

Research Article

RADIATION-ACTIVATED NANOPLATFORMS FOR PRECISION ONCOLOGY: EMERGING DESIGN STRATEGIES, BIOLOGICAL MECHANISMS, AND CLINICAL TRANSLATION

Author: Mubarak Lawal¹, Ibrahim Yusuf¹, Abdullahi M. Hassan¹ and Osaro Jibrin²

¹Department of Physics, University of Jos, Plateau, Nigeria

²Department of Pure and Applied Physics, Federal University Wukari, Nigeria

KEYWORDS:

Radiation-activated nanoplatform, precision oncology, radiosensitization, nanomedicine, cancer theranostics

ARTICLE HISTORY

Received Date: 04/07/2026

Revised Date: 06/07/2026

Accepted Date: 12/08/2026

Published Date: 04/09/2026

DOI: 10.69557/2czdkk06

CORRESPONDING AUTHOR

Mr. Osaro Jibrin

osaro.jibrin@fuwukari.edu.ng

ABSTRACT

Radiation-activated nanoplatforms are emerging as a promising strategy to overcome the biological and physical barriers of conventional radiotherapy by integrating radiation-induced therapeutic processes with nanoscale material engineering. This review critically assesses the radiation-activated nanoplatforms in relation to the correlation between the structure of the nanomaterials, radiation-nanomaterial interactions, tumor biology, tumor therapeutic mechanisms, and clinical translation of the nanomaterials in precision oncology. high-Z nanoparticles, radiation-responsive nanocarriers, nanomaterials that generate ROS, nanozymes, oxygen-modulating systems, hypoxia-responsive systems, and multifunctional core-shell nanoparticles. Particular attention to the secondary generation of electrons, amplification of ROS, the regulation of oxygen, the controlled release of drugs, the destruction of DNA, the dysfunction of mitochondria, ferroptosis, and immune-cell death. Their combination with chemotherapy, immunotherapy, photothermal/photodynamic therapy, and theranostic imaging are also discussed. A novel nanostructure–radiation–biology–clinical outcome framework that serves to bridge nanoscale radiation physics to molecular damage, regulated cell death, controlled remodeling of the tumor microenvironment, and antitumor immunity is one of the novelty features. A new paradigm of precision translation that incorporates molecular profiling, nanoparticle biodistribution, image-guided nanodosimetry, personalized radiation dosing and AI-driven treatment adaptation is also encouraged by the review. Challenges like the heterogeneous tumor penetration, off-target accumulation, long-term toxicity, variability in manufacturing process, complexity in regulations as well as nanoscale dosimetry are critically assessed. Opportunities for the future include self-regulating therapeutic systems, biodegradable nanomaterials, sustainable synthesis, and AI-guided design. Overall, one can imagine smarter, intelligent, and clinically fabricable nanoplatforms that would transform the approach to radiation application to elicit a therapeutic response in personalized cancer therapy.

INTRODUCTION

Cancer continues to be one of the leading causes of morbidity and mortality worldwide and there is a critical need for effective therapies that can obtain long-term tumor control without excessive toxicity. The current global estimates show that the number of new cases of cancer and cancer deaths per year are estimated to be 20.6 million and 9.8 million respectively all over the world in 2024 and an ever-increasing demand of better and more precise treatment options ^[1]. Radiotherapy (RT) is a primary treatment of cancer and is an important part of treatment of most types of tumors as a single modality or in combination with surgery, chemotherapy, targeted therapy, and immunotherapy. The therapeutic effect is however limited by the fact that sufficient doses of radiation cannot be given to the target cancer without exceeding the dose limit of the surrounding normal organs ^[2, 3].

Moreover, tumors are biologically complicated, and therefore, conventional RT is ineffective. The radiosensitivity of cancer-cell populations changes significantly within the same tumor (intra-tumoral heterogeneity) and less responsive regions are hypoxic meaning that they do not respond to radiation in the absence of oxygen to repair radiation-induced DNA damage. In addition, intrinsic or acquired radioresistance that could be attained by enhanced DNA-damage repair, regulation of cell-cycle, antioxidant responses and adaptive responses of the tumor microenvironment can also play a role in radiation resistance ^[2, 3]. Traditional systemic radiosensitizers and chemotherapeutic agents may improve the tumor response to irradiation but may result in an increase in the systemic toxicity of the treatment, because they do not selectively target the irradiated tumor site. All these have stimulated the creation of strategies that can concentrate therapeutic action in tumors and triggering them selectively in response to irradiation.

With the emergence of nanotechnology, an entirely new way of improving radiation has appeared the possibility of creating therapeutic agents on the level of cellular and sub-cellular biological processes. Also, the first steps to nanomedicine were passive drug delivery and improved tumor targeting, and the current platforms are more accommodating targeting, radiation sensitization, controlled drug release, imaging, and immune modulation capabilities into multifunctional platforms ^[4]. Nanoparticles can alter radiation-matter interactions, increase the local energy deposition, generate reactive oxygen species (ROS), impair the repair of DNA, influence hypoxia, and deliver radiosensitizing drugs or biological agents into tumor cells ^[2, 3].

The transition is significant as nanosystems may provide numerous functions. They can be targeted using targeting ligand on their outer surfaces and have chemotherapeutics, nucleic acid, immunomodulators or radiosensitizers within their cores or matrices. These architectures have the potential to be further developed to help solve some of the issues in pharmacokinetics, protection of therapeutic payloads against premature degradation, their controlled release and integration with other therapies like radiotherapy ^[4, 5]. Nanotechnology is thus taking the radiation oncology field beyond the conventional radiation dose-delivery concept to the spatiotemporally modulated therapeutic activation concept.

Radiation-activated nanoplatfroms tend to mean nanosystems that are rendered more active, reactive or localized by exposure to ionizing radiation. These have several conceptually identical but mechanistically distinct platforms. Radio enhancement effect of nanoparticles is associated with their physical energy deposition, increase of ROS, catalytic reaction, and interference with the cellular repair pathways. Radiation-responsive nanocarriers on the other hand are tiny particles that respond to radiation to cause a structural change in the particle or to release an encapsulated therapeutic cargo. These characteristics are found in other systems, such as chemotherapy, phototherapy, gene therapy, and/or immunotherapy ^[2, 5].

This is a fascinating concept as radiation can be a source of energy as well as an external control stimulus. High-atomic number nanomaterials enhance local radiation interactions and secondary electron generation and multifunctional nanoplatfroms utilise radiation-induced ROS and cellular stress to activate other possible therapeutic routes ^[3]. These systems are then beginning to transform into passive nanocarriers to actively engineered systems that can couple the characteristics of the system to radiobiological responses. Physical dose enhancement is not the only reason to use radiation-activated nanomedicine as a form of therapy. Ionizing radiation produces DNA damage in two mechanisms: direct and indirect DNA damage,

the latter being a substantial part of oxidative stress induced by ROS. Nanomaterials can enhance these effects through an enhanced production of ROS, catalytic reactions, antioxidant depletion, or an increase in energy deposition locally ^[2, 3]. This type of process can trigger DNA double-strand breaks, damage the mitochondria, damage membranes, and activate multiple cell death pathways, such as apoptosis and ferroptosis.

The tumor–immune interface may also be modified by radiation. Radiation-induced immunogenic cell death is believed to cause release of tumor antigens and damage-associated molecular pattern that can stimulate antigen presentation and consequently cause anti-tumor immunity ^[6, 7]. Thus, it is possible that nanoplateforms that can enhance this mechanism can result in the transformation of not only the local radiation injury into systemic antitumor immunity but also the more powerful effects. In addition, there is a possibility of further overcoming biological barriers to radiotherapy, through the modulation of hypoxia, redox balance, extracellular matrix properties, and immunosuppressive tumor microenvironment ^[3].

Although significant advances have been made, there are significant challenges to the translation of nanomaterials into the clinic. Nevertheless, most of the reported systems are very radiosensitizing in simplified cellular models, but have problems with tumor-specific biodistribution, heterogeneously distributed penetration into the tumor, pharmacokinetics, long-term toxicity, scalable manufacturing, batch-to-batch reproducibility, and regulatory characterization ^[4, 5]. Moreover, nanoparticles, energy of radiation, dose, fractionation, tumor biology and timing of treatment may all interact in complicated manners and thus it may prove hard to normalize comparisons of studies.

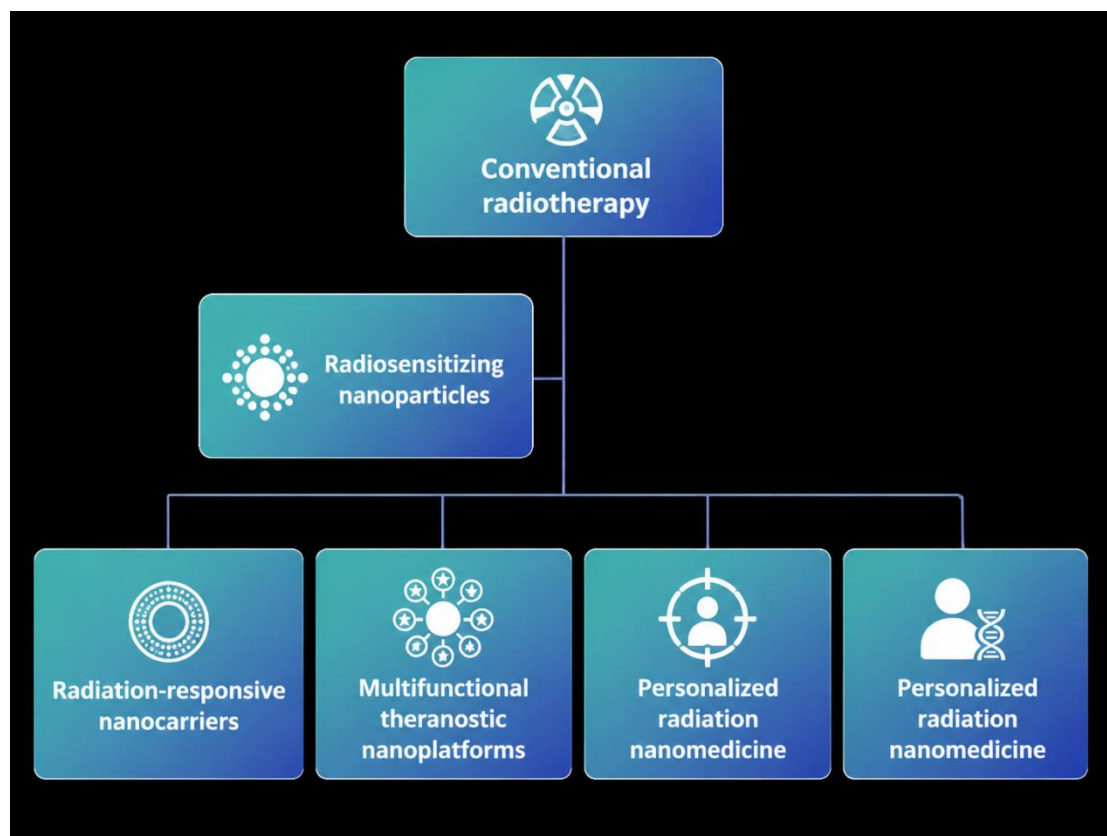


Figure 1. AI-Driven Radiation Nanomedicine

Figure 1 shows how radiation-based cancer therapy has advanced through the years in the development of the conventional radiotherapy techniques to the advanced methods of precision nanomedicine. The conventional radiotherapy is the classical approach, wherein ionizing radiation is directly employed to cause tumor cell damage, but some of the shortcomings, including radioresistance, hypoxia, and lack of tumor selectivity, prompted the creation of radiosensitizing nanoparticles that can amplify radiation energy

deposition and produce other cytotoxic effects. Later developments saw the development of radiation-responsive nanocarriers that release therapeutic agents or trigger biological reactions in response to radiation exposure to enhance the spatial and temporal locality of treatment. The development of multifunctional theranostic nanoplatfroms further incorporated therapeutic functions with diagnostic imaging, targeting, oxygen control, immune modulation, and real-time monitoring of treatment. Finally, these advances have led to the development of personalized radiation nanomedicine where the design of the nanoplatfrom is customized based on the specifics of the tumor, molecular biomarker profiles, and the individual tumor response to therapeutic radiation, resulting in the achievement of specific, effective, and safer treatment of cancer.

Method

Focusing on Design Strategies, Biological Mechanisms, and Clinical Translation, a structured narrative review was performed to critically assess the recent advances in molecular and structural design, radiation–nanomaterial interaction, biological mechanisms, therapeutic applications of radiation–activated nanoplatfroms, and their clinical translation. PubMed/MEDLINE, Web of Science, Scopus, ScienceDirect and Google Scholar databases were searched, but a primary search covered the period 2020–2026; seminal studies were considered significant only when they presented the background to the concepts or major technological advances. Radiation-activated nanoplatfroms, radiotherapy nanomedicine, radiosensitizing nanoparticles, radiation-responsive nanoparticles, X-ray activated nanomaterials, radiotherapy immunotherapy nanoparticles, tumor hypoxia nanomedicine and clinical translation radiotherapy nanoparticles were searched. Relevant to the design and application of nanomaterials in radiotherapy or radiation induced therapy it was inclusive of in vitro, in vivo and in vivo clinical studies, including aspects of in vivo nanoplatfrom development, tumor response to radiotherapy, radiosensitisation, therapeutic efficacy, safety, hypoxia, radioresistance, tumor heterogeneity, and translational development. Non-radiation-based cancer therapy studies, non-editorials on cancer therapy, and non-radiation-based editorials without evidence and reports that had little or no methodological details were eliminated. The information was systematically searched along the lines of nanomaterials composition, particle size and morphology, radiation type and dose, radiation-activation, therapeutic payload, type of cancer to be targeted, biology, experimental tumor, therapeutic, toxicity and translation development. The retrieved evidence was organized into themes according to five broad questions (i) How are radiation-activated nanoplatfroms molecularly and structurally engineered, (ii) How do nanomaterials interact with ionizing radiation, (iii) What are the biological processes that mediate radiosensitization and therapeutic response, (iv) How do these platforms overcome hypoxia, radioresistance, and tumor heterogeneity, and (v) What are the scientific, manufacturing, safety, regulatory, and clinical challenges that currently still ensure that support translation into precision oncology?

MOLECULAR DESIGN AND CLASSIFICATION OF RADIATION-ACTIVATED NANOPLATFROMS

Multifunctional platforms are being developed using a new generation of radiation-activated nanoplatfroms, with the physicochemical properties of nanomaterials designed to match the physical properties of the radiation, and the biological susceptibilities of the tumor. Modern designs exploit radiation-nanoparticle interaction and associated catalytic action, redox modulation, oxygen control, controlled drug delivery and immune remodeling to improve the therapeutic ratio of radiotherapy as opposed to viewing the nanoparticle as a passive carrier. The platforms can be roughly divided into four groups: high-atomic-number (high-Z) nanoparticles, radiation-responsive nanocarriers, ROS-amplifying nanomaterials, hypoxia-modulating systems and multifunctional/core-shell systems ^[2, 3].

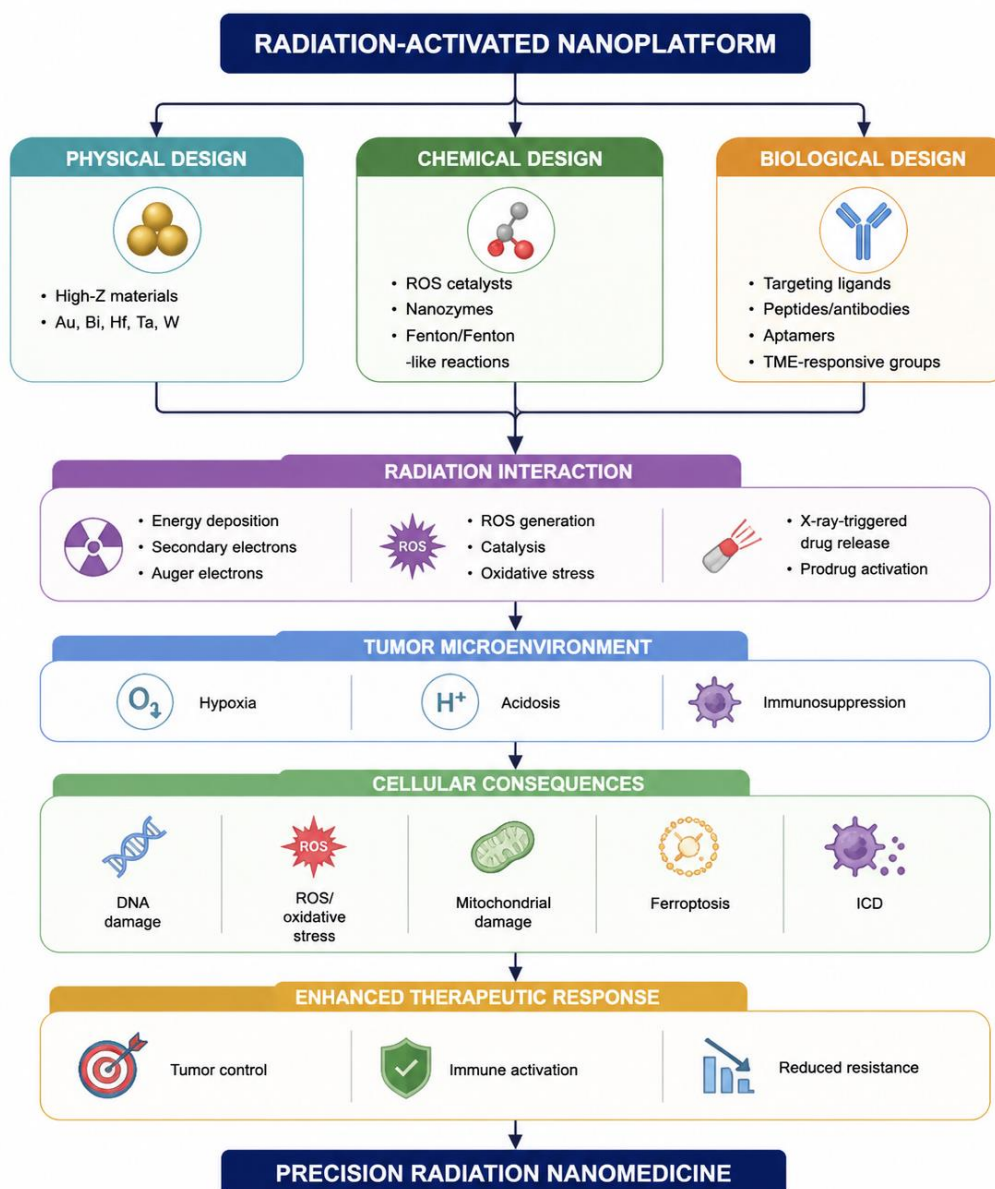


Figure 2. Molecular and Functional Design Architecture of Radiation-Activated Nanoplatfoms for Precision Oncology

Figure 2 presents the integrated molecular and functional architecture underlying the design and therapeutic operation of radiation-activated nanoplatfoms in precision oncology. The framework demonstrates how nanoplatfom performance is governed by the coordinated integration of physical, chemical, and biological design strategies. Physical design incorporates high atomic number (high-Z) materials such as gold, bismuth, hafnium, tantalum, and tungsten to enhance radiation absorption and generate secondary electrons, while chemical design introduces ROS-generating components, nanozymes, and catalytic systems capable of amplifying oxidative stress through radiation-induced reactions. Biological design incorporates targeting ligands, peptides, antibodies, aptamers, and tumor microenvironment (TME)-responsive elements to improve tumor selectivity and therapeutic localization. Upon radiation exposure, these engineered nanoplatfoms promote enhanced energy deposition, ROS generation, catalytic activation, and radiation-triggered drug release, leading to modulation of key tumor microenvironmental barriers including hypoxia, acidosis, and immunosuppression. These interactions subsequently induce multiple cellular responses, including DNA damage, oxidative stress, mitochondrial dysfunction, ferroptosis, and immunogenic cell death (ICD), resulting in improved tumor control, immune

activation, and reduced therapeutic resistance. Ultimately, this hierarchical design strategy enables the development of precision radiation nanomedicine platforms that integrate targeted delivery, multimodal therapy, and personalized cancer treatment approaches.

High-Z Nanoparticles for Radiation Dose Amplification

One of the oldest methods of physical radiosensitization is the use of high-Z nanoparticles. High atomic number elements have stronger interactions with X-rays and other forms of ionizing radiation, especially by the photoelectric effect and the production of secondary electrons. If these materials are deposited inside and/or near the tumor cells, radiation energy can be focused at the nanoscopic level to add the local ionization level, which may be helpful to enhance the damage on the DNA and damage on the organelles. However, the efficacy of this approach is not just limited to atomic number but also to the concentration of nanoparticles, their size, their intracellular localization, the energy of radiation, the photon spectrum, and the distribution of tumors ^[2, 3].

Gold Nanoparticles

The high atomic number ($Z = 79$) and high electron density of gold, along with its surface chemistry properties, make it an ideal candidate for a radiation-enhancing agent, which is why gold nanoparticles (AuNPs) have been widely studied. Gold can increase local energy deposition via photoelectric interactions and the generation of secondary electrons, including those with energies in the range able to cause local molecular damage upon x-ray irradiation. The impacts can lead to elevated oxidative stress and DNA damage and could be especially significant if nanoparticles are situated near vulnerable cellular structures ^[2, 8].

An important design advantage of AuNPs is their highly modifiable surface. They can be functionalized with thiolated polymers, peptides, antibodies, aptamers, and other ligands to enhance their colloidal stability, tumor targeting, cellular uptake, and/or intracellular targeting. In addition, gold nanostructures can be coupled with photothermal, imaging, or drug-delivery capabilities so that a standard radiosensitizer can be converted to a theranostic platform. However, there remain unanswered questions regarding the penetration and heterogeneous uptake, clearance, retention, and dose response between the nanoparticle dose and radiation dose.

NANOMATERIALS COMPRISED OF BISMUTH, HAFNIUM, TANTALUM, AND TUNGSTEN

The use of bismuth-based nanoparticles has garnered considerable interest due to bismuth's high atomic number, high X-ray attenuation capabilities, relatively low (compared to other potential heavy elements) reported toxicity, and relatively low material cost. These properties render bi-based nanomaterials as a promising material to enhance radiation doses. Their morphology, size, surface chemistry, and composite structure can be modified to have an impact on tumor accumulation and radiation interaction ^[9].

The nanomaterials are especially relevant for translational applications because they are based on hafnium. The radiosensitizing effect of hafnium oxide nanoparticles has been shown, and they have advanced significantly towards clinical use compared with many nanomaterials that are still in the experimental stage. They work by increasing radiation interaction and the following damage to the tumor cells by the biosynthetic amplification of radiation effects. The clinical progress of hafnium oxide-based NBTXR3 shows how nanoscale radiosensitization can progress to a clinically developed radiation enhancement technology.

Materials with high atomic numbers, such as tantalum and tungsten, are also being studied due to their high capacity of absorbing radiation. These materials can be integrated into nanoscale architectures to

enhance the energy deposition in the local tissue, but their potential applicability ultimately relies on the physicochemical stability, biological compatibility, tumor localization, manufacturability, and clearance. However, high-Z materials should not be considered as simply "high number" materials. Their behavior depends upon the interplay of radiation energy, mass attenuation properties, amount of nanoparticles, surface chemistry, cellular localization, and biological response. Therefore, comparative studies should include physical dose enhancement and biological endpoints.

Mechanical Relationship of Atomic Number and Radio-sensitization

The high-Z effect is primarily related to the increased interaction of the ionizing radiation with those materials that contain high electron density. Absorption of the photon may result in the production of the characteristic X-ray and Auger electron by subsequent relaxation processes or the production of energetic photoelectrons. The secondary electrons may ionize and excite other biological molecules in the region and can travel for short distances.

This localized energy deposition can boost the chances for DNA damage and ROS formation. The link between the number of atoms and the biological radiosensitization is not linear, however, under all irradiation conditions. Compton scattering is more significant at megavoltage energies typically used in external-beam clinical radiation therapy, whereas the photoelectric interactions are more significant at lower photon energies. Thus, the actual clinical radiation spectrum should be used for designing nanoparticles and not evaluated under conditions with limited clinical relevance.

Radiation-Responsive Nanocarriers

The difference between radiation-responsive nanocarriers and conventional radiosensitizers is that the radiation field can be used as an external trigger for therapeutic activation or drug release. This can provide a chance to match the spatial and temporal delivery of a therapeutic payload with the irradiated tumor volume. The research has mostly been directed to X-ray-responsive chemical bonds, radiation-sensitive polymers, scintillating nanoparticles, liposomal systems, hydrogels, and radiation-activated prodrugs ^[10].

Radiation-Induced Drug Release

There are several ways that can induce drug release by radiation. Ionizing radiation can cause direct or indirect breakage of radiation-sensitive chemical links, formation of radiation-induced reactive species that can break a carrier, or a secondary photochemical process. Thus, radiation-sensitive polymers and nanogels can be designed to change their structure after exposure to radiation, leading to the release of chemotherapeutic and molecularly targeted agents only in the vicinity of the target.

A key approach is the use of cleavable bonds, such as diselenide bonds, in nanostructures. Recent studies have shown that the diselenide bonds can be cleaved by X-rays to destroy the nanoparticle carrier and release therapeutic molecules in the tumor. These materials absorb X-ray energy and release a portion of that energy as lower energy photons, which activate neighboring (therapeutic) molecules. The resulting method can result in a localized depot of the drug in an irradiated tumor. For instance, a study from 2024 showed a brilliant nanoparticle drug depot that can be activated for a cytotoxic payload after relatively low-dose X-ray exposure in preclinical tumor models.

X-Ray-Responsive Nanoplatforms

The use of X-rays as an external stimulus is especially appealing, as they have much greater penetrating power than ultraviolet and visible light. They can therefore be used as a trigger and activate nanocarriers in tumors deep in the body. Additionally, the clinical radiotherapy technologies of radiation dose, treatment field, fractionation, and timing can be controlled.

The challenge with the design is to provide enough response at clinically realistic radiation doses. Clinical use of the therapy is limited, as some of the chemical systems used are sensitive to radiation and require larger doses for their application than are normally used in radiotherapy. Research is therefore progressing towards catalytic amplification, scintillation-assisted activation, and highly sensitive radiation-cleavable linkers that are sensitive to clinically relevant radiation doses.

Radiation-Activated Nanoprodrugs

Nanoprodrug systems give spatial control with additional therapeutic inactive or less-toxic precursors that are transformed into therapeutic agents upon exposure to radiation. These systems are able to decrease early systemic exposure, thereby enhancing the levels of active drug in the irradiated tumor.

The idea can be expanded to multipurpose nanoprodrugs, where the radiation field could also trigger the release of the drug and boost ROS formation. This provides the opportunity for a coordinated response involving radiation as a trigger and therapeutic amplifier. The kinetics of activation, stability in circulation, requirements for radiation dose, and off-target activation need to be carefully characterized before clinical translation, however.

Nanomaterials for ROS Amplification by Irradiation

The enhancement of radiotherapy by nanomaterials is a major route in biology by which ROS amplification takes place. Ionizing radiation already creates ROS by the radiolysis of water and subsequent cellular reactions. This response can be exacerbated by nanomaterials that can either mediate electron transfer, catalyze reactions that produce ROS, decrease the antioxidant capacity of cells, or create additional ROS. The current methods are metal oxide nanoparticles, semiconductor nanomaterials, catalytic nanozymes, and redox-active nanocomposites [2, 3].

This oxidative stress can lead to the damage of DNA, proteins, membranes, and mitochondria. Importantly, ROS amplification can also influence programmed cell-death mechanisms like ferroptosis and apoptosis, potentially offering avenues for multimodal radiosensitization.

Catalytic Nanoplatfoms

The enzyme-like catalytic activities of the nanozymes, combined with the structural stability and tunable surface chemistry compared to many natural enzymes, render them particularly interesting. Endogenous hydrogen peroxide can be converted into highly reactive hydroxyl radicals by peroxidase-like nanomaterials, which further enhances the oxidative damage in the tumor cells.

An additional important mechanism is the fenton and fenton-like reactions. Nanomaterials with Fe, Cu, Mn, or redox-active components have the ability to catalyze reactions with the generation of hydroxyl radicals under appropriate tumor microenvironmental conditions. The synergistic effect of radiative activity and catalytic activity can be achieved when the nanoparticle turns the endogenous substrate into very reactive species and, at the same time, the radiation provides more oxidative stress.

This is especially enticing for the tumors with elevated hydrogen peroxide levels but relatively low oxygen levels. However, careful control of catalytic activity is required, as too much ROS production outside the tumor may result in toxicity of normal tissues. Therefore, it is still very important to activate the tumor, to engineer the surface, and to control the biodistribution of the particles.

Hypoxia-Responsive and Oxygen-Modulating Nanoplatfoms

Hypoxia of tumors is one of the most significant biological obstacles to successful radiotherapy. Radiation-induced damage to DNA is stabilized by oxygen, and oxygen-depleted regions of tumors can have significantly less radiosensitivity. There are multiple strategies to solve this issue in nanotechnology,

such as oxygen carriers, oxygen-producing systems, catalase-mimicking nanoparticles, metabolic modulators, and hypoxia-responsive drug-delivery systems [2].

Oxygen-Generating Nanoparticles

Endogenous tumor substrates can be utilized to generate oxygen at the site of the tumor using oxygen-generating nanoparticles. For example, manganese dioxide (MnO_2) can undergo chemical change when it reacts with hydrogen peroxide (H_2O_2) and produce oxygen gas (O_2). Such a strategy has gained more and more popularity since it can simultaneously change tumor hypoxia and redox conditions. Recent research has also focused on the integration of theranostic properties in MnO_2 -based systems, in which imaging capabilities have been merged with oxygen generation for MR-guided radiotherapy.

Catalase-Mimetic Nanomaterials

Catalase-like nanomaterials can help speed up the breakdown of hydrogen peroxide into water and oxygen, which could boost oxygen in regions of hypoxia within a tumor. This could be especially beneficial in areas where natural hydrogen peroxide levels are adequate for providing oxygen.

Perfluorocarbon-Based Oxygen Delivery

Nanostructures containing PFCs (NPS) are able to physically dissolve and transport relatively large quantities of oxygen. After accumulation in the tumor, a release of oxygen can occur to the oxygen-deficient areas, which may enhance the efficacy of the subsequent radiation treatment. Oxygen-carrying is especially appealing as it does not involve in situ chemical production of oxygen [8].

Hypoxia-Responsive Drug Release

Instead of suppressing hypoxia, another approach is to leverage hypoxia as a molecular trigger. Hypoxia-responsive linkers and prodrugs are kept relatively inactive in oxygenated tissues and get activated when the tissue is under reducing or oxygen-deficient conditions. Hypoxia-responsive activation and radiation is a dual approach of a nanoplatform that is triggered by the intrinsic tumor microenvironment and the externally controlled radiation field.

This is a significant paradigm switch from radiosensitization to adaptive nanomedicine, in which the spatial variation in tumor biology is encountered by the nanoparticle.

Multifunctional and Core–Shell Nanoplatforms

In this context, the development of single-function nanoparticles has been pushed back, leading to the creation of multifunctional architectures that are able to tackle the physical, chemical, and biological mechanisms of radioresistance simultaneously. Multifunctional therapeutics can be combined within a single nanoformulation, such as core–shell nanoparticles, nanocomposites, metal–organic architectures, polymeric nanocarriers, and biomimetic systems.

A multifunctional system might comprise high-Z elements that enhance radiation dose, catalysts that amplify the concentration of ROS, a shell containing a drug for chemotherapy, and targeting ligands to target the tumor. Other components may have a photothermal, a photodynamic, an imaging, or an immunomodulatory activity. The combination of such integration allows for the targeting of multiple resistance mechanisms instead of a single pathway for radiosensitization.

Radiosensitizer and Chemotherapy

Radiation-activated nanoplateforms are able to co-deliver both a radiosensitizer and a chemotherapeutic agent, thereby enhancing the delivery of the drug or enhancing the activity of the drug in the irradiated tumor. This may help optimize the spatial arrangement of chemotherapy and radiotherapy treatment, as well as limit exposure to the body.

Radiosensitizer and Immunotherapy

The potential advantages of combining radiation nanomedicine with immunotherapy involve the ability of radiation to induce immunogenic cell death and the ability of nanomaterials to increase antigen release, recruit immune cells, or deliver immune-modulating agents. It is thus possible to remodel the tumor microenvironment using nanoparticles to induce a global tumor immune response following radiation treatment.

Radiosensitizer and Photothermal Therapy

Optical energy can be converted to localized heat by the photothermal components, which can disrupt tumor cells and change tumor perfusion. Thermal stress and radiation-induced molecular damage could synergize with radiation. However, the penetration of much of the optical spectrum of tissue is less than that of X-rays, and so they are more suitable for accessible tumors or image-guided/interventional applications.

The future generation of platforms will probably shift from combinations to more mechanistically integrated systems in which every component will have a clearly defined complementary function: Absorption of radiation, amplification of energy, production of ROS, modulation of hypoxia, therapeutic release, and activation of immunity.

This integration can generate a greater therapeutic effect than just adding complexity to the nanoparticles. In future designs, it would be important to take note of functional necessity, repeatability, safety, and clinical feasibility over the number of components.

Table 1. Classification of Radiation-Activated Nanoplateforms

Nanoplateform	Primary Function	Radiation Interaction	Major Advantage	Major Challenge
Gold nanoparticles	Radiosensitization	Photoelectric interactions and secondary-electron generation	Strong radiation-enhancement capability; versatile surface functionalization	Tumor penetration, clearance, and potential long-term retention
Bismuth-based nanoparticles	Dose enhancement	X-ray attenuation and secondary-electron generation	High-Z effect, strong X-ray attenuation, relatively low cost	Surface stability, biodistribution, and biological validation
Hafnium-based nanoparticles	Radiation amplification	Enhanced local energy deposition	Strong radiotherapy synergy and advanced translational development	Manufacturing, tumor distribution, and clinical implementation
Tantalum-based nanomaterials	Radiation dose enhancement	High-Z radiation interaction	High attenuation and multifunctional	Limited clinical evidence and manufacturing

			material potential	complexity
Tungsten-based nanomaterials	Radiosensitization	Enhanced photon interaction and energy deposition	High-Z properties and potential imaging/radiation functions	Biocompatibility and translational validation
Radiation-responsive polymers	Controlled drug release	Radiation-induced bond cleavage or structural disruption	Spatiotemporal drug release	Radiation sensitivity and structural stability
Scintillating nanoparticles	Radiation-triggered activation	X-ray absorption followed by photon emission	Can couple radiotherapy with localized drug or photodynamic activation	Scintillation efficiency and clinical-dose responsiveness
Nanozymes	ROS amplification	Radiation-enhanced catalytic/redox processes	Catalytic amplification of oxidative stress	Tumor specificity and control of off-target ROS
Iron/Cu/Mn-based catalytic nanoparticles	Chemodynamic radiosensitization	Fenton/Fenton-like reactions coupled with radiation	Strong ROS amplification and potential ferroptosis induction	Dependence on TME chemistry and systemic safety
Oxygen-generating nanoparticles	Hypoxia correction	Indirect enhancement of radiation response	Addresses a major mechanism of radioresistance	Limited oxygen-generation capacity and spatial heterogeneity
Catalase-mimetic nanoparticles	Oxygen generation	Decomposition of endogenous H ₂ O ₂	Potentially improves oxygen availability in hypoxic tumors	Dependence on endogenous substrate concentration
Perfluorocarbon nanocarriers	Oxygen delivery	Radiation response enhanced by increased local O ₂	Direct oxygen transport and hypoxia alleviation	Oxygen loading, retention, and controlled release
Hypoxia-responsive nanoplatforms	Selective therapeutic activation	Radiation combined with hypoxia-triggered response	Exploits tumor-specific microenvironment	Heterogeneous hypoxia and variable activation
Core-shell nanoplatforms	Multifunctional therapy	Multiple radiation and biological mechanisms	Spatial organization of several therapeutic functions	Complex synthesis and regulatory characterization
Radiosensitizer-chemotherapy systems	Combined chemoradiotherapy	Radiation-enhanced drug activation/release	Synergistic tumor killing	Drug toxicity and formulation complexity
Radiosensitizer-immunotherapy	Radioimmunotherapy	Radiation-induced ICD plus	Potential systemic antitumor	Immune toxicity and

systems		immune modulation	immunity	heterogeneous response
Radiosensitizer–photothermal systems	Multimodal therapy	Radiation photothermal energy conversion +	Combines physical and biological tumor damage	Limited light penetration for deep tumors
Multifunctional theranostic systems	Diagnosis + therapy + monitoring	Radiation activation with imaging and therapeutic functions	Personalized, image-guided treatment potential	High manufacturing and regulatory complexity

BIOLOGICAL MECHANISMS AND THERAPEUTIC APPLICATIONS OF RADIATION-ACTIVATED NANOPLATFORMS

Radiation-activated nanoplateforms are a step away from the traditional radiosensitization paradigm and toward multilevel therapeutic amplification involving nanomaterials and their interaction with radiation and subsequent effects on DNA damage, mitochondrial function, regulated cell death, tumor hypoxia, and antitumor immunity. In addition to radiation deposition, these therapeutic effects are also related to the composition, size, surface chemistry, intracellular localization, penetration into the tumor, radiation properties, and interactions with the tumor microenvironment (TME) of the nanoparticles. Recent developments in radiation nanomedicine have focused on the ability of nanoplateforms to integrate radiation enhancement with drug delivery and immune regulation and other therapeutic strategies ^[4, 12]. A key emerging concept is radiation to immunity: radiation-induced physicochemical changes are sequentially transduced to molecular damage, regulated cell death, subsequent release of immunostimulatory signals, activation of immune cells, and, finally, systemic tumor control. This framework offers a wider understanding of the nanoparticles than that of mere dose enhancers in radiation therapy.

Radiation-Induced DNA Damage

The therapeutic effects of ionizing radiation have been attributed to one of its main biological targets, DNA. Radiation causes DNA damage by direct energy deposition and indirectly via the production of reactive species after the radiolysis of water. Some of the lesions produced are single-strand breaks (SSB), double-strand breaks (DSB), oxidized bases, abasic sites, DNA–protein crosslinks, and complex clustered lesions.

Of these lesions, DSBs are especially relevant, as the improper or partial correction of these lesions can lead to chromosomal changes, genomic instability, mitotic catastrophe, senescence, or cell death. The biological effects are affected by the type of radiation, dose distribution, oxygenation, DNA repair, and cell context ^[4].

There are multiple complementary ways in which radiation-activated nanoplateforms can enhance DNA damage. High-Z materials have the ability to increase local radiation interaction and produce secondary electrons; catalytic and redox-active nanoparticles will increase the amount of DNA oxidation through ROS. Therefore, nanoparticles can enhance the physical and chemical aspects of radiation-induced damage of DNA.

Nanoparticle-Mediated Enhancement of DNA Damage

There has been significant interest in high-Z nanoparticles because of the ability to enhance interactions with incident radiation that can be accomplished with high atomic number elements like gold, hafnium, bismuth, tantalum, tungsten, etc. Some short-range products created during the radiation–nanoparticle interaction, such as secondary and Auger electrons, can enhance the localized energy deposition [4, 12]. But there is no simple correlation between atomic number and radiosensitization efficiency. The therapeutic performance can be significantly influenced by the size of the nanoparticles, their concentration, their aggregation state, their surface functionalization, their intracellular distribution, the radiation energy, and the localization of the tumor. This implies a better design guideline:

The radiosensitization is the material composition times the radiation characteristics times spatial localization times the biological context.

The structure–radiation–localization relationship should be taken into account in the design of next-generation radiosensitizers.

Reactive Oxygen Species and Oxidative Stress

Reactive oxygen species (ROS) are one of the main biochemical mediators of radiation injury to cells. Ionizing radiation can create hydroxyl radicals, superoxide, hydrogen peroxide, etc. When present in high concentrations, they deplete cellular antioxidant defenses and cause damage to DNA, proteins, lipids, and intracellular organelles.

Radiation-enhanced electron transfer, redox cycling and catalytic reactions, and interference with the endogenous antioxidant pathways are possible mechanisms by which nanomaterials can cause this oxidative imbalance. The production of ROS has been highlighted as a crucial mechanism in nanomedicine to address treatment resistance and promote multiple modes of regulated cell death [13].

ROS Amplification as a Radiosensitization Strategy

The ROS-mediated mechanism can be shown as follows:

The steps are radiation, activation of nanoparticles, increased electron/energy transfer, increased production of ROS, decreased availability of antioxidants, biomolecular damage, and cell death.

The catalytic nanomaterials and nanozymes can also produce more ROS by mimicking enzyme reaction. Nanocatalysts and Fenton-like nanocatalysts can produce highly reactive hydroxyl radicals from endogenous hydrogen peroxide, while redox-active nanocatalysts can either consume glutathione or disrupt the antioxidant defense mechanisms.

This approach is especially promising for tumors with elevated basal oxidative stress. The level of ROS generated by cancer cells is frequently near the limit of adaptive capacity, so that a relatively small further increase in ROS can exceed adaptive capacity. ROS can therefore be enhanced using nanoparticles, which can result in a therapeutic difference between malignant and normal cells [12].

But too much systemic ROS production can cause damage to healthy tissues. Hence, it is important to promote tumor-specific activation, stimulus-triggered release, targeted delivery, and proper control over the distribution of nanoparticles in future systems.

Overcoming Tumor Hypoxia

Tumor hypoxia is one of the most important factors leading to radioresistance. Regions of inadequate oxygen availability exist due to poor vascularization, abnormal blood flow, high metabolic rate, and heterogeneous architecture. Oxygen is involved in repairing radiation-induced molecular damage so that hypoxic tumor cells may be greatly less responsive to radiation.

Nanoplatfroms can tackle hypoxia in various ways, such as via generating oxygen, transporting oxygen, catalase-like catalytic activity, vascular modulation, and hypoxia-responsive drug release. The oxygen effect, combined with radiation sensitization, is of special interest because it addresses one of the basic biological restraints of radiotherapy.

The oxygen-generating nanotechnology can generate molecular oxygen using endogenous hydrogen peroxide, and the oxygen-carrying technology can carry oxygen to poorly oxygenated tumor regions. Hydrogen peroxide can also be converted to oxygen and water by catalase-mimetic nanomaterials.

It is important to remember that hypoxia is not a limiting factor. Can also act as a biological activation signal. Hypoxia-responsive nanoplateforms are designed to be relatively inert in normal tissues but change their structure or chemistry in hypoxic tumor areas.

The idea is aligned with the general trend of tumor-responsive nanomedicine that leverages endogenous factors like hypoxia, acidic pH, ROS, enzymes, and reductive conditions to achieve spatially controlled therapeutic activation ^[13, 14].

Mitochondrial Dysfunction and Metabolic Reprogramming

The mitochondria are significant targets within the cells for radiation-activated nanoplateforms, as they control and regulate energy metabolism, redox homeostasis, apoptosis, and cellular stress responses. Too much ROS can lead to changes in mitochondrial membrane potential, affect electron transport, reduce ATP production, induce mitochondrial permeability, and trigger cytochrome-c release.

Mitochondrial targeting can thus help to "double" the radiosensitization of the initial interaction between radiation and nanoparticles. Mitochondria-targeting ligands on nanoplateforms can enhance the amount of ROS-producing or catalytic entities near the mitochondrial membrane.

Subsequent steps in the initiation of the damage to the mitochondria:

- Alteration of the mitochondrial membrane potential; and
- ATP depletion;
- mitochondrial ROS accumulation;
- cytochrome-c release;
- caspase activation;
- metabolic dysfunction; and
- apoptotic or non-apoptotic cell death.

Metabolic reprogramming is another therapeutic target. These are generally observed characteristics of cancer cells, including changes in glucose metabolism, increased production of reactive oxygen species, alterations in iron metabolism, and specific lipid needs. These weaknesses can be effectively harnessed by multifunctional nanoplateforms that can deliver radiation, catalytic, metabolic, and/or redox-based interventions.

Therefore, metabolic radiosensitization, which involves reducing the metabolic resilience of tumor cells prior to or during radiation exposure by the nanoplateform, can be considered as a new class of radiosensitization. Metabolic radiosensitization can thus be envisioned as metabolic weakening of tumor cells either before or during administration of radiation by the nanoplateform.

Ferroptosis and Other Non-Apoptotic Cell-Death Pathways

Apoptosis and mitotic catastrophe have been classically the two mechanisms at play following radiotherapy. However, recent research has shown that radiation-activated nanomedicine can trigger multiple regulated pathways of cell death, such as ferroptosis, autophagy-associated death, necroptosis, and pyroptosis. The cytotoxicity of nanomedicines is strongly related to the composition of nanoparticles, their intracellular location, their ability to produce ROS, and their interaction with cellular metabolic pathways ^[13].

Ferroptosis

Ferroptosis is a regulated cell death process that involves iron-dependent excessive lipid peroxidation leading to disruption of cellular membrane integrity. It is strongly linked to iron availability, glutathione depletion, GPX4 dysfunction, and oxidized polyunsaturated fatty acids.

Radiation can induce oxidative stress and alter cellular redox balance, which can be conducive to ferroptosis. This response can be enhanced by nanomaterials via:

- iron delivery;
- Fenton/Fenton-like catalysis;
- glutathione depletion;
- GPX4 inhibition;
- increased intracellular ROS;
- disturbances of iron metabolism; and
- enhancement of lipid peroxidation.

This pathway is especially relevant for those tumors where the normal apoptotic pathway is impaired. Moreover, the presence of danger-associated molecular patterns (DAMPs) and the shift in the availability of tumor antigens in the context of ferroptosis and other regulated cell death mechanisms can serve as mechanisms for immune activation ^[15, 16].

Autophagy and Necroptosis

The effects of autophagy in radiotherapy are complex. Autophagy is beneficial for the survival of tumor cells in moderate amounts, but it can lead to cell death if there is too much or it is regulated incorrectly. Nanoplatfroms can modulate the autophagy process by modifying the lysosome function, mitochondrial homeostasis, ROS generation, and metabolic activities of the cell.

A second pathway of regulated cell death is the process of necroptosis. It is especially significant in cases of tumors with dysfunctional apoptotic signaling. Nanoplatfroms that are able to modulate both ROS and mitochondrial activity and cell-death signaling may therefore be able to bypass resistance to a single cell-death pathway.

There is a general implication that radiation nanomedicine has the potential to overcome the apoptosis resistance by triggering other pathways of cell death.

Immunogenic Cell Death and Cancer Immunity

One of the most promising new applications of radiation-activatable nanoplatfroms is the capacity to trigger tumor destruction by radiation into an antitumor immune response. Immunogenic cell death (ICD) is the process of cell death that generates innate and adaptive immune system responses, unlike immunologically silent cell death.

- Signals associated with major ICDs are
- Exposure to calreticulin on the surface of the tumor cell;
- extracellular ATP release;
- HMGB1 release;
- inflammatory cytokine and chemokine signaling; and
- Ejection of tumor-associated and tumor-specific antigens.

These signals can lead to the recruitment and maturation of dendritic cells, augment antigen presentation, and activate T cells. Recent studies highlight the increasing significance of nanomaterials for the enhancement of ICD and for the remodeling of the tumor immune microenvironment (TREM) ^[15, 7, 16].

Radiation Nanomedicine for Immunotherapy

Local eradication with radiation-activated nanoplateforms offers a potential opportunity to link local eradication with systemic immunity.

Nanoplateforms can also be used to carry immune checkpoint inhibitors, cytokines, immune agonists, nucleic acids, or other immunomodulators. These components can be selectively released in response to various TME conditions, such as pH, ROS, hypoxia, enzymes, ATP, or others ^[13, 14].

Recent cancer nanomedicine research is thus shifting the focus from the amount of therapeutic material that is delivered to a tumor to specifically targeting immune cells. These strategies aim to modulate the dendritic cells, macrophages, T cells, and other elements of the cancer-immunity cycle ^[17].

Radiation with nanomedicine may, thus, revolutionize radiation treatment from a local cytotoxic therapy to an immune-priming treatment.

Targeted Delivery and Tumor Microenvironment Modulation

The accumulation of nanoparticles in tumors can be influenced by the permeability of the blood vessels, blood flow, interstitial pressure, extracellular-matrix density, particle size, and surface properties, as well as protein corona formation and immune clearance. These factors can result in significant delivery variability of the nanoparticles.

Thus, it cannot be expected to be equally effective in every tumor, simply by passive accumulation. Active targeting is becoming a more common feature in modern nanomedicine, where molecules such as antibodies, peptides, aptamers, receptor-ligands, and tumor-penetrating molecules target specific cell receptors. Increasingly, engineering approaches are targeted towards stromal and immune-cell populations, in addition to cancer cells ^[18].

Tumor-responsive systems are another source of selectivity. These systems can be exploited by:

- acidic tumor pH;
- elevated ROS;
- hypoxia;
- reductive conditions;
- overexpressed enzymes;
- elevated ATP;
- abnormal properties of extracellular matrix; and
- locoregional tumor characteristics.

These properties can cause changes in the characteristics of the nanoparticles, release of the payload, and surface modification or activation. Tumor-responsive nanomaterials could take advantage of the various features of TME to enhance therapeutic selectivity and decrease systemic exposure, as noted by Linderman et al. ^[13].

The tumor microenvironment can also be modified by cancer cells. Cancer cells also have the capacity to modulate the microenvironment.

Radiation-activated nanoplateforms can have the potential to alter multiple components of the TME at once. Cancer-associated fibroblasts (CAFs): Nanoplateforms can decrease the stromal barriers and increase the penetration.

Tumor-associated macrophages (TAMs): Nanomaterials can modulate macrophage polarization and may decrease immunosuppressive signaling.

Extracellular matrix: The matrix-modulating agents can be added to nanoplateforms for better tissue penetration.

Tumor vasculature: Manipulation of the vascular function can enhance delivery of nanoparticles and oxygen.

Improved radiosensitization for oxygen-generating systems in hypoxic regions.

Combination nanoplatfroms can help with checkpoint blockade and activation of T-cells.

This helps the understanding of tumor ecosystem engineering, where the nanoplatfrom is not only used to attack cancer cells but also to change the physical and biological environment around them. Defining strategies for the engineering of interactions between nanoparticles and the tumor, stromal, and immune compartments is particularly important for recent targeted-nanomedicine studies to achieve the desired therapeutic outcomes while minimizing off-target toxicity ^[19].

Association of radio-induced cell death and antitumor immunity

Given that these processes of radiation damage, ferroptosis, ROS amplification, and ICD are all converging, they represent a particularly promising route for next-generation radiation nanomedicine. DNA damage, oxidative stress, cell death, and immunity should not be seen as separate but can be seen as part of one therapeutic cascade.

For example:

High-Z nanoparticles lead to increased interaction with radiation, which leads to secondary electron generation, ROS amplification, DNA and mitochondrial damage, ferroptosis/apoptosis, DAMP release, dendritic-cell activation, and T-cell response.

This dual resistance to both radiation and the immune system is particularly important for tumors that are both radioresistant and immunologically 'cold.' Nanoplatfroms that could enhance the immunogenicity of tumor cells while simultaneously suppressing immune suppression would be able to overcome two therapeutic hurdles.

New research in nanomedicine has increasingly lent support to this convergence of radiotherapy, ICD induction, TME modulation, and immunotherapy ^[7].

Table 2. Biological Mechanisms Underlying Radiation-Activated Nanoplatfrom Efficacy

Mechanism	Nanoplatfrom Contribution	Principal Biological Outcome
Radiation absorption	High-Z Au, Bi, Hf, Ta and W-based materials	Increased local radiation interaction
Secondary-electron generation	High-Z nanoparticles	Localized ionization and enhanced DNA damage
ROS amplification	Redox-active and catalytic nanomaterials	Oxidative damage
Chemodynamic amplification	Fenton/Fenton-like nanoparticles	Hydroxyl-radical generation
Oxygen generation	Catalase-mimetic/O ₂ -generating systems	Hypoxia reduction
Oxygen transport	Oxygen-carrying nanomaterials	Improved tumor oxygenation
DNA damage	High-Z/nuclear-targeted nanoparticles	Increased SSBs and DSBs
DNA-repair interference	Nanocarrier-mediated delivery of repair inhibitors	Reduced DNA repair
Mitochondrial targeting	Organelle-targeted nanoparticles	Mitochondrial dysfunction
Metabolic disruption	Metabolically active nanoplatfroms	Reduced tumor-cell adaptation
Ferroptosis	Iron/redox-active nanomaterials	Lipid peroxidation
Apoptosis	Mitochondrial/ROS-activating systems	Caspase-dependent cell death

Autophagy modulation	Lysosome/metabolism-targeting systems	Altered tumor survival
Necroptosis	Multifunctional nanoplateforms	Alternative regulated cell death
Immunogenic cell death	ROS-generating multifunctional systems	DAMP and antigen release
Dendritic-cell activation	ICD-inducing nanoplateforms	Enhanced antigen presentation
T-cell activation	Nanoplateform + immunotherapy	Increased adaptive antitumor immunity
Drug release	Radiation-responsive carriers	Spatially controlled chemotherapy
Hypoxia-responsive activation	Hypoxia-sensitive nanocarriers	Selective treatment of resistant regions
Tumor targeting	Antibodies, peptides and aptamers	Enhanced tumor localization
CAF modulation	Stromal-targeting nanoplateforms	Improved tumor penetration
TAM modulation	Immune-targeting nanoparticles	Reduced immunosuppression
ECM remodeling	Matrix-responsive nanoplateforms	Improved nanoparticle penetration
Immune checkpoint modulation	Nanoparticle-mediated checkpoint delivery	Enhanced T-cell activity
Multimodal therapy	Core-shell/multifunctional systems	Simultaneous targeting of multiple resistance pathways

Novel Mechanistic Framework: From Radiosensitization to a Radiation-to-Immunity Cascade

The main idea of this review is to not only consider the radiation sensitivity enhancement property of nanoplateforms as a central consideration but also evaluate them based on their other potential properties. Rather, their therapeutic action needs to be evaluated on five interrelated levels of biology:

Level II Medical Physics and Engineering of Medical Devices

The energy deposition, the production of secondary electrons, and the degree of ionization are determined by the interaction of radiation with the nanoparticles.

Level II Redox and Chemical Amplification

The deposited energy turns into ROS, catalytic reactions, redox imbalance, and oxidative stress.

Level III Cellular Damage: The severity of the damage, if any, to the cells.

The DNA, mitochondria, proteins, membranes, iron metabolism, and cellular energetics are damaged.

Regulated Cell Death (RCD) is now at Level IV. RCD is now at Level IV.

Cumulative damage leads to apoptosis, ferroptosis, necroptosis, autophagic cell death, or other regulated cell death pathways.

This relates to level V, immunological amplification.

Immunogenic cell death releases DAMPs and tumor antigens, which activate dendritic cells, T cells, and, if the tumor is systemic, systemic antitumor immunity.

In view of this, the model proposed is

Radiation physics → nanoscale energy conversion → redox amplification → damage to cells → controlled cell death, immunogenic signaling, adaptive immunity, and systemic tumor control.

This enables the identification of radiation-activated nanoplatforms as distinct from the more traditional radiosensitizers, which are passive materials that increase the radiation dose. The idea is closely related to recent advances in tumor-responsive nanomaterials, targeted cancer nanomedicine, ICD-inducing nanoplatforms, and nanomedicine-assisted immunotherapy [13].

PRECISION ONCOLOGY, THERANOSTICS, AND CLINICAL TRANSLATION

Increasingly, radiation-activated nanoplatforms are being incorporated into precision oncology, in which therapy is tailored to the molecular, anatomic, radiobiological, and microenvironmental properties of each tumor. The advanced nanoplatforms can be used as radiosensitizers but can also integrate tumor targeting, radiation enhancement, controlled drug delivery, molecular imaging, and immune modulation into a single therapeutic platform. The convergence opens new avenues for patient-specific radiation nanomedicine, but translation demands a multifaceted approach to considerations of biodistribution, dosimetry, pharmacokinetics, manufacturing, toxicity, and regulatory requirements [4].

Nanoplatforms for Patient-Specific Radiotherapy

The ability of radiation-activated nanoplatforms to be effective relies greatly on the degree to which the nanoparticles can be delivered into and persist in the tumor while reducing exposure to healthy tissues. Tumor heterogeneity is a great challenge because molecular and cellular properties of patient-to-patient tumors, as well as within each tumor, such as vascular permeability, receptor expression, the density of the extracellular matrix, hypoxia, infiltration by immune cells, and accumulation of nanoparticles, can vary significantly from one tumor to another.

To achieve patient-specific nanotherapy, molecular profiling, imaging biomarkers, biodistribution of nanoparticles, radiation dosimetry, and response to treatment are therefore all elements that must be integrated. Targeting can be achieved by using the antibody, peptide, or aptamer, or receptor-specific molecule to aid localization, if appropriate molecular targets are expressed. Targeted delivery is not necessarily the best approach, however, because the formation of protein-corona, receptor heterogeneity, immune clearance, and interpatient variation can affect the behavior of nanoparticles [18].

Thus, for a specific tumor, a future precision framework might choose to include a component with high Z for radiation dose enhancement when the tumor is radiation-resistant, oxygen-generating systems for hypoxic tumors, catalytic nanoparticles for the amplification of ROS in other tumors, and ferroptosis-inducing systems in other tumors that have the appropriate metabolic vulnerabilities.

Image-Guided Radiation Nanomedicine

The integration of imaging in radiation nanomedicine makes nanoparticles capable of acting as a therapeutic agent and a spatial information carrier. MRI-compatible nanomaterials can provide anatomical and functional information, and high-Z nanoparticles have the potential to provide CT contrast. Platforms that are PET and/or SPECT compatible could be used to quantify biodistribution, tumor accumulation, and radiation dose.

This approach enables a “see–treat–monitor” approach for the evaluation of localization of the nanoparticles prior to treatment, delivery of radiation based on the localization information, and subsequent evaluation of therapeutic response. Another analysis has recently highlighted the need for assigning imaging signals to treatment planning and biological response, instead of imaging simply as an ancillary function of diagnosis [4].

Theranostic Nanoplatforms

Theranostic platforms combine diagnosis with therapy into a single platform:

Diagnosis, tumor localization, accumulation of nanoparticles, delivery of radiation, therapeutic activation, and monitoring of the treatment.

The nutrients, targeting ligand, drug payload, and stimulus-responsive element can be combined with the imaging component and radiosensitizing material in a multifunctional nanoparticle. These systems could also help minimize the number of distinct treatment steps and help determine if enough nanoparticles have been collected to irradiate before treatment.

The main difficulty, however, is the need to make multifunctionality more and more without making structures too complex. Adding additional components may add new variables that may impact stability, pharmacokinetics, immunogenicity, manufacturing, and regulatory characterization. Therefore, it is not necessary for an optimal theranostic platform to have the highest number of functions but rather the least number of components necessary to provide a clinically relevant therapeutic benefit.

Combination Strategies

Radiotherapy + Chemotherapy

The synergic delivery of radiosensitizers and chemotherapeutic agents in the same nanocarriers can be achieved by using them, which are activated by radiation, thus enabling the release of drugs locally. This could potentially lead to elevated levels of the drug in the tumor and lower levels in the bloodstream. Stimulus-responsive systems can also be used to further time chemotherapy release based on radiation exposure or tumor-specific conditions.

Radiotherapy + Immunotherapy

Another key translational avenue is the use of radiation in conjunction with immune checkpoint blockade. While radiation can help to release antigens and induce immunogenic cell death, nanoplatforms can provide checkpoint inhibitors or immune agonists to boost immune activation. One of the most appealing applications of nanomaterials is the ability to focus immunomodulatory activity on the tumor microenvironment ^[13].

Radiotherapy + Photothermal/Photodynamic Therapy

The energy conversion nanomaterials can be used to couple radiotherapy with the photothermal and/or the photodynamic effect. In the case of photothermal therapy, the local temperature can be elevated, and in the case of photodynamic mechanisms, ROS can be produced. These mechanisms can be in addition to radiation-induced DNA and oxidative damage when rationally designed.

Radiotherapy + Ferroptosis

Oxidative stress due to radiation can be followed by lipid peroxidation induced by iron, leading to ferroptosis. Nanoplatforms can provide iron and damage the antioxidant system or trigger an increase in ROS production, thus complementing the action of eliminating radiation-resistant tumor cells. These multi-mechanism radiosensitization approaches represent a paradigm shift from single-pathway radiosensitization to multi-pathway resistance suppression.

Preclinical Evidence and Clinical Translation

Although there is a lot of preclinical data, the translation of the radiation-activated nanoplatforms is still challenging. While excellent radiosensitization is observed in in vitro experiments in which only artificial conditions are evaluated, animal models add additional factors such as circulation, protein corona

formation, mononuclear phagocyte-system clearance, tumor penetration, heterogeneous accumulation, and systemic toxicity.

Therefore, translation should be in a sequence:

Material characterization, cellular validation, 3D tumor models, small animal pharmacokinetics, biodistribution, efficacy and toxicity studies, large animal validation (where possible), GMP manufacturing, and clinical investigation.

Special emphasis is needed on clearance of nanoparticles, organ retention, immunological effects, chronic toxicity, and the connection between the administered dose, tumor concentration, radiation dose, and biological response. Zhang et al. ^[8] pointed out that despite the significant efforts in nanomedicine research, there remains a significant gap between fundamental research and clinical translation, and they identified the formulation optimization, manufacturing, quality-by-design, and risk management as key steps required for translation.

In the case of radiation nanomedicine, individualized dosimetry is an important future need since there could be significant differences in the distribution of nanoparticles between patients. New radiotheranostic strategies are increasingly aiming to link localization of nanoparticles with quantitative delivery of radiation and with treatment response ^[4].

Manufacturing and Regulatory Challenges

To achieve clinical translation, the production of nanoparticles must be reproducible, including the size, morphology, composition, surface chemistry, drug loading, radiation sensitivity, and biological behavior. Pharmacokinetics and therapeutic activity can vary significantly from batch to batch.

Another significant hurdle is scale-up since the techniques developed for producing nanoparticles with very uniform properties at the lab level may not be scaled up to the industrial level. Sterilization, storage stability, aggregation, contamination control, and compliance with Good Manufacturing Practice (GMP) requirements, therefore, need to be taken into account during the initial development and not only after preclinical validation.

Manufacturing reproducibility, formulation complexity, quality control, nanotoxicology, and regulatory uncertainty are all recently cited as significant roadblocks to nanomedicine in the clinic. Multifunctional systems can be especially complex to regulate due to the various safety and characterization requirements that each component can bring to the system. Harmonization of characterization and regulatory strategies of nanomedicine is thus more and more crucial at the global level ^[20].

Table 3. Translational Readiness of Radiation-Activated Nanoplatforms

Development Stage	Key Requirement	Major Translational Barrier	Priority Validation
Material discovery	Defined composition and stable nanostructure	Reproducibility	Physicochemical characterization
In vitro studies	Demonstrated radiosensitization	Limited biological complexity	Mechanistic and cytotoxicity studies
3D tumor models	Tumor penetration and spatial activity	Poor prediction of human tumors	Organoid/spheroid validation
Small-animal studies	Tumor suppression and biodistribution	Species-dependent pharmacokinetics	PK, imaging and dosimetry
Large-animal studies	Safety and translational pharmacology	Cost and model availability	Toxicology and biodistribution
Scale-up	Reproducible GMP-compatible production	Batch variability	Quality-by-design
Clinical trials	Demonstrated safety and efficacy	Patient heterogeneity	Biomarker-guided trials

Regulatory approval	Standardized quality and safety profile	Complex characterization	CMC and toxicology documentation
Clinical implementation	Reproducible manufacturing and treatment workflow	Cost, infrastructure and expertise	Standardized clinical protocols

CHALLENGES AND OPPORTUNITIES TODAY AND PROSPECTS FOR THE FUTURE

Although significant progress has been made in the development of radiation-activated nanoplatforms, the translation to precision therapeutic applications in the clinic is still hindered by biological, physicochemical, dosimetric, manufacturing, and regulatory hurdles. The field has now advanced from just proving that nanoparticles improve the effectiveness of radiation to characterizing what type of nanoplatform is best for which patient, at what concentration, with what dose of radiation, and under what biological circumstances. Such a transition demands the incorporation of nanomaterial engineering into quantitative radiobiology, sophisticated imaging techniques, computational models, and clinical trial design [4].

Biological and Translational Challenges

One key challenge is that many nanoplatforms do not have the ability to evenly distribute within solid tumors. Nanoparticles may be limited by abnormal tumor vasculature, increased interstitial pressure, thick extracellular matrix, necrotic areas, and varying blood flow. Thus, in certain regions of the tumor, the amount of nanoparticles is significant, but the distribution of these nanoparticles is not uniform [18].

Proteins also form a protein corona around the nanoparticles after exposure to the physiological fluids, which changes the biological identity of nanoparticles. This is a dynamic interface that is able to affect cellular uptake, immune recognition, circulation time, biodistribution, and clearance. Nanoparticles also can localize in the organs of the mononuclear phagocyte system, raising concerns for off-target exposure and chronic toxicity.

Patient-to-patient variability is another challenge to consider. Therapeutic effects can be vastly different depending on the differences in tumor vascularization, receptor expression, immune status, hypoxia, metabolic state, and nanoparticle clearance. Therefore, future clinical studies would benefit from incorporating patients' stratification based on biomarkers instead of the uniformity of the patient population.

Radiation Dosimetry and Nanoparticle Distribution

One outstanding question is how to incorporate the concentration of nanoparticles, their three-dimensional spatial distribution, radiation dose, and nanoscale energy deposition within a single dosimetric framework. In most traditional radiotherapy dosimetry, radiation deposition is at the macroscopic or voxel level. Biological effects, however, may be related to the distance between the nanoparticles and critical intracellular structures, but secondary electrons with short ranges can be generated by high-Z nanoparticles. Therefore, in the clinical context, the quