Characterization and Application of Nanomaterials 2025, 8(4), 11797.
https://doi.org/10.24294/can11797

Article

Advances in AI-based immunotoxicity prediction for cancer nanotheranostics

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CITATION

Mehreen A, Yousafzai IK, Noreen N et al. (2025). Advances in AI-Based Immunotoxicity Prediction for Cancer Nanotheranostics. Characterization and Application of Nanomaterials. 8(4): 11797. https://doi.org/10.24294/can11797

ARTICLE INFO

Received: 15 June 2025
Accepted: 17 November 2025
Available online: 19 December 2025

Abstract: The fast-growing field of nanotheranostics is revolutionizing cancer treatment by allowing for precise diagnosis and targeted therapy at the cellular and molecular levels. These nanoscale platforms provide considerable benefits in oncology, including improved disease and therapy specificity, lower systemic toxicity, and real-time monitoring of therapeutic outcomes. However, nanoparticles' complicated interactions with biological systems, notably the immune system, present significant obstacles for clinical translation. While certain nanoparticles can elicit favorable anti-tumor immune responses, others cause immunotoxicity, including complement activation-related pseudoallergy (CARPA), cytokine storms, chronic inflammation, and organ damage. Traditional toxicity evaluation approaches are frequently time-consuming, expensive, and insufficient to capture these intricate nanoparticle-biological interactions. Artificial intelligence (AI) and machine learning (ML) have emerged as transformational solutions to these problems. This paper summarizes current achievements in nanotheranostics for cancer, delves into the causes of nanoparticle-induced immunotoxicity, and demonstrates how AI/ML may help anticipate and create safer nanoparticles. Integrating AI/ML with modern computational approaches allows for the detection of potentially dangerous nanoparticle qualities, guides the optimization of physicochemical features, and speeds up the development of immune-compatible nanotheranostics suited to individual patients. The combination of nanotechnology with AI/ML has the potential to completely realize the therapeutic promise of nanotheranostics while assuring patient safety in the age of precision medicine.

Keywords: nanotheranostics; cancer nanomedicine; artificial intelligence (AI); machine learning (ML); computational nanotechnology; personalized nanomedicine

1. Introduction

The situation posed by the cancer worldwide is a constantly challenging factor to the search of new diagnostic and treatment options; the traditional methods of cancer treatment are rather effective but tend to be rather general, causing significant off-target effects, severe systemic toxicities and drug resistance emergence. Nanotechnology has become a pioneering field in the world of oncology offering unmatched variety of advanced instruments to overcome these shortcomings. Through operating on the nanoscale (1-100 nm), nanotheranostics can exploit the otherwise inaccessible physicochemical characteristics to engage biological systems in entirely

new manners, enabling the simultaneous diagnostic imaging and therapeutic cargo to be carried on a single platform, and the incorporation of highly tailored features. This synergetic strategy is bound to give real time information on tumor morphology, metabolic activity and therapeutic response and also deliver powerful anticancer agents to the disease site thus maximizing the effects and minimizing collateral damage to normal tissues [1]. Nanotheranostics has great potential in the oncology field because there are several benefits. Passive targeting via the Enhanced Permeability and Retention (EPR) effect can help nanoparticles to increase the solubility and absorption of drugs previously insoluble in water, prolong their systemic circulation time, decrease therapeutic agent degradation and preferential accumulation in tumors. Moreover, even more precise delivery is possible with active targeting with molecules binding to receptors that are plentiful on cancer cells or tumor blood. The theranostics go beyond delivery of drugs, and include multimodal imaging (e.g., MRI, CT, PET, optical imaging), photothermal therapy (PTT), photodynamic therapy (PDT), gene therapy, and immunomodulation, all in a single nanoscale object. Nanodrugs, including liposomal doxorubicin (Doxil(r)) and albumin-bound paclitaxel (Abraxane(r)), are some of the high-profile clinical examples of nanodrugs that have shown the practical application of the nanotechnology technique in improving the treatment and prognosis of various kinds of cancer [2]. Although such powerful developments and tremendous promise exist, the therapeutic application of nanotheranostics suffers severe challenges. Reducing the intrinsic toxicities of nanoparticle exposure is a major challenge that should be understood. Nanoparticles have a large multiplicity of physicochemical properties, including size, shape, surface charge, surface chemistry, composition, and crystallinity, unlike regular small-molecule drugs, which profoundly affect their interactions with biological systems [3]. Such interactions may have unpredictable and often complex toxicological effects. Immunotoxicity is among the most important issues, where nanoparticles may drastically disrupt the balance of the human immune system. This may manifest in acute hypersensitivity reactions, chronic inflammation, cytokine storm syndromes, or even inadvertent immunosuppression, which may pose a serious risk to patient safety and block therapeutic action [4]. Such a traditional, reductionist concept of toxicological evaluation, which can be limited primarily to time-intensive in vitro and in vivo experiments, cannot be applied to a large and rapidly growing number of nanomaterials. Experimental testing is also not economically and temporally possible since there are a large number of design parameters and their potential combinations. In addition, this bottleneck requires a paradigm shift to more efficient and predictive methodologies. ritual: using advanced computational algorithms to analyze large datasets, detect complex patterns, and develop predictive models, AI/ML provides an unprecedented opportunity to predict the toxicity of nanoparticles, design and develop them to have a better safety profile, and translate them to clinical use Despite significant progress, the clinical translation of nanotheranostics remains hampered by unanticipated immunological interactions and the constraints of traditional toxicity testing. Existing papers cover nanotoxicology or AI applications separately, but none combine the two to illustrate how AI/ML can explicitly address immunotoxicity, the most significant impediment to safe nanomedicine development [5].

This review will describe the recent progress in cancer nanotheranostics, critically focusing on the interaction of nanoparticles and the immune system. Mechanisms of nanoparticle-induced toxicities, especially immunotoxicity, shall be discussed, and shortcomings of the current evaluation strategies shall be critically evaluated. Notably, we are going to talk about the growing position of AI and ML as the revolutionary means of predictive toxicology with the quick screening of emerging nanomaterials and the informed design of safer and more beneficial nanotheranostics. Lastly, we will enter the field of integration of AI-optimized nanotheranostics used in clinical cancer therapy, describe the issues that may arise with respect to regulation and ethics, and project an evolutionary outlook of the future of this collaboration in the establishment of precision oncology.

2. Developments in nanotheranostic platforms

The various kinds of nanotheranostic platforms have taken cancer research to a new level by providing sophisticated approaches to more accurate diagnosis and targeted therapy. They are made of a very diverse variety of materials. All such materials impart varying properties to these systems, thereby making them suitable for specific oncological applications.

Theranostics literally implies the combination of diagnostic and therapeutic functions into a single nanoscale construct, such as imaging agents, drugs, genes, and light- or heat-activable components. The section offers a description of a summary of major nanotheranostic platforms, their design principles, recent developments, and advantages in targeted cancer treatment and real-time cancer monitoring [6].

2.1. Overview of current nanotheranostic systems

Nanotheranostic systems are broadly classified by their core material composition, which dictates their physical and chemical features, biocompatibility, and degradation pathways. Liposomes and Lipid Nanoparticles (LNPs) are self-assembling spherical vesicles made of lipid bilayers (liposomes) or a lipid mixture (LNPs) that can hold both hydrophilic and hydrophobic medicines. Their biocompatibility and biodegradability make them extremely appealing. Recent advances include sterically stabilized liposomes (e.g., PEGylated liposomes) for longer circulation and LNPs for nucleic acid delivery, particularly mRNA vaccines and siRNA treatments. For theranostic applications, imaging agents such as gadolinium chelates for MRI or fluorescent dyes can be introduced into the lipid bilayer or aqueous core . Polymeric Nanoparticles are created from materials that are compatible with the body and can break (e.g., PLGA, PLA, chitosan, PEG-PLA), offering a great deal of flexibility of their size, shape, and surface modification. They can carry a wide array of therapeutic agents and can be designed to release them in a controlled manner. Polymeric nanoparticles are also amenable to surface conjugation with targeting ligands (e.g., antibodies, peptides, aptamers) and imaging moieties (e.g., iron oxide nanoparticles for MRI, radioisotopes for PET). Inorganic Nanoparticles are an extensive class that consists of gold nanoparticles (AuNPs), silver nanoparticles (AgNPs), iron oxide nanoparticles (IONPs), quantum dots (QDs), and mesoporous silica nanoparticles (MSNs). Gold Nanoparticles are types of nanoparticles, renowned

for their tunable plasmonic properties. AuNPs are excellent candidates for photothermal therapy (PTT), where they convert absorbed light into heat to ablate tumor cells. They can also serve as contrast agents for CT and photoacoustic imaging and are readily functionalized for drug delivery and targeting. Iron Oxide Nanoparticles are mostly used as T2 contrast agents in MRI, but they may also be designed to provide magnetic hyperthermia. Their superparamagnetic features enable external magnetic field guiding, which enhances tumor accumulation. Quantum Dots (QDs) are semiconductor nanocrystals that show quantum mechanical features. When stimulated, they produce light at specified wavelengths, making them superb fluorescent imaging agents with great photostability and brightness. While its cytotoxicity (due to high metal content) has been a source of worry, subsequent research has focused on "greener" or core-shell designs to address this. They can be conjugated with medications for theranostic purposes. Mesoporous Silica Nanoparticles (MSNs) are characterized by their porous structure. MSNs offer high drug loading capacity and facile surface functionalization. They can be engineered for stimuli-responsive drug release and multimodal imaging by incorporating various probes. Dendrimers are highly branching, monodisperse polymeric nanostructures with an abundance of surface functional groups. Their tight structure allows efficient drug loading and multivalent conjugation of targeted ligands along with imaging agents. Dendrimers have demonstrated potential for gene transfer and MRI contrast enhancement . Exosomes and biomimetic nanoparticles are nanoscale vesicles originating from biological membranes and play a role in intercellular communication. Because of their innate biocompatibility, minimal immunogenicity, and capability for crossing biological barriers, they represent a perfect vehicle for the delivery of drugs. Biomimetic nanoparticles, which imitate biological membranes or structures, are an emerging strategy to increase stealth capabilities and targeted distribution .

