapeutics enhance the immunity of the innate immune cells, and as a result, they can fight well with tumors. The immune cells can replicate quickly and outbreaks at upcoming threats by secreting specific chemicals, such as cytokines. Nanotherapeutics boost the immunity of these cells and can be applied as immunotherapy. Similarly, a few immune checkpoint inhibitors applied as immunotherapy for treating cancer, but in the presence of an immunosuppressive microenvironment, these remedies are ineffective [3]. Nanomedicine and immune checkpoint inhibitors are collectively effective. As, inflammation regulates tissue homeostasis, but in adverse conditions, the physiology of inflammation loses its natural sensation and triggers the pathogenesis of a disease [4]. By considering the verified facts that nanomedicine enhances drug durability in the blood and the potential of phagocytic immune cells, these remedies can be applied for improving immunotherapy for treating cancer. Meanwhile, unwanted cellular events, including DNA damage, replication, apoptosis, angiogenesis, origin of disturbances in growth signaling, and tissue metastasis instigated further progression of the diseases [5]. So many pieces of evidence proved the association between chronic inflammation and cancer, specifically lung cancer.

Mitochondria control life- and death-signaling pathways and also play a crucial role in the biology of cancer and inflammation. When mitochondrial dysfunction occurred, the phenomenon of mitochondrial reactive oxygen species and downstream signaling atone originated that finally promoted the growth of inflammation-associated cancer. For exploring the pathology of inflammation-associated cancers, the routes of concerned signaling pathways should be investigated, and then the innovative strategies for developing novel nanotherapeutics can be applied for successful treatment of inflammation-induced cancer. The innovation of nanotransporters will open new avenues that can be used for therapeutic, imaging and diagnostic agents. The insight on the pathophysiology of inflammation can further boost the innovative nanomedicine approaches for the resolution of inflammatory disorders, and, finally, scientists can focus on conducting clinical trials. Recently developed nanomedicines redefine the role of macrophages and transforming them as potential clinical therapeutic agents that are capable treating inflammation and cancer [6]. Similarly, a nanotherapy treated colon cancer and regulate tumor microenvironment simultaneously [7]. Nanoparticles based strategies exploit the inflammatory pathways and target the tumor-associated microenvironment for therapeutic and diagnostic purposes selectively [8]. A metabolic-based method was applied for cancer detection through functional computed tomography imaging [9].

Nanotherapeutic applied with an effective systemic metastasis-targeted approach for combating tumor metastasis and reinforcing tumor surgical resection [10]. Macrophage-biomimetic nanoparticles were developed for suppressing local inflammation and sequestration of proinflammatory cytokines [11]. Self-illuminating nanoparticles, which generate bioluminescence resonance energy and transfer singlet oxygen ($1O_2$) from the nanoparticle, applied for in vivo imaging and cancer therapy [12]. The biomimetic nanotherapy, a core–shell structured nanocomplexes based on the neutrophil membrane, inhibit the expression of inflammatory factors and induce apoptosis of lymphoma cells [13]. Cell membrane biomimetic nanoparticles inheriting specific biological functionalities can evade immune elimination, prolong circulation time, and even target location inflammation and cancer [14, 15]. Fumagillin prodrug nanotherapy that can induce $\alpha v\beta 3$-integrin-targeted perfluorocarbon nanocarriers suppresses macrophage inflammatory response via endothelial nitric oxide [16]. Drivers of macrophage that can target cancer-related inflammation, and performed in any therapeutic condition [17]. Nano formulated resveratrol inhibits metastasis and angiogenesis by reducing inflammatory cytokines and targeting tumor associated macrophages [18, 19]. Iron based nanotherapeutics, which can define a central role of iron in ferroptosis, inducted for ferroptosis-induced cancer therapy [20]. A review published on the current applications of clinically approved nanomedicines, role of nanomedicines in clinical trials, and the persisted challenges in development of the nanomedicines for cancer treatment [21]. Cancer drug delivery in the nano era, a review article published that covering the key constituents of the nanotechnology, including liposomes, polymer nanoparticles, dendritic polymers, and nanomicelles, for the diagnosis and treatment of various cancers [22].

Recently developed nanotools were reported for inhibiting cancer inflammation caused by the viral infection, such as SARS-CoV-2 [23]. and can differentiate between normal and cancer cells, were applied as nanotherapeutic strategy for breast cancer therapy [24, 25]. Nano-gold remedies displayed anti-inflammatory activities, ameliorate production of inflammatory mediators and reduce oxidative stress via NF-kB pathways by suppressing COX-2 activity [26]. Hesperidin loaded gold nanoparticles were developed as a drug delivery system that can inhibit the secretion of IL-1β, IL-6 and TNF, significantly and can be applied for a successful biocompatible, anti-cancer, anti-inflammatory and phagocytosis inducer model [27]. A Transferrin-conjugated hollow nanoplatform that can elevate glutathione level inside tumor cells, reduce inflammatory reactions, improve anticancer efficacy both in-vitro and in-vivo for redox-controlled and targeted chemotherapy of tumor were reported [28]. Nanomedicine applied as immunostimulatory therapies to suppress the tumor microenvironment as well as inhibit angiogenesis, remodel matrix, and modulate immune responses [29]. Nanomedicine methods in enzymology that comprehensively used for the treatment of cancer, cardiovascular, diabetes, pulmonary and inflammatory diseases, recently published [30]. H_2O_2-responsive liposomal nanoprobes that are capable for photoacoustic inflammation imaging and tumor theranostics were developed [31]. Smart cancer nano-theranostics that can perform in the acidic tumor microenvironment utilized the precise diagnosis and effective treatment of cancer [32]. Nano-peroxidase were used as a promising anti-inflammatory, antibacterial agent against bacteria and inflammation induced cancer [33]. Nano for freezing to destroy cancer augments cryosurgical injury on human prostate cancer were reported that can pre-inflame prostate cancer promises also recommended as pre-treatment for inflammation induced by TNF-alpha [34]. Bioactive nanotherapeutic were employed to combat triple negative breast cancer [35]. A book entitled "Multifunctional Nanoparticles for Drug Delivery Applications: Imaging" covered different features of nanomaterials and nanomedicines, including their application in targeting, therapy, imaging, delivery, and diagnostics. Inflammation initiate DNA damage and induce mutations, these unwanted events initiate cancer and cancer recurrence [36].

Nanotherapeutics were applied for medical diagnosis, monitoring and treatment at the level of single molecules to gain increased understanding of underlying disease for better clinical results [37]. One more review article was published that focus on the progression of inflammatory diseases, available biological therapies, and covering the concepts of macrophage repolarization for treating inflammatory diseases [38]. Nanocarrier-mediated immunotherapy discussed for treating cancer in vitro and in vivo [39]. and interrelated gray zone of nanomedicine were highlighted [40]. The progress, challenges and opportunities in cancer nanomedicine was discussed in a review article and also discussed novel engineering approaches for understanding of tumour biology. These findings can be used for designing novel nano-bio interactions that can be more effective in the development of more effective cancer nanotherapeutics (Figure 2).

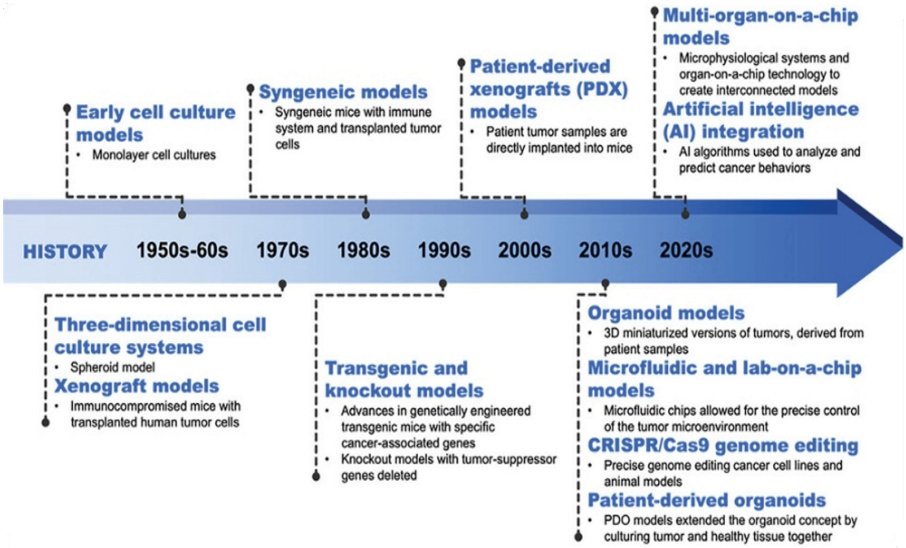


Figure 2 An illustration of history of tumor models since the first human cancer cell line was established. Reprinted (adapted) with permission from Wu et al. (2024) [41]. Copyright (2024) John Wiley & Sons, Inc.

Complexities and heterogeneity of tumour biology, incomplete understanding of nano–bio

interactions and the challenges regarding chemistry, manufacturing and controls required for clinical translation and commercialization are still great concerns [42]. Targeting neutrophils can be a novel strategy for tumor theranostics and may open up new avenues that can be helpful in designing nanomedicine that can exploit tumor microenvironment [43]. Nanomedicine and cancer immunotherapy target immunosuppressive [44]. Translational nanomedicine is bridging the gap between the laboratory bench top and the clinical trials conducted for the search of the treatment for inflammatory diseases [45–47].

2 Neutrophils and tumor theranostics

Particular depiction of gainful neutrophil populaces and designated hindrance or re-polarization of cancer advancing neutrophils has shown significant potential in growth treatment [48]. Neutrophils and their subsidiaries (films and extracellular vehicles (EVs) are viewed as cutting edge drug conveyance transporters for upgraded growth focusing on and worked on restorative viability [49]. Tumor-associated neutrophils (TANs) that have accumulated locally have the ability to change their phenotype from pro- to anti-tumor in response to external inputs from the tumor microenvironment [50]. By inducing cytotoxicity and triggering adaptive immune responses, anti-tumor neutrophils destroy tumor cells both directly and indirectly. In contrast, in TME, cell proliferation, angiogenesis, and immunosuppression may be linked to neutrophils' pro-tumor phenotype [51]. All the more as of late, neutrophils have been proposed as a likely objective in malignant growth treatment for their capacity to lessen the supportive of cancer pathways, for example, by safe designated spot barricade.

One strategy for adjuvant cancer treatment might be the prevention or reversal of neutrophil reprogramming. Reprogramming of mature neutrophils may result in neutrophil reprogramming because cancer patients' neutrophils are heterogeneous [52]. Cancer cells create the environment that supports the reprogramming of neighboring neutrophils and mold the cancer microenvironment by secreting a range of cytokines, chemokines, and other substances. The hypothesis is supported by neutrophils acquiring new transcriptional activity, which could be classified as distinct neutrophil subsets based on single cell RNA sequencing analysis in a particular microenvironment. Neutrophil Extracellular Traps (NETs) are extracellular scaffolds derived from neutrophils that have been linked to the development of sterile inflammation-associated diseases like diabetes, cancer, and autoimmune diseases [53]. This survey features and examines the later examinations on the jobs of NETs in malignant growth improvement, with an extraordinary spotlight on disease metastasis. In addition, it discusses methods for focusing on NETs prior to tumorigenesis (Figure 3).

The outcomes on growth antigens (TANs) in cellular breakdown in the lungs feature the tremendous impacts of the host's resistant framework and the cancer microenvironment in applying a favorable to cancer-causing or hostile to cancer-causing impact [54]. Growth cells are just pitifully immunogenic as a rule, which is one of the significant motivations behind why diseases with such ease go through safe getaway. The neoantigen vaccine method is one way that TANs can be used in cancer treatment. As demonstrated by the BCG vaccination, increasing evidence suggests that vaccines alter neutrophil function over time. Essentially, during inoculation with the pneumococcal form immunization, sufficient neutrophil capability and initiation are an essential. When BCG is administered, the concentrations of the cytokines tumor necrosis factor (TNF), interleukin (IL) 1, IL 6, and TNF-related apoptosis-inducing ligand rise in the target areas and neutrophils have a direct lethal impact. It is hypothesized that neutrophils promote the recruitment of these proinflammatory chemicals, hence amplifying the anticarcinogenic action of the BCG vaccination.

Neoantigens as therapeutic targets with greater immunogenicity have become increasingly the focus of research in recent years, with the goal of developing novel immunotherapeutics [56]. TANs, likewise being antigen-introducing cells in the growth microenvironment, may likewise assume a critical part in the improvement of immunotherapeutic specialists, i.e., the age of neoantigen immunizations against tumors [57]. Neoantigens that could be the basis for vaccines against cancer can thus be identified. Neoantigens in tumor cells differentiate them from healthy cells in terms of how they affect immunity [58]. In principle, neoantigen immunizations as a future sort of immunotherapy might be utilized to prompt a particular enemy of growth reaction in the host, creating a steady remedial impact. Tumor neoantigens interact with MHC molecules to trigger an anti-tumor immune response in the host. The aberrant expression of targeted neoantigens by cancer cells and normal cells is linked to the therapeutic efficacy of tumor vaccines. T cells that are stimulated by the neoantigens of cancer cells can result in the production of highly active T cells, whose receptors have a strong affinity for MHC–neoantigen-

peptide complexes, making it less likely that central immune tolerance will clear them up. Strongly clonal driving mutations are present in a large number of tumor cells. In a work by Schumacher et al., a mutation in is citrate dehydrogenase type 1 (IDH1) was used to create an anti-tumor vaccine [59]. The IDH1 mutation, which results in aberrant enzyme action and malignant transformation, is seen in several cancer forms.

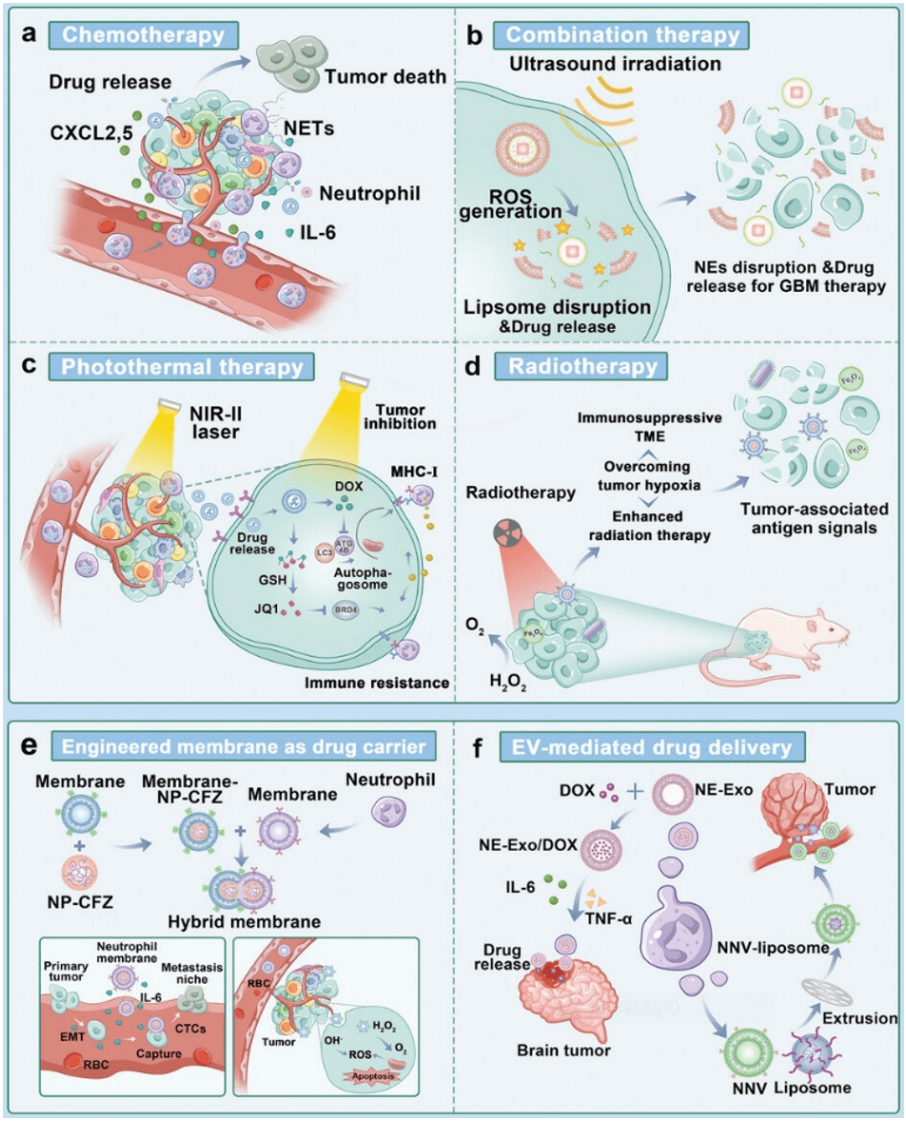


Figure 3 Drugs delivered by neutrophils. a) Chemotherapy: Neutrophils laden with drugs move to nearby tumor locations and have stronger effects on tumor inhibition. b) Sonodynamic treatment: Neutrophil-loaded acoustic sensitizers improve the effects of sonodynamic therapy on deep tumors by overcoming removal from blood circulation. c) Photothermal therapy: photosensitizers supplied by neutrophils to the tumor site cause hyperthermia when exposed to NIR laser radiation, which triggers an immune response against the tumor. d) Radiotherapy: radiation causes the immunogenic death of tumor cells and releases a significant amount of antigens connected to tumors following the injection of neutrophils laden with nanoparticles. e) An example of how medication carriers for cancer treatment can be made from nanomaterials covered with neutrophil membranes. Applying a coating made of neutrophil membranes or hybrid membranes effectively increases nanomaterial penetration via microvascular endothelium and produces long-term cancer treatment effectiveness. f) Neutrophil-derived EVs may directly inhibit tumor growth and introduce chemotherapy medications, including DOX, into the tumor. The Blender program was used to create the picture. Reprinted (adapted) with permission from Zhang et al. (2024) [55]. Copyright (2024) John Wiley & Sons, Inc.

Clinical preliminaries of conventional enemy of cancer antibodies focusing on growth related antigens have shown restricted accomplishment because of the steady end of Immune system microorganisms that perceive cancer related antigens by the thymus. In clinical studies, neoantigen vaccines based on tumor-specific mutations have shown more promising results. As antigen-presenting cells in the tumor microenvironment, TANs have not yet been used to create cancer vaccines, according to our knowledge [60]. TAN-presented neoantigens might also be used to make vaccines against cancer in the future. A blend of both a neoantigen immunization and explicit enrollment of the antigen-introducing TAN aggregate in diseases might be a promising restorative choice as an original way to deal with hostile to growth resistant treatment.

3 Complexities and heterogeneities of tumor biology

Human tumor intratumor heterogeneity is a great phenomenon that performs an essential function in tumor development and healing response [61]. It starts within the early levels of neoplasms and is a byproduct of the tumor boom as genetic abnormalities accumulate. Almost all phenotypic characteristics, which include cell morphology, motility, proliferative, angiogenic, gene expression, metabolism, and metastatic potential, regularly showcase big intra-tumor heterogeneity in most cancer cells [62]. The interactions of heaps of macromolecules prepared into multimolecular complexes and practical modules that have interaction supply upward thrust to complicated phenotypes. These modules shape utilitarian corporations in wellness and illness, and know-how boom behavior ought to cope with atomic in addition to boom mobile heterogeneity through thinking about sickness tissue hereditary and epigenetic networks [63], portraying adjustments within the sorts, pieces, and cooperations of homes and corporations in numerous portions of most cancer tissues, and spotting simple facilities that interface them in existence. The interaction of these functional modules in various tissue components leads to the development of intricate intracellular or intercellular processes like DNA replication, chromosome isolation, and movement [64].

Mutations will have an effect on a number of pathways that manipulate how a mobile functions, usually on the cell level. One study, for instance, observed that people who smoke are much more likely to have a specific mutation within the gene KRAS (Ki-ras2 Kirsten rat sarcoma viral oncogene homolog) [65]. This mutation hijacks a regular pathway for mobile boom and differentiation, resulting in atypical mobile proliferation and overactivation of boom signals. In a comparable vein, several different cell pathways may be hijacked by means of a number of mutations, resulting inside the exclusive mobile abnormalities and boom styles that result in most cancers. Tumors are labeled as “hot” or “cold” primarily based on their potential to become aware of and get rid of most cancer cells that might be living inside tissues. The immune system plays a critical role within the improvement and development of most cancers. Lung tumors are classified as “hot” because immune cells have penetrated the malignant region, whereas pancreatic or mental malignancies are classified as “cold” because immune cells are absent [66, 67]. An excellent predictor of diagnosis and treatment response is the immune cell composition surrounding tumors; “hot” tumors typically respond more strongly to treatments that activate the immune system [68]. Notwithstanding, concentrating on the secure cells encompassing boom cells, their cooperations, and their task in illness remains testing.

Understanding the mobile-intrinsic and mobile-extrinsic elements that have an effect on tumor improvement and healing reactions is receiving renewed interest because of technological advancements. In tumor biology, intramoral heterogeneity is now a broadly studied subject matter that has caused new paradigms and reinterpretations of present ones [69]. However, the query of whether or not mitochondrial respiration or glycolysis is more essential in relation to defining the metabolic heterogeneity of tumors has been the subject of prolonged debate.

4 Clinical translation of the nanomedicines and nano-bio interactions

Nanomedicines have shown promise for achieving targeted delivery, lowering toxicity, and increasing therapeutic efficacy. However, due to our inadequate comprehension of nanomaterial/ nanomedicine-biology (nano-bio) interactions, their clinical utility and efficacy remain unsatisfactory [70]. The dynamic bioidentity of nanoformulations at each site is influenced by the non-equilibrated, complex, and diverse biological milieu [71]. A nanomedicine’s ongoing interaction with biological molecules and structures in biological environments has the potential to alter cellular uptake or completely alter the intended function of the drug [72]. For the intelli-

gent design of nanomedicines that are both safe and effective, a comprehensive comprehension of the underlying mechanisms of nano-bio interaction is essential. The driving force and redox reaction at the nano-bio interface, which are recognized as the primary factors that regulate the functions and toxicities of nanomedicines, have been the focus of recent research into the nano-bio interaction of nanomedicines [73]. Both the nanoparticle and the biomolecule have different physicochemical properties, which makes proteins lose their bioactivity and recombine their structure. Surface properties, biological functions, intracellular uptake pathways, and nanomaterials (NMs) fate are all affected by this.

Preclinical studies on nanomedicines' biodistribution and pharmacokinetics have demonstrated the value of imaging modalities in this context. The behavior of NMs in biological systems can be extensively characterized thanks to advancements in real-time in vivo visualization. In the pharmaceutical evaluation of NMs, imaging techniques can provide valuable additional information that conventional methods cannot [74]. This idea would essentially speed up the beginning phase of improvement and advance the way to effective clinical interpretation. Imaging-directed assessments of nanomedicines face a few limits, including the steadiness of the connection between the imaging test and NMs it marks. Breaking this bond can result in inaccurate results because it is necessary for accurate distribution kinetics and parameter values [75]. After release, the drug's localization may differ from that of the nanocarrier because the imaging tag is frequently attached to the nanocarrier rather than the drug. The NMs' physicochemical properties, labeling strategies, and spatial level (organ, tissue, or cellular level) all play a role in determining the best imaging method. Depending on the assessment objectives, image resolution and study duration should also be taken into consideration. For instance, X-ray have restricted applications in checking the biodistribution of NMs because of their unfortunate responsiveness and hardships in proving entire body imaging [76].

Atomic imaging strategies have the best awareness and take into consideration the apparent pharmaceutic assessment of NMs at follow, they experience the ill effects of low spatial resolution, the absence of physical data, and the need of utilizing radioactive specialists [77]. Additionally, controlling and maintaining the fundamental physicochemical properties of NMs remains a formidable obstacle. Targeting properties, drug release rate, biodistribution, and excretion of NMs are significantly influenced by the particle size distribution, shape, and surface characteristics of NMs [78]. For accurate pharmaceutical assessments, it is essential to keep these characteristics consistent. Biomedical imaging techniques have the potential to be incorporated into preclinical drug delivery research in order to enhance NMs-based treatments. Their primary focus is on monitoring the pharmacokinetic and pharmacodynamic behavior of NMs [79]. However, complicated evaluation procedures that go beyond the capabilities of imaging methods prevent non-invasive imaging techniques from adequately assessing the toxicity of NMs. These provokes urge interdisciplinary researchers to team up to speed up the clinical interpretation of nanomedicines [80]. Through investigating the associations among preclinical and clinical demonstrating, coordinating dynamic focusing on ligands and savvy upgrades responsive materials, and conquering obstructions of controllable, reproducible, and adaptable nanoparticle creation, cost, and poisonousness, the up and coming age of nanomedicines with one of a kind sub-atomic modules and helpful specialists will be rapidly advanced into clinical turn of events.

5 Limitations and challenges of current nanomedicine strategies

Nanotechnology can possibly altogether influence human wellbeing by working on the finding, avoidance, and treatment of infections. Nanomedicines regularly exemplify restorative and imaging compounds in submicrometer-sized transporter materials, determined to expand the remedial list of mixtures by permitting more effective conveyance to the objective site and limiting amassing in sound body locales to diminish poisonousness. Nanoencapsulation can likewise shield therapeutics from corruption in organic conditions and provide solubilization [81]. New nanomedicine plans and novel uses of nanomedicinal drugs are consistently accounted, however, modern acknowledgment and clinical interpretation are being taken a gander at progressively fundamentally [82]. In order to make it easier for nanomedicines to be used in clinical settings, this editorial addresses five major obstacles. It approaches the development process from the point of view of end-users and works from the top down, beginning with central and more general concerns about practical and clinical feasibility and moving on to more specific preclinical, clinical, and pharmaceutical aspects of nanomedicinal product development. The clinical results of nanotherapeutics show clear benefits over traditional small-molecular medicines. The field of nanomedicine has seen a great deal of study during the past three decades.

This has resulted in a pipeline of candidates being translated and a large number of nanomedical devices being commercialized globally [83]. Still, nanomedicine is not particularly successful for a wide range of applications. Advancement in the sector requires a full understanding of the obstacles that are currently in the way, the issues that may be resolved, and the demands that will emerge in the future.

Nanomedicine blends nanotechnology and clinical sciences for the conclusion, board, and fix of deadly infections for the solid and sickness free living of humanity [84]. Nanoparticles' small dimensions and high surface-to-volume ratio make it possible for them to be used in gene therapy. Numerous nanomedicine products are now available worldwide as a result of extensive research in this area. However, the clinical application of nanomedicines is hindered by a number of significant obstacles, including procedures that are time-consuming, difficult, and resource-intensive and require the mobilization and allocation of resources, strong alliances, and collaboration among leading collaborators on a national and international scale [85]. This part investigates different difficulties encountered by nanomedicine-intervened quality treatment and serious issues observed by nanomedicines during drug treatment [86]. In addition, it demonstrates a variety of therapeutic approaches to gene delivery, directing socially responsible, adaptive, and innovative research in this area so that nanomedicine may one day play a more significant and revolutionary role in medicine and public health.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability statement

Due to the nature of the research, [ethical, legal/commercial] supporting data is not applicable and thus not available.

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