2.2. Case studies: Unlocking theranostic potential

Multiple case studies exemplify the innovative integration of diagnostic and therapeutic functionalities within various nanoplatforms, demonstrating their advantages in targeted therapy and real-time monitoring in cancer.

Lin et al. performed the first biomedical application of 2D tantalum carbide (Ta_4C_3) MXene nanosheets, developed for dual-mode imaging and photothermal cancer therapy (PTT). He achieved Complete 4T1 breast cancer tumor ablation (at 60-68 degrees) in mice via both intravenous and intratumoral injection and saw clear tumor visualization by both photoacoustic and computed tomography modes. The SP-coated nano sheets showed viable biocompatibility and led to zero damaged organs or weight loss in mice after 30 days [6].

Svenskaya et al. Created non-toxic, magnetically guided capsules that successfully accumulated at breast cancer tumour 3x more than normal capsules, and magnetite nanoparticles present inside the capsules gave it strong T_2-weighted MRI contrast, allowing real-time tracking in vitro and in vivo [7]. Josefssons et al. tagged PD-L1 with Indium-111 (^{111}In) to form ^{111}In-DTPA-anti-PD-L1 for SPECT imaging. In mice with PD-L1–positive tumors, imaged at 1–72 hours post-injection, showed strong, specific uptake in tumors and PD-L1–rich organs. Co-injecting excess

unlabeled antibody reduced spleen binding and improved tumor signal, confirming specificity. The same antibody was evaluated for radioimmunotherapy, replacing Indium-111 with therapeutic isotopes Lutetium-177 or Yttrium-90. Dosimetry analysis predicted the highest radiation doses in the spleen, followed by the tumor, with safe bone marrow exposure [8].

2.2.1. Liposome-based delivery of chemotherapeutics with imaging agents

Traditional chemotherapy using liposomes, like Doxil for Kaposi's sarcoma, ovarian cancer, and multiple myeloma, takes advantage of the EPR effect. For theranostic purposes, imaging agents are co-encapsulated or integrated within the liposomal double-layered membrane. For example, gadolinium-loaded liposomes are being developed for MRI-guided drug delivery. These formulations allow for simultaneous visualization of the tumor, assessment of liposome accumulation, and real-time monitoring of drug release or therapeutic response. Recent work focuses on thermo-sensitive liposomes (e.g., ThermoDox®), which release their payload (doxorubicin) when subjected to mild hyperthermia (e.g., from focused ultrasound or radiofrequency ablation). The imaging component (e.g., fluorescent dye or MRI contrast agent) can confirm the accumulation of liposomes and monitor local temperature, thus guiding the precise release of the drug at the tumor site. This approach enhances local drug concentration while minimizing systemic exposure, significantly improving the therapeutic index**.** Studies have shown that thermo-sensitive liposomes containing both doxorubicin and a temperature-sensitive MRI contrast agent can enable real-time tracking of drug delivery to tumors and localized drug release upon heating, leading to improved tumor regression in preclinical models of liver cancer [9].

2.2.2. Quantum dots for simultaneous imaging and drug delivery

QDs have distinctive photophysical features, such as wide excitation spectra and limited, adjustable emission, making them excellent for multiplexed imaging. Their high quantum yield and photostability outperform traditional organic dyes. When coupled with medicinal drugs, they transform into strong theranostic instruments. Despite early worries about the cytotoxicity of cadmium-containing QDs, great work has been made in finding safer alternatives, such as indium phosphide (InP)-based or silicon QDs, which are frequently enclosed in biocompatible shells (e.g., silica, polymers). QDs are often coupled to anticancer medicines, small interfering RNA (siRNA), or antibodies. In a pioneering study, researchers conjugated doxorubicin to PEGylated core-shell quantum dots (e.g., CdSe/ZnS or InP/ZnS) modified with tumor-targeting peptides (e.g., RGD peptide for integrin overexpression). These nanoconjugates enabled real-time fluorescence imaging of tumor uptake in vivo, offering highly resolved anatomical and functional information. Simultaneously, when cellular internalization occurred, the acidic tumor microenvironment or intracellular enzymes triggered drug release, resulting in significant anti-tumor efficacy. This system not only diagnosed tumor but also delivered therapy, with the imaging component facilitating the monitoring of delivery efficiency and therapeutic response. The exceptional brightness of QDs also enables very sensitive detection, particularly useful in identifying small metastatic foci.

2.3. Advantages in targeted therapy and real-time monitoring

The evolution of nanotheranostic platforms offers different advantages than the classic approaches, which change the face of cancer management, enhanced targeted delivery represents a distinct advantage; nanoparticles can be designed with particular ligands capable of binding to receptors overexpressed on tumor cells or in the tumor microenvironment for example, folate receptors, EGFR, HER2, integrins, and tumor vasculature indicators. This active targeting enhances local drug concentration and minimizes systemic exposure with related off-target toxicities. This is especially useful for very effective chemotherapeutics or immunomodulatory drugs [10]. More so, the possibility to integrate several imaging modalities on one nanoplatform, such as MRI for anatomical detail, PET for metabolic activity, and optical imaging for real-time cellular processes, gives a more comprehensive and complementary image of the tumor. This multimodal imaging thus allows early and precise diagnosis, correct localization of cancer and metastases, and real-time monitoring of therapy responses. For example, a nanotheranostic agent might be designed with both a near-infrared fluorescent dye for intraoperative guiding and an MRI contrast agent for pre-operative planning and post-operative assessment [11].

Nanotheranostics, therefore, enable doctors to assess treatment efficacy without resorting to invasive assessments of treatment outcomes in real time for immediate modifications of the therapeutic regimen. Examples include monitoring changes in tumor size, metabolic activity, angiogenesis, or even molecular biomarkers. For example, a nanoparticle system engineered to emit a fluorescent signal when broken down by enzymes that are specific to tumors can provide direct proof of drug release and therapeutic action within the tumor itself [12]. Nanotheranostics, by concentrating on therapeutic substances at the illness site, minimize healthy tissues' systemic exposure to cytotoxic medicines. This immediately corresponds to fewer severe side effects, increased patient quality of life, and potentially permits bigger dosages to be delivered to the tumor, hence increasing therapeutic efficacy [13].

2.3.1. Overcoming drug resistance

Some nanotheranostic designs are engineered to overcome the pathways of multidrug resistance in tumor cells. Thus, nanoparticles can be engineered to avoid efflux pumps that strongly push medicines out of tumor cells or transport inhibitors of those pumps, such as siRNA against P-glycoprotein. The imaging component can simultaneously analyze the success of these resistance modulation tactics [14].

Continuous developments in material science and bioconjugation technologies are propelling the development of more complex nanotheranostic devices. As shown in **Figure 1**, these technologies combine targeting, imaging, and therapy into a single nanoparticle, allowing for tumor-specific delivery and real-time monitoring of treatment responses. However, as their structural complexity and interactions with biological systems increase, assessing and controlling potential toxicities—particularly immunotoxicity—become more important. This challenge is the focus of continuous debate in the field [15].

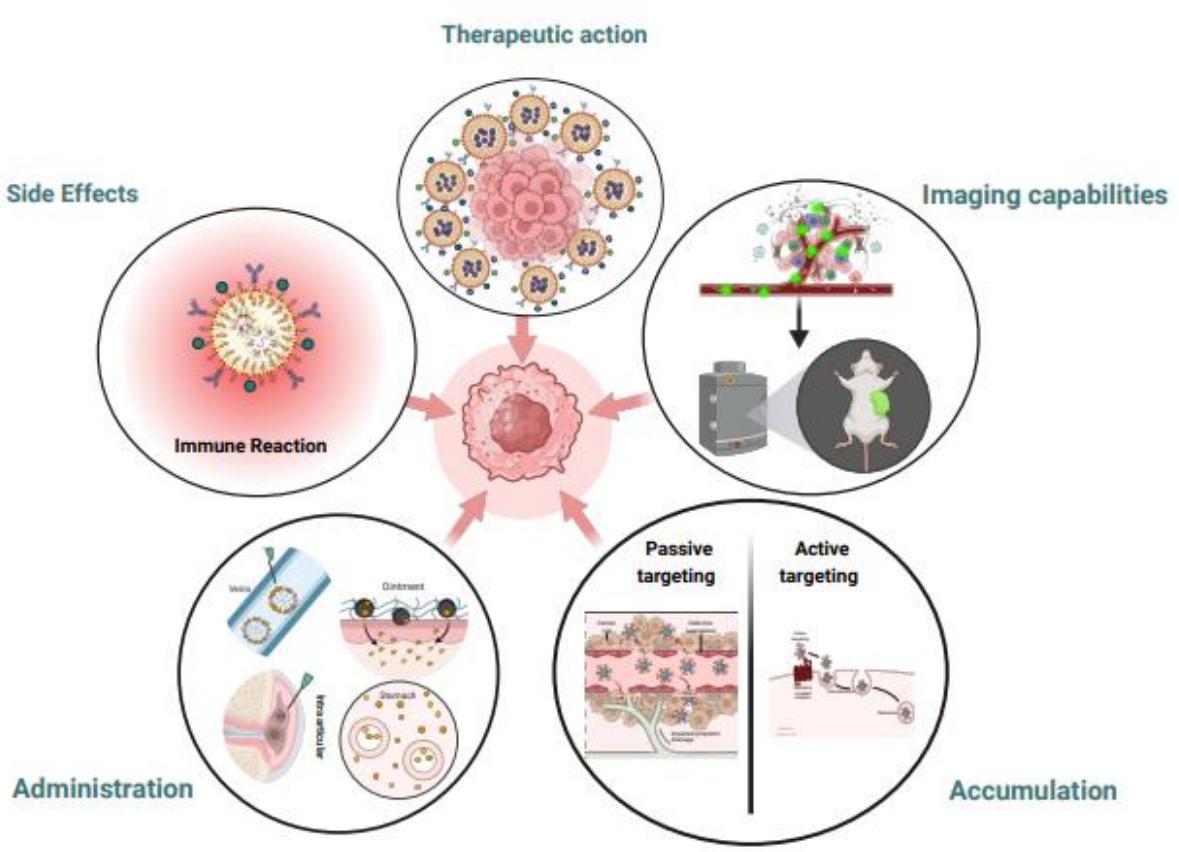

Figure 1. Schematic of Nanotheranostic Mechanism in Cancer Therapy.

Table 1. Comparison of Nanotheranostic Platforms.

Platform Type	Core Materials	Key Physicochemical Properties	Targeting Mechanisms	Therapeutic Agents (Examples)	Diagnostic Modalities (Examples)	Advantages in Cancer Therapy	Associated Toxicity Concerns (General)	References
Liposomes/LNPs	Phospholipids, Cholesterol, PEGylated lipids	Size (50-200 nm), Hydrophilic/hydrophobic core, Lipid bilayer	Passive (EPR), Active (Ligand-receptor), pH/Temp-sensitive	Doxorubicin, Paclitaxel, siRNA, mRNA	MRI (Gd-chelate), Fluorescence, PET (radioisotopes)	Biocompatible, Biodegradable, High drug loading, Versatile	CARPA, Hypersensitivity reactions, Drug-specific toxicity	[2]
Polymeric NPs	PLGA, PCL, Chitosan, PEG	Size (20-500 nm), Encapsulation (core), Surface tunable	Passive (EPR), Active (Antibodies, Peptides, Aptamers)	Chemotherapeutics, Proteins, Genes	MRI (IONPs), Fluorescence, CT (AuNPs)	High stability, Controlled release, Surface functionalization	Immunogenicity (some polymers), Bioaccumulation, Solvent residues	[3]
Gold Nanoparticles	Gold	Size (5-100 nm), Surface plasmon resonance, High Z	Passive (EPR), Active (Ligands, Antibodies)	PTT (Heat), Chemotherapeutics (conjugated)	CT, Photoacoustic, SERS, Optical	Photothermal efficacy, Excellent biocompatibility, Tunable properties	Long-term accumulation, Size-dependent toxicity, Biopersistence	[4]
Iron Oxide NPs	Fe_3O_4, γ-Fe_2O_3	Superparamagnetic, Size (5-50 nm), Large surface area	Passive (EPR), Active (Ligands),	HyperthermiaDrug delivery (magnetic targeting)	MRI (T2 contrast)	Non-toxic at low doses, MRI contrast,	Oxidative stress, Inflammation,	[5]

			Magnetic guidance			Magnetic guidance	Biodegradation products	
Quantum Dots	CdSe, InP, CSe, Carbon (dots)	Tunable fluorescence, High quantum yield, Photostable	Passive (EPR), Active (Peptides, Antibodies)	Chemotherapeutics, Gene delivery	Fluorescence (multicolor), CT (heavy metal)	High brightness, Multiplex imaging, Deep tissue penetration	Heavy metal toxicity (Cd), Long-term retention, Phototoxicity	[9]
Mesoporous Silica NPs	Silica	Porous structure, High surface area, Tunable pore size	Passive (EPR), Active (Surface ligands)	High drug loading (various drugs), Gene delivery	Optical, CT, MRI	High loading capacity, Biocompatible, Chemical stability	Solubility, Biodegradability, Surface charge-dependent toxicity	[10]
Dendrimers	Poly(amidoamine) (PAMAM), Poly(propyleneimine) (PPI)	Highly branched, Monodisperse, High surface groups	Passive (EPR), Active (Ligands)	Chemotherapeutics, siRNA, DNA	MRI (Gd-chelate), Fluorescence	Precise structure, High drug loading, Multivalent targeting	Cationic toxicity, Immunogenicity (some types)	[9]

Figure 1 demonstrates the general mechanism of nanotheranostics in cancer therapy, emphasizing how nanoparticles combine personalised medication delivery and diagnostic imaging. The schematic shows the sequence of tumor targeting, cellular absorption, stimulus-responsive drug release, and imaging feedback, giving readers a visual understanding of how theranostic platforms work in vivo.

This chapter examined the key nanotheranostic platforms, their structural variety, and functional benefits in cancer diagnosis and treatment. The part emphasised the importance of material composition and surface engineering in targeting precision, imaging clarity, and treatment efficiency through major examples and case studies. These advances lay the groundwork for the following chapter, which critically assesses the biological repercussions of nanoparticle-host interactions, particularly their toxicological and immunological effects.

3. Nanotoxicology in nanotheranostics

To ensure success and safety of clinical translation of nanotheranostics, diverse problems in toxicology are inevitably caused by the complex interactions between engineered nanomaterials and complex biological systems. Some of the unique physicochemical properties of nanoparticles that distinguish them against the traditional small molecules are size, shape, surface charge, surface chemistry, composition, crystallinity, and aggregation state. These properties act in combination to influence the biodistribution of the particles, cellular intake, degradation, and possible toxicity. The therapeutic advantages were already discussed on the foregoing section, yet this section will analyze the intrinsic toxicological risks, and more importantly, the most vital and highly unpredictable area of immunotoxicity [16].

3.1. Widespread toxicological concerns in nanotheranostics

When nanoparticles are delivered systemically, they are exposed to different biological interactions, which may result in an adverse outcome in various organs and systems. One of the most widely observed toxicological issues is cytotoxicity. Direct

damage of cells that causes cell death is often mediated by the processes of oxidative stress, mitochondrial dysfunction, and membrane disruption. This is possible in target (cancer) and non-target (healthy) cells. The other issue is the Genotoxicity which is noted to be the capability of nanoparticles to cause DNA damage, chromosomal aberration or mutagenesis, which may be followed by carcinogenesis or inheritance effects. This may be as a result of direct contact with DNA or indirectly through reactive oxygen species (ROS) production. When the nanoparticles settle in other organs, then this results into Organ-specific Toxicity these are liver, spleen, kidney, lungs, and brain. This particular problem results in inflammation, fibrosis, malfunction. As with the example of the reticuloendothelial system (RES), which is common in the liver and spleen, it is often the main site of clearance of nanoparticles, and these organs are therefore particularly vulnerable. Furthermore, hemocompatibility Problems can occur, the Interaction of components of the blood mass can provoke hemolysis (rupture of red blood cells), platelet coagulation, and the activation of coagulation cascades, which creates a risk of thrombosis or embolism [17]. When it comes to Bioaccumulation and the Long-Term Effects, a few nanoparticles, namely non-degradable inorganic, might remain longer in the body, creating an issue of chronic toxicity, long-term inflammation, and possible pathologies in the late stages. The clearance or degradation of nanoparticles by the body depends greatly on the material content and size of the nanoparticles [18]

3.2. Immunotoxicity

A Nanotherapy Crisis to Nanotheranostics. Immunotoxicity is one of the various issues of toxicology that have remained a current and unpredictable challenge to nanotheranostics. The immune system is the major defense mechanism of the body, which is able to recognize and respond to external invaders. Nanoparticles are foreign entities, and once introduced into a systemic environment, are inevitably interact with a variety of elements of the innate and adaptive immune system. The response that these interactions may elicit can include positive immune response (Examples: anti-tumor immunity, vaccination adjuvancy) as well as confounding adverse responses that may be life-threatening [19].

3.2.1. Mechanisms of nanoparticle-induced immunotoxicity

The diverse mechanisms that cause immunotoxicity are complicated and require a close relationship between nanoparticle characteristics and immune conditions of the host. The adsorption of a protein coat to the nanoparticles occurs when they enter the body fluids forming the so-called protein corona. The biological identity of the nanoparticle and its interaction with the immune cells of the body largely depends on the composition of the corona.Opsonin proteins (e.g., complement components, immunoglobulins) in the corona are detected by phagocytic cells (macrophages, dendritic cells), this results in fast clearance via the reticuloendothelial system (RES), lowering medication effectiveness and possibly inducing splenomegaly and hepatomegaly. The corona may potentially reveal neo-epitopes that cause immunological responses [20]. One of the most prevalent acute immunotoxicities associated with intravenous nanomedicines, (namely liposomal formulations and micellar systems) is called Complement Activation-Related Pseudoallergy (CARPA).

It is distinguished by an acute, non-IgE mediated hypersensitive event that resembles anaphylaxis and occurs within minutes of dosing. CAPRA is initiated by the fast activation of the complement system, which results in the production of anaphylatoxins (C3a, C5a) that induce mast cell degranulation and histamine release. Symptoms might be moderate (flushing, rash, dyspnea) or severe (hypotension, bronchospasm, cardiac arrest). While frequently self-limiting, severe CARPA can be life-threatening, resulting in clinical pauses for promising nanodrugs [21].

Cytokine Storm Syndrome (CRS) occurs when Certain nanoparticles, particularly those designed to activate the immune system (such as nucleic acid-based nanovaccines or nanoparticles containing TLR agonists), may mistakenly cause a massive and uncontrollable systemic inflammatory response. The production of pro-inflammatory cytokines (e.g., IL-6, TNF-α, IL-1β) is known as a "cytokine storm", progression of a cytokine storm leads to systemic inflammatory response syndrome (SIRS), which can result in multiple organ failure and even death. Although more commonly associated with certain immunotherapies such as CAR-T cell treatment, nanoparticles engineered to interact with immune receptors might cause symptoms comparable to cytokine release syndrome (CRS) [22].

Nanoparticles can directly interact with and modulate the function of various immune cells, causing a condition known as direct Immune Cell Modulation. Additionally, Macrophages can activate nanoparticles by phagocytosis, resulting in the production of pro-inflammatory cytokines, chemokines, and reactive oxygen/nitrogen species (ROS/RNS). This can cause systemic inflammation and tissue damage. In contrast, certain nanoparticles can cause M2 polarization, resulting in immunosuppression and pro-tumorigenic effects. Nanoparticles can also influence dendritic Cells (DCs) to mature, cause antigen presentation, and subsequent T cell priming. While desired for nano vaccines, unintended DC activation or suppression can lead to adverse immune responses or diminished anti-tumor immunity. Moreover, nanoparticles can impact T cell and B cell activation, proliferation, and differentiation. This can lead to autoimmune responses, chronic inflammation, or, conversely, immunosuppression, increasing susceptibility to infections or promoting tumor escape [23]. Aside from systemic effects, localized immune responses can induce inflammation and injury in organs where nanoparticles collect. For example, nanoparticle buildup in the liver and spleen can cause persistent inflammation, granuloma formation, and fibrosis, which are mediated by activated Kupffer cells and other immune cells. Inhaled nanoparticles can cause pulmonary inflammation, as well as neuroinflammation if they breach the blood-brain barrier [24]. While generally beneficial for vaccine development, an inadvertent adjuvant action of a nanocarrier might result in an excessive or inappropriate immune response when paired with a non-immunogenic medication, possibly worsening undesirable consequences [24]. This leads to Adjuvant-like Effects.

3.2.2. Limitations of traditional toxicological assessments

The conventional toxicological paradigms, which are mainly designed to work with small molecules, are facing mounting criticism due to the complexity and diversity of nanoparticles. Among high-throughput screening limitations, there are those that arise in cases where traditional vitro assays are often not biologically

complex, cannot effectively characterize the in vivo setting, like the formation of protein corona, dynamic fluid flow, and intra- and intercellular interactions. They are often limited in throughput and do not screen the broad nanoparticle variations. Furthermore, there is a form of animal model discontinuity, which is that, although animal models are indispensable, they do not necessarily recapitulate human physiological response, particularly of the interactions of the immune system. The differences in activity of the species-specific RESs, complement system, and population of immune cells may result in differences in toxicity patterns, and it is difficult to translate them to humans [25]. Nanoparticle synthesis, characterization, and toxicity testing in various laboratories have a severe deficiency of standardized protocols, which results in an inability to reproduce such protocols and makes comparative studies impossible. This variability in data complicates the ability to make generalizable conclusions on nano-bio interactions. Also, nanoparticle interactions with biological systems are dynamic, and further complicate the processes, such as degradation, aggregation, and dissolution are transformed in vivo, which may be hard to measure using end-point measures. Finally, the restriction on high cost and time Consumption is considered. In vivo toxicity investigations in their entirety are highly resource-intensive and time-consuming, which poses a major bottleneck in the process of developing new nanotheranostics [26]. It is based on these restrictions that new methods are urgently required that can rapidly and predictively determine the immunotoxin capabilities of nanoparticles, which in turn can be used to rationally design less toxic and more effective nanotheranostic drugs. That is exactly where the synergetic potential of AI and machine learning is of colossal potential.

3.3. Artificial intelligence and machine learning predictive toxicology

The rapid increase in the number of manmade nanomaterials, coupled with the inherent constraints and high cost of conventional toxicity assays, has introduced a significant obstacle to the clinical implementation of nanotheranostics. In order to overcome this critical bottleneck, the scientific community is turning to the transformational capabilities of artificial intelligence (AI) and machine learning at a rapid pace. These computational paradigms are powerful methods of complex data analysis, discovery of hidden interactions and constructing valid predictive models that can rapidly evaluate new nanomaterials on their potential toxicities, a hugely accelerating design, test, and learn cycle. This part will discuss the leading concepts of AI/ML in nanomedicine and highlight its application in the case of toxicity prediction, and especially in the context of immune-mediated adverse effects [27]. The field of artificial intelligence and machine learning is a new paradigm of scientific studies and engineering. These technologies are based at their core on algorithms that learn using the available data to make predictions or decisions without being coded specifically into individual situations. AI/ML in nanomedicine may be used to analyze large amounts of experimental data (e.g., physicochemical properties, cellular behaviour, and in vivo toxicity data) to find previously unexplored relationships between attributes of nanoparticles and biological effects. This ability especially applies to nanoparticles, since a vast combinatoric space is created through the interplay of the different design parameters (size, shape, surface charge, coating,

composition), and it is difficult to access exhaustively through standard experimental methods [28, 29]. With the help of AI/ML, scientists are able to screen faster; they can quickly estimate the toxicity of hundreds or thousands of new nanoparticle designs in silico before costly and time-intensive syntheses and experimentation can begin. Researchers can also determine important descriptors by determining which of the specific physicochemical properties of nanoparticles are most effectively related to specific toxicological endpoints, thereby informing rational design. By developing more accurate *in silico* models that can potentially reduce the reliance on animal models for preliminary toxicity assessments, researchers can reduce animal testing and uncover complex relationships by identifying intricate, non-linear relationships between nanoparticle features and biological responses that might be missed by human intuition or simpler statistical methods [30].

3.3.1. Predictive modeling for toxicity assessment

Predictive toxicity using AI/ML entails developing models that can predict the frequency and severity of adverse biological effects based on a nanoparticle's structure and physicochemical features. As shown in **Figure 2**, the AI/ML workflow for predicting nanotoxicity demonstrates how nanoparticle characteristics and biological data are combined to generate toxicity predictions. This approach commonly falls under the umbrella of Quantitative Structure-Activity Relationships (QSAR) or Quantitative Structure-Property Relationships (QSPR), modified for nanomaterials (nano-QSAR/QSPR) [31].

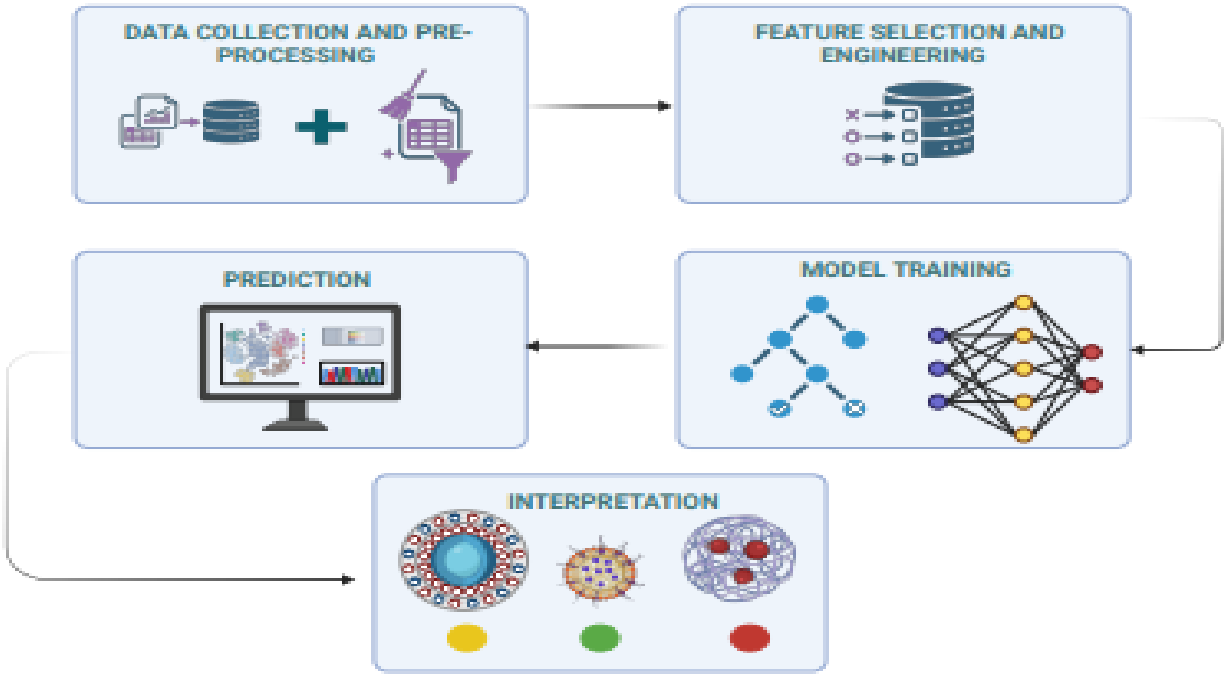

Figure 2. AI Workflow in Predictive Nanotoxicity.

3.3.2. Use of algorithms like random forest, svm, and neural networks

A variety of ML algorithms have been successfully employed in predictive nanotoxicity. Random Forest (RF) is an ensemble learning approach that builds numerous decision trees during training and returns the mode of the classes (for

classification) or the mean prediction (for regression) of the individual trees. RF is resilient against overfitting, can handle high-dimensional data, and gives insights into feature relevance, making it useful for discovering significant toxicological drivers among nanoparticle features. Secondly, Support Vector Machines (SVMs) are a form of supervised learning model used for classification and regression. Their primary premise is to find the appropriate hyperplane that best differentiates data points from distinct categories inside a high-dimensional space. SVMs are especially well-suited for datasets with complex, non-linear connections, and they have been used successfully to predict nanoparticle toxicological endpoints such as cytotoxicity, genotoxicity, and inflammatory reactions [32]. Lastly, Neural Networks (NNs) and Deep Learning (DL), inspired by the human brain, NNs are made up of linked nodes (neurons) structured in layers. Deep learning, a subset of machine learning, uses neural networks with several hidden layers (deep neural networks) to learn hierarchical data representations. DL models are extremely effective at managing huge, complex, and heterogeneous datasets, such as those generated by high-throughput screening or omics technologies. They can automatically learn useful features from raw data, minimizing the requirement for human feature engineering [33].

3.3.3. Case studies: AI models predicting nanoparticle-induced toxicity

Recent advancements have demonstrated the tangible utility of AI/ML in predicting various forms of nanoparticle toxicity, including immunotoxicity. AI models are able to predict Nanoparticle-Induced Cytotoxicity, as scientists have developed Random Forest models that can predict the cytotoxicity of a wide spectrum of metal oxide nanoparticles (including ZnO, TiO_2, and CeO_2) across several cell types. These models obtained great prediction accuracy by including characteristics such as particle size, surface area, and dissolution rate, allowing for the rapid detection of potentially hazardous chemicals. These models can assist in selecting which nanoparticles should be tested further in laboratories and on animals, so greatly speeding up the safety evaluation process [34]. Moreover, deep neural networks have been employed to predict the cytotoxicity of carbon-based nanomaterials (e.g., graphene oxide, carbon nanotubes) by learning complex features from high-dimensional datasets that include both physicochemical properties and biological assay results. These models can identify subtle patterns that contribute to cellular damage, guiding the design of less toxic carbon nanomaterials for biomedical applications .

There are also Machine Learning Approaches for Assessing Immunotoxic Responses. The intricacy of immune responses makes it especially difficult to predict immunotoxicity. However, ML models are becoming increasingly useful. For example, Support Vector Machine (SVM) models have been created to predict the immunomodulatory potential of specific gold nanoparticles based on their size, shape, and surface functionalization. These models can correctly identify AuNPs as either pro-inflammatory or anti-inflammatory, giving critical insights for creating immunologically inert or immunologically active nanotheranostics. Additionally, Ensemble learning methods, using numerous machine learning algorithms may accurately predict cytokine release patterns (e.g., TNF-α, IL-6) caused by different nanoparticle kinds (e.g., polymeric, inorganic). These models may predict the

likelihood of a cytokine storm-type reaction by examining a large dataset of nanoparticle properties and in vitro immune cell stimulation data, which is critical for avoiding serious adverse events like CARPA. Furthermore, AI has been used to assess high throughput immunophenotyping data. For example, ML algorithms may analyze flow cytometry data from immune cells exposed to nanoparticles to detect minor changes in cell populations, activation indicators, and cytokine secretion that may indicate an immunotoxic reaction before overt symptoms manifest. This enables early detection of possible difficulties and the refining of nanoparticle design [33]. Recent research has used graph neural networks (GNNs) to mimic interactions between nanoparticles and biological macromolecules, including proteins and lipids, in the protein corona. Understanding these molecular interactions allows GNNs to anticipate how alternative protein corona compositions may affect immune cell identification and subsequent immunotoxic reactions [34]. These case studies underscore the transformative potential of AI/ML in moving beyond reactive toxicity testing to proactive, predictive safety assessment. By leveraging these computational tools, researchers can design nanotheranostics with an intrinsic understanding of their likely immunological footprint, paving the way for safer and more effective cancer therapies.

Table 2. AI Algorithms in Toxicity Prediction for Nanomaterials (Focus on Immunotoxicity).

AI/ML Algorithm	Input Parameters (Examples)	Predicted Outcome (Examples)	Key Advantages	Limitations	Representative Application (Reference Type)	References
Random Forest	Size, shape, surface charge, composition, protein corona data	Cytotoxicity (IC50), ROS generation, Inflammatory cytokine levels (IL-6, TNF-α)	Robust to noise, Handles high-dimensional data, Feature importance ranking	Can be slow on very large datasets, Less interpretable than single trees	Predicting metal oxide NP cytotoxicity (Research Paper)	[22]
Support Vector Machine (SVM)	Zeta potential, Hydrodynamic diameter, Surface functionalization	Immunomodulatory potential (pro/anti-inflammatory), Cell viability, Genotoxicity	Effective for complex, non-linear relationships, Good generalization with limited data	Sensitive to parameter tuning, Less interpretable ("black box")	Classifying AuNP immunogenicity (Review Article)	[22]
Deep Neural Networks (DNN)	Omics data (transcriptomics, proteomics), High-throughput assay data, Physicochemical descriptors	Multi-organ toxicity, Complex immune responses, Biomarker identification, Drug-induced liver injury	Learns complex features automatically, High accuracy on large datasets, Handles diverse data types	Requires very large datasets, Computationally intensive, Poor interpretability (true "black box")	Predicting carbon nanomaterial cytotoxicity (Research Paper)	[23]
K-Nearest Neighbors (KNN)	Size, surface charge, hydrophobicity	Hemolysis, Complement activation, Cellular uptake efficiency	Simple, Interpretable, No explicit training phase	Sensitive to irrelevant features, Computationally expensive for large datasets	Predicting nanoparticle hemocompatibility (Research Paper)	[23]
Gradient Boosting (e.g., XGBoost)	Physicochemical properties, *in vitro* assay results	Cytokine release, Apoptosis, Cell proliferation	High predictive accuracy, Handles missing values, Robust to outliers	Can be prone to overfitting if parameters not tuned carefully	Predicting inflammatory responses to NPs (Research Paper)	[25]
Graph Neural	Molecular structure of NP components,	Protein corona composition, Binding affinity to immune	Captures relational data, Learns from	Requires specialized data representation,	Modeling NP-protein corona interactions (Conceptual/Review)	[23]

Networks (GNN)	Protein interaction networks	receptors, Cellular internalization pathways	complex network structures	Computationally intensive

Figure 2 represents the AI/ML approach utilized for predictive nanotoxicity assessment. It shows how physicochemical descriptors, biological assay data, and omics datasets are used in machine learning models to predict toxicity, identify essential nanoparticle properties, and drive safer nanomaterial design. This visual picture highlights the computational pathway that enables AI-driven toxicology.

3.3.4. AI-optimized design of nanotheranostic agents

Beyond predictive toxicology, AI and machine learning have actual revolutionary capacity in guiding the de novo design and iterative optimization of nanotheranostic drugs. Instead of relying on trial-and-error experimental approaches, AI can facilitate a rational, data-driven design process, predicting optimal nanoparticle characteristics that balance therapeutic efficacy, targeted delivery, and, most importantly, a favorable safety profile, particularly in terms of immunotoxicity. This section goes into how AI is being used to build nanoparticles with better performance and less adverse effects [34].

4. Utilizing AI for the design and optimization of nanoparticles

The possibilities for nanoparticle design are limitless, with changes in material composition, size, shape, surface charge, coatings, and the type and amount of therapeutic or diagnostic chemicals they carry. Historically, improving these parameters has been a time-consuming procedure, frequently confined to studying one variable at a time or investigating a small number of combinations. However, AI and machine learning algorithms can quickly navigate this complicated, multifaceted design space, identifying the optimum combinations of attributes to accomplish desired biological effects.

In a recently published study, lipid optimization using neural networks, a deep-learning strategy for ionizable lipid design was explored. 1.6 million Lipids were evaluated and out of these two structures were identified both of which efficiently delivered mRNA to ferret lungs. Highlighting the utilization of deep learning for nanoparticle delivery. In another study, a machine learning (ML) workflow was developed using high-quality plasmid DNA lipid nanoparticle (LNP) transfection datasets from six cell types. It lead to the identification of consistent trends such as optimal charged, helper lipid content, the role of ionizable and helper lipid ratios. The study provided a data-driven algorithmic framework for designing LNP formulations tailored for specific cell types [35].

Overall, this chapter discussed the main toxicological problems related with nanotheranostic platforms, including how physicochemical features influence biodistribution, cellular uptake, and bad outcomes. Immunotoxicity was given special attention because of its unpredictable nature and essential role in restricting clinical translation. These issues underscore the critical need for better predictive frameworks, which naturally leads to the following chapter, which investigates how AI and machine learning offer faster, more accurate, and mechanistically informed toxicity prediction.

4.1. Predicting optimal size and surface modifications for reduced toxicity

One of the primary applications of AI in nanoparticle design is to predict the physicochemical parameters that minimize toxicity while maintaining or enhancing therapeutic function.

AI can be used for size optimization. AI algorithms, trained on datasets connecting nanoparticle size to cellular uptake, biodistribution, and other toxicity endpoints (e.g., cytotoxicity, immunogenicity), can predict the optimal size range for a given application. For example, models may show that nanoparticles between 50 and 100 nm display optimum tumor formation by EPR while decreasing quick clearance by the RES and reducing the risk of triggering complement activation compared to very tiny or very big equivalents [36].

Surface Modification for Immunosuppression/Immune Stealth is another AI application. AI can aid in the development of nanoparticle surface coatings that improve "immune stealth" or generate particular immunomodulatory effects. For example, machine learning algorithms can identify immune modulators, densities, or zwitterionic coatings (such as phosphorylcholine-based polymers) that minimize opsonization and reduce the occurrence of CARPA by analyzing the protein corona formed on various surface-modified nanoparticles and their resulting immune responses. AI can anticipate the optimal PEG grafting density on a nanoparticle surface to increase circulation time while decreasing immune system recognition.

Lastly, AI can assist in charge neutralization/optimization, given that highly cationic nanoparticles frequently exhibit increased cytotoxicity and immunogenicity due to strong interactions with cell membranes and serum proteins. AI models can predict surface modifications or co-formulations that effectively neutralize surface charge in vivo or optimize it for specific cellular uptake pathways while mitigating adverse immune responses.

4.2. Designing nanoparticles with enhanced targeting capabilities

AI can considerably improve the design of actively targeted nanotheranostics by anticipating the appropriate ligand selection and conjugation procedures. ML algorithms can analyze large databases of ligand-receptor interactions to predict the binding affinity and specificity of various targeting ligands (e.g., antibodies, peptides, aptamers) to tumor-specific receptors. This allows for the *in silico* selection of the most effective targeting moieties for a given cancer type, reducing the need for extensive experimental screening.

For enhanced binding avidity, nanoparticles often employ multivalent targeting, where multiple copies of a ligand are presented on the surface. AI can optimize the number, spacing, and orientation of these ligands to maximize binding efficiency and internalization by cancer cells while minimizing non-specific binding to healthy tissues [30]. This is a form of Multivalent Targeting Optimization. The stimuli-responsive design by AI can help create "smart" nanoparticles that release their payload in reaction to certain tumor microenvironmental signals (such as low pH, hypoxia, high enzyme levels, and specific temperature). ML models may predict the best chemical linkages or material compositions for precise and regulated drug release

kinetics, which improves therapeutic efficacy while lowering systemic toxicity. For example, an AI model may predict the most pH-sensitive cleavable linker for a medicine that will only be released in an acidic tumor environment.

The use of AI in the design process elevates nanoparticle engineering from an empirical pursuit to a predictive science, as shown in **Figure 3**, the AI-driven design cycle, demonstrating how computational prediction, nanoparticle production, and testing are used to optimize nanotheranostic platforms. Researchers can use computational intelligence to rapidly iterate through design options, identify optimal parameters for safety and efficacy, and ultimately accelerate the development of next-generation nanotheranostics that are not only effective against cancer but also inherently safer for patients [37].

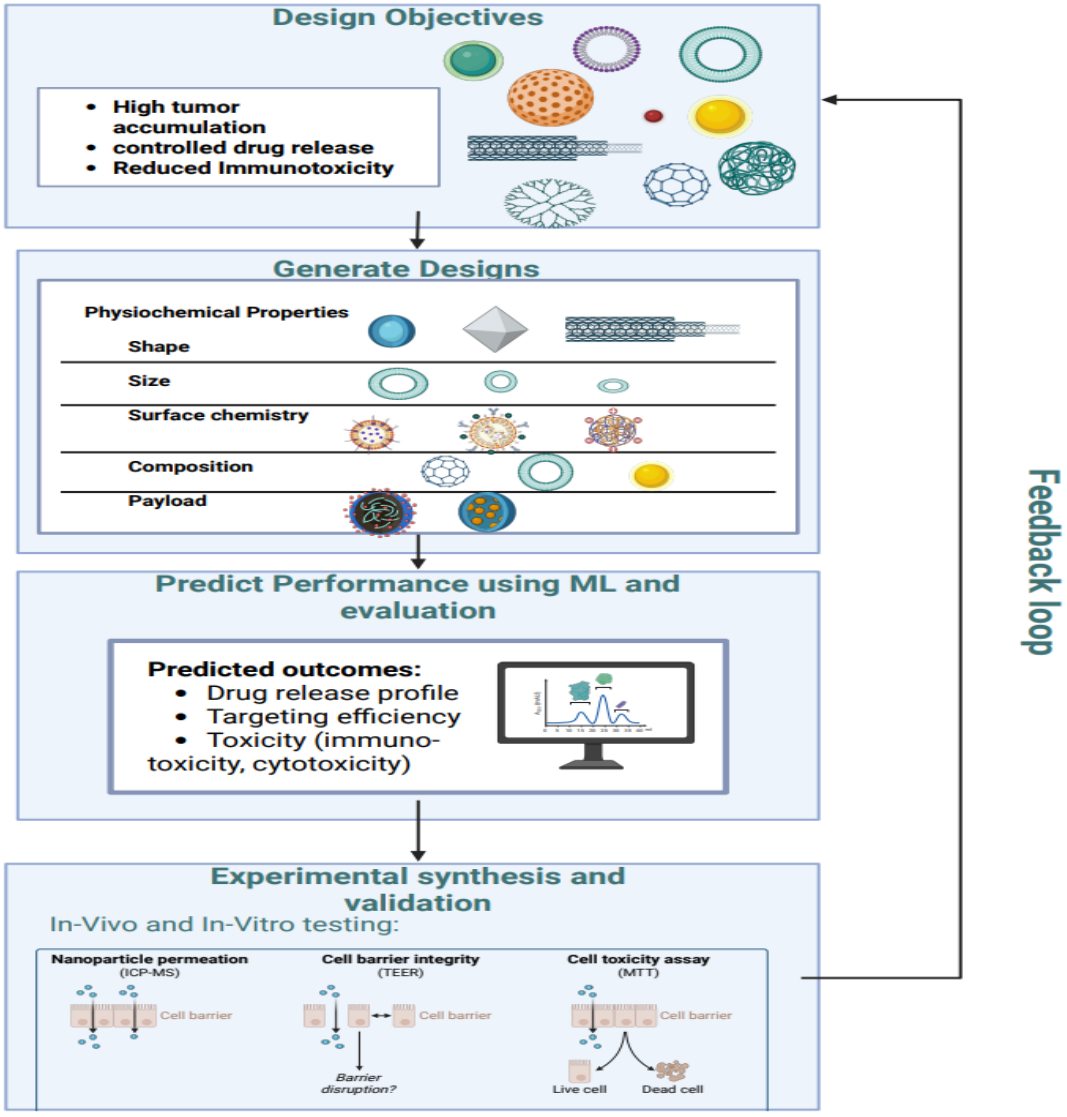

Figure 3. Design Optimization Process with AI/ML for Nanotheranostics.

Figure 3 illustrates the AI-driven design optimization process for nanotheranostics, featuring an iterative cycle of computer predictions, nanoparticle manufacturing, biological testing, and model refinement. The image highlights how

artificial intelligence (AI) speeds up the identification of suitable size, surface chemistry, and functionalization parameters, enabling the rational development of safer, more effective nano platforms.

This chapter illustrated how artificial intelligence and machine learning are reshaping nanotheranostic research by providing quick toxicity prediction, structural optimisation, and rational nanoparticle engineering. AI, through predictive modelling and algorithm-guided material design, offers a strong alternative to sluggish and expensive experimental testing. These increasing capabilities also have an impact on real-world translational pathways, which are discussed in the following chapter, which focusses on clinical integration and cancer-specific applications of AI-optimized nanotechnology.

5. Integration into cancer therapy

The end point of developing AI-optimized nanotheranostics is successful implementation in clinical cancer therapy. These enhanced nanoplatforms can transform the therapeutic environment of a broad range of malignancies by design through improved specificity, decreased toxicity, and real-time tracking effects enabled by AI-driven design. The section will examine the application of AI-optimized nanotheranostics to specific cancer types and highlight the advantages of solving the current limitations in therapy and provide their advancement in clinical trials [37].

5.1. Nanotheranostics

Applied to a wide variety of Cancers with AI-Optimized Nanotheranostics. The flexibility of nanotheranostic systems allows customizing treatment to most types of cancer, each of which presents unique biological challenges and treatment requirements. These systems are optimized through AI to enhance the most significant impact.

5.1.1. Breast cancer targeted delivery and imaging

Breast cancer, in particular, HER2-positive subtypes, may be aggressive and systemic adverse effects are often caused by conventional chemotherapy. Treatment is only possible by early and accurate detection of primary tumors and metastases. An AI-Optimized solution is AI-designed nanotheranostics that in the case of breast cancer, typically entail active targeting strategies using ligands that specifically interact with receptors on breast cancer cells (such as HER2, folate receptor, CD44). The density and geographical distribution of these ligands on the surface of the nanoparticle are also important components that are determined by AI algorithms. The goal of this optimization is to optimize the interaction with the cancer cells and their uptake of the nanoparticle and deliver the chemotherapeutic drugs (e.g., doxorubicin, paclitaxel) or gene-editing agents (e.g., siRNA) with high precision [38]. In the case of imaging, AI may guide the insertion of MRI contrast agent (e.g., superparamagnetic iron oxide nanoparticles, gadolinium chelates) or fluorescent dye in the nanocarrier. This allows sensorimants to be identified very sensitively, tumor margins to be assessed during surgery, and real-time observations to be made on how a medication builds up in the tumor. As an example, an AI-based model may be used to determine

the best size and surface coating of a lipid nanoparticle that should contain chemotherapeutic and fluorescent dye so that the tumor absorbs it and the liver does not accumulate it, eliminating the possibility of immunotoxicity. The Immunological Aspect of AI involves optimization of the surface of these nanoparticles to reduce interactions of the immune cells that could cause rapid clearance or inflammatory responses, which would result in effective and safe delivery of the therapeutic payload into the tumor. As an example, PEGylation plans calculated through AI may increase the circulation time significantly and enhance the accumulation of tumors [38].

5.1.2. Lung cancer

Curing Drug Resistance. Multidrug resistance (MDR) in lung cancer, especially non-small cell lung cancer (NSCLC) is frequently observed and caused by overexpression of efflux pumps (e.g., P-glycoprotein) or the activation of survival pathways, which leads to treatment failure. The AI Optimized Solution is AI based nanotheranostics currently under development to circumvent MDR processes. This may involve entrap of efflux pump substrates into nanoparticles that escape efflux pump action, and com-delivery of drugs with efflux pump inhibitors (such as verapamil and siRNA against MDR genes). The physical properties of the nanoparticle (e.g. size, charge, surface stiffness, etc.) can be programmed by AI algorithms to enhance cellular uptake and intracellular drug retention in resistant cells . One Theranostic Benefit of AI is Imaging agents (e.g., PET tracers, fluorescent probes) that can be combined to report the success of overcoming resistance in vivo, e.g. the intracellular concentration of a drug or the downregulation of resistance-associated proteins. AI is able to forecast the combination that will yield the most efficient synergistic effect between drug and resistance-modulating agent within one nanocarrier. Finally, the Immunological Aspect of AI is assistance in the creation of nanoparticles that do not only address drug resistance, but also regulate the tumor microenvironment to promote anti-tumor immunity. As an example, AI can be used to optimize nanoparticles targeting immune checkpoint inhibitors (e.g. anti-PD-L1 antibodies) to deliver them to immune cells specifically in the tumor to reduce systemic immune-related adverse effects [38].

5.1.3. Glioblastoma: Across the blood-brain barrier

Glioblastoma (GBM) is a virulent cancerous tumor in the brain that is infamously hard to treat because of the formidable blood-brain barrier (BBB) that limits the uptake of the majority of therapeutic agents [40]. The application of nanoparticles created by an AI to cross the blood-brain barrier (BBB) is an AI-Optimized solution to the treatment of the condition. This will involve maximizing surface alterations with specific ligands that engage receptor-mediated transcytosis (e.g., transferrin receptor, insulin receptor) or coming up with nanoparticles that can temporarily and safely break the integrity of the BBB. Artificial intelligence (AI) models have the ability to anticipate the most effective size, shape, and surface functionalization of different forms of nanoparticles (e.g., liposomes, polymeric nanoparticles, and exosomes) to cause optimal BBB penetration and minimal nervous system and systemic immunological reactions. In the case of GBM, theranostic nanoparticles have the potential to integrate therapeutics (e.g., temozolomide, gene therapies) and imaging (e.g., MRI contrast agents to visualize tumors, PET tracers to monitor drug delivery

or metabolic activity) modalities. The principle with which AI can be applied is the optimization of the co-loading and release kinetics of these agents to achieve effective imaging and therapeutic concentrations in the brain tumor. Moreover, due to the immune-privileged state of the brain and the potential of the neuroinflammatory process, AI-based design is essential to decrease the neuroimmunotoxicity of brain-targeting nanoparticles. AI can predict changes on the surfaces that suppress microglial activation and cytokine release in the CNS, such that the therapeutic benefits are not nullified by adverse brain immunological reactions [38].

The above chapter discussed how AI-optimized nanotheranostics were used to treat key cancer types, demonstrating how computational design increases targeting, imaging precision, drug resistance, and transport across physiological barriers. These developments highlight the transformational clinical potential of AI-guided nanoparticle engineering. However, real-world implementation necessitates traversing difficult regulatory and ethical frameworks, which are addressed in the subsequent chapter.

6. Regulatory and ethical issues

Although AI-based nanotheranostics can potentially benefit medicine to an enormous extent, a new stream of regulatory and ethical issues must be taken into consideration. The intricacy of the nanomaterials as well as the AI algorithms require an active stance by the regulatory organizations and a well-structured framework covering the ethical issues related to data, transparency, and patient safety [39].

6.1. Challenges in regulatory approval of ai-designed nanomedicines

The current regulatory systems, which are mostly intended to serve traditional medicine and traditional medical devices, have a major challenge when it comes to accommodating the specifics of nanomedicines, and even those that are developed or optimized using AI. Nanoparticles are also size dependent, highly surface reactive, and dynamic in vivo (e.g., aggregation, degradation, formation of protein corona) and are challenging to characterize and assess their safety. Regulators demand detailed information about these properties, their stability, and their location within the body, which can be more complex than that of small molecules. The "black box" nature of some advanced AI/ML algorithms (particularly deep learning models) poses a transparency challenge. Regulators need to understand *how* an AI model arrived at a particular design recommendation or toxicity prediction. Simply knowing the output is insufficient; the interpretability and explainability of the AI model are crucial for building trust and ensuring accountability. This is especially pertinent when AI models identify non-intuitive relationships between nanoparticle features and biological outcomes [40].

AI models are only as good as the data they are trained on. Regulators will require high-quality, standardized, and sufficiently large datasets for nanoparticle properties and their biological interactions, including immunotoxicity. The heterogeneity of existing nanotoxicity data, often collected under varying experimental conditions, presents a significant hurdle for training robust and generalizable AI models that meet regulatory standards. Beyond validating the nanomedicine itself, regulatory agencies

will need to establish guidelines for validating the AI models used in its design and toxicity prediction. This includes assessing model accuracy, robustness, generalizability, and the potential for bias. What constitutes a "validated" AI model for drug development will need to be clearly defined.

Monitoring the long-term safety and efficacy of AI-designed nanomedicines post-approval will require sophisticated surveillance systems, potentially incorporating real-world data and continuous learning AI models to detect rare or delayed adverse events, particularly those related to chronic immunomodulation or bioaccumulation.

6.2. Ethical concerns regarding data privacy and algorithmic transparency

This closed-loop optimization technique might accelerate the development process. Another concern that the use of AI in nanomedicine brings is several ethical considerations. First, information safety and security, the creation of tailored nanotheranostics, which may be based on individual patient data of omics (genomics, proteomics, clinical history), requires a strong level of data privacy and data security. There is a real need to protect patient-sensitive information by preventing attacks and misuse, particularly when such data is utilized to train AI models that may end up being used to make treatment decisions. Secondly, AI algorithms can also unintentionally reproduce or improve biases in their training data. Unless the datasets to train AI models to predict nanotoxicity are diverse and representative (e.g., they lack the data on some groups of patients or some types of nanoparticles), the algorithms might give biased predictions, which can potentially introduce discrepancies in treatment- or safety-related decisions. Another ethical issue related to AI-enhanced nanomedicine is the necessity to achieve justice and equity. Besides, the black box issue of AI not only influences the approval of regulatory authorities but also poses ethical concerns in terms of accountability. Should something go wrong with an AI-developed nanomedicine, who is to bear the blame: the AI developer, the nanomedicine developer, the clinician, or the AI? It is also necessary to define a clear set of accountability and make AI decisions explainable to clinicians and patients [41]. Informed Consent is essential; the more AI is incorporated into treatment choice and drug development, the more the concept of informed consent might require transformation. Patients must know whether and how AI has affected the development or choice of their nanotherapy, and what the consequences are with respect to their therapy. Finally, the danger exists that incredibly developed, AI-created nanotheranostics may increase healthcare inequalities when it is costly or unavailable to every group of patients. The ethical aspects should incorporate mechanisms of making these novel therapies a fair access [42].

6.3. Guidelines on standardized evaluation procedures

The way forward in these problems lies in concerted effort on the side of regulatory bodies, academic institutions, industry, and international organizations to come up with standardized assessment regimes. It is important to characterize nanoparticles through internationally agreed parameters through standardized

nanomaterial characterization of the physicochemical characterization (i.e., size, shape, surface charge, composition, purity). This makes data creation consistent, and this is necessary in training accurate AI models. Furthermore, Standardized toxicity testing guidelines are also involved, like the establishment of harmonized in vitro and in vivo protocols to measure different toxicities, including immunotoxicity (e.g., cytokine profiling, immune cell phenotyping, complement activation assays) will enhance the data comparability and reproducibility, and therefore will fortify AI model training datasets [42]. Good Machine Learning Practice" (GMLP) Guidelines. Regulatory organizations, including the FDA, are beginning to suggest GMLP principles for medical devices using AI. Other AI applications, such as drug research, will need similar criteria such as data management, model building, validation, deployment, and continuous monitoring. The main focus of these recommendations should be on openness, interpretability, and avoidance of bias. Also, the encouragement of open science and compilation of standardized, curated databases of high-quality nanotoxicity information will play a crucial role in speeding up the process of building AI models and validating them. Efforts to do so include the Nano Commons or the European Union Nano Safety Cluster. Nano scientists, toxicologists, immunologists and AI experts, physicians, and regulatory bodies also need to work hand-in-hand to come up with holistic and flexible regulatory frameworks that can match the rapid advances in AI-manipulated nanomedicine. By focusing on the human-in-the-loop strategy in which AI models act as decision-support instruments and not as independent decision-makers, it is possible to increase safety and responsibility. The human supervision and critical assessment of the AI results are still necessary [43]. Through such forward-looking regulatory and ethical concerns, the discipline can guarantee that the AI-based nanotheranostics are created and used responsibly so that their therapeutic potential is maximized, and at the same time ensure that the health of people remains intact, and so that society does not lose trust.

To finish this chapter, legal and ethical implications for AI-enabled nanotheranostics were discussed, with a focus on data quality, model transparency, validation, and equitable access. These problems highlight the significance of standardised approaches and appropriate AI integration. The following chapter discusses how future technological, computational, and biological improvements can improve the safety and personalisation of nanotheranostics.

7. Future perspectives

Artificial intelligence with nanotheranostics is a powerful combination that can entirely transform the sphere of cancer treatment. Though much has been achieved, the full potential of AI-optimized, immunologically compatible nanomedicines is yet to be achieved. This part introduces significant perspectives of the future, including the need to make critical advancements in data integration, AI algorithms, and the potential of highly personalized nanotherapeutic treatments.

7.1. Advancements needed in ai algorithms for better predictive accuracy

Despite new progress, AI algorithms in the medical field of nanomedicine have their problems to solve to be more predictive and useful. Further AI development

should focus on developing more interpretable and explainable AI (XAI) algorithms as the next step in overcoming black box models. The XAI techniques (LIME, SHAP, and deep learning attention processes) will be needed in order to understand the causes of a particular nanoparticle design to be toxic or effective. This interpretability is essential to gaining regulatory approval, establishing a sense of trust with clinicians, and providing pragmatic guidance to support rational design, especially of complex immunological outcomes. Machine learning Physics-Informed machine learning Physics-Informed machine learning (PIML) is essential because basic physical and chemical principles are integrated into AI models that can greatly enhance forecast accuracy and extrapolation. Physics-informed machine learning (PIML) methods achieve this by integrating traditional rules that govern nano-bio interactions (like diffusion, surface chemistry and protein adsorption kinetics) into the AI model directly. This allows the models to be learned more effectively when using small datasets thus making the predictions more reliable, especially when using new materials. State-of-the-art generative models, such as Generative Adversarial Networks (GANs) and Variational Autoencoders (VAEs), hold vast potential to the de novo creation of completely new nanoparticle structures with given qualities. These models can be used to synthesize entirely novel molecular or nanoscale structures that would be predicted to exhibit optimum performance and lowest immunotoxicity, which is why the groundbreaking nanotheranostics can be identified quickly [43]. Autonomous Optimization The reinforcement learning (RL) approach is essential in the creation of autonomous experimental platforms, or so-called self-driving labs, in which AI-based agents autonomously design, synthesize, characterize, and test nanoparticles. The result of every trial enables these bots to improve the following versions. Identification and development of nanotheranostic drugs with finely tailored immune characteristics. And lastly, Multi-Fidelity Modeling, which works by combining data from diverse levels of fidelity (e.g., quick in silico predictions, medium-throughput in vitro experiments, and low-throughput in vivo research) inside a single AI framework, might improve resource use. AI can direct which tests are most informative at each stage, ensuring that costly in vivo research is only undertaken on the most promising candidates.

7.2. Integration of multi-omics data for comprehensive toxicity assessment

The implementation of multi-omics data in a comprehensive manner is the way in which nanomedicine predictive toxicology will emerge in the future. Conventional toxicology research often involves a small number of endpoints, and it may not fully reflect the multifaceted chemical and physiological alterations induced by nanoparticles. To start with, Changes in gene expression (transcriptomics) in reaction to nanoparticle exposure can monitor active signaling pathways that are engaged in inflammation, oxidative stress, DNA damage, and the activation of the immune cells. AI will be able to identify certain signature genes in immunotoxicity or response to treatment. Secondly, the examination of the protein profile (proteomics) of cells or tissues after exposure to nanoparticles can provide information on the interaction of proteins with nanoparticles, protein corona, and protein changes in cellular machinery

attributable to toxicity or therapeutic action. And finally, disruptions in cell processes can be determined by analyzing metabolic changes (metabolomics) and disclosing biomarkers of toxicity or efficacy. Also, AI algorithms are unique in their ability to assimilate various high-dimensional information of omics. Deep learning models have the potential to show detailed interactions at the genomic, proteomic, and metabolomic scales, which will give a complete picture of the interaction of nanoparticles with biology. This holistic approach will assist not only in predicting acute toxicity but also the long-term, non-obvious, and insidious immunomodulatory activity, which could not be detected otherwise. An example of this type of application would be identifying a relationship between specific nanoparticle surface chemistries and various profiles of proteomes in immune cells, so as to preempt the potential of a chronic inflammatory response [44].

7.3. Potential for personalized nanotheranostic therapies

The end point of AI-based nanotheranostics is to deliver totally personalized therapy. Cancer is unique in each patient, and the immune system of the patient is different in responding to external factors. Nanotheranostics in the future will no longer have a one-size-fits-all model. A specific nanotheranostic drug response in each patient can be forecasted using AI algorithms that have been trained on personal patient data (e.g., genetic background, immune cell profiles, microbiome composition, tumor biopsy features, etc.). This includes predicting individual sensitivity to immunotoxicity (e.g., CARPA, CRS) and using an approximation of the likelihood of an effective antitumor immune response. AI can personalize nanotheranostic medicines to the individual biological makeup of a patient to suggest how to optimize formulation, dose and delivery timing to maximize efficacy with minimal side effects. As an example, when the immunological profile of a patient indicates that it is at a high risk of CARPA with a particular liposomal formulation, AI can provide an alternative nanocarrier or a pre-medication approach aimed at reducing the risk. In addition, A combination of AI with the current imaging and biosensing technologies could enable real-time tracking of nanotheranostic delivery, tumor reaction, and systemic immune reactions in vivo. The AI algorithms may then actively change therapy (e.g. change dose, change medicine) to favorably change outcomes and prevent emergent toxicities thus creating a closed-loop personalized treatment system. Interestingly, in the future artificial intelligence could be employed to develop the concept of artificial twins that will be the presence of a biological system of a patient in the virtual world. These digital twins would replicate the actions of nanotheranostics in the body of a person, and they can test a variety of treatment scenarios in-silico and then before an individual is treated, this will enhance personal safety and efficacy even more [44].

7.4. Overcoming remaining hurdles

Notwithstanding these thrilling possibilities, there are several major challenges that are still to be overcome. The significance of high-quality, standardized, and publicly accessible datasets in the characterization of nanoparticles and in biological interactions could not be stressed. International cooperation is also very vital in this

aspect. Secondly, there should be powerful and universally accepted validation frameworks of AI models in nanomedicine to guarantee their reliability and acceptability by the regulators. The development of a new scientific community that understands nanotechnology and AI/ML equally is essential to overcome the gaps in the disciplines and promote innovation. In addition, AI designs will demand scalable and reproducible synthesis processes to bring their designs to clinical reality as AI designs get more complex nanoparticles. Finally, the future of cancer nanotheranostics is directly related to the development of AI and machine learning. Through these advanced computational methods, discipline can accelerate the process of innovative therapies, address the recurrent toxicity issues, and eventually fulfill the dream of precision, personalized, and immune-compatible cancer medicines.

To summarise, future advances in nanotheranostics will be dependent on increased AI interpretability, the integration of multi-omics data, personalised digital-twin modelling, and autonomous design-test pipelines. These advancements offer safer, smarter, and more personalised cancer nanotherapies. The final conclusion summarises how these discoveries combine position AI-driven nanotheranostics as a key component of next-generation oncology.

8. Conclusion

Nanotheranostics provides a potent approach to cancer treatment by integrating imaging and targeted therapy, but its clinical success is sometimes hampered by intricate immunological interactions that can have negative consequences. Conventional toxicity testing lags the fast development of nanomaterials. Artificial intelligence (AI) and machine learning are critical for predicting toxicities, including immunotoxicity, which enables the development of safer and more effective nanoparticles. AI-optimized nanoparticle features can reduce adverse immune reactions and improve cancer treatment, including medication targeting breast cancer, overcoming resistance in lung cancer, and bridging the blood-brain barrier in glioblastoma. Continuous clinical data collection increases AI model accuracy, enabling personalized nanomedicine via explainable AI, multi-omics integration, and AI-driven nanomaterial creation. Finally, patient-specific digital twins can replicate therapy reactions in real time. This involves multidisciplinary collaboration and standardized nanomaterial testing. The combination of AI with nanotheranostics is a step towards safer, smarter, and more personalized cancer treatment.

Author contributions: Conceptualization, Aqsa Mehreen; literature search and data collection, Aqsa Mehreen, Imran Khan Yousafzai, and Abdullah Tariq; methodology and organization of review structure, Aqsa Mehreen and Imran Khan Yousafzai; formal analysis and synthesis of literature, Imran Khan Yousafzai and Aqsa Mehreen; writing,original draft preparation, Aqsa Mehreen and Imran Khan Yousafzai; writing review and editing, Nadia Noreen, Nayab Ahsan, and Khadija Tariq; visualization (figures and diagrams), Khadija Tariq; data curation, Abdullah Tariq and Noor Fatima; references compilation and formatting, Nadia Noreen, Abdullah Tariq, and Noor Fatima; proofreading and final corrections, Nayab Ahsan and Noor Fatima;

supervision and project administration, Aqsa Mehreen. All authors have read and agreed to the published version of the manuscript.

Conflict of Interest: The authors declare no conflict of interest.

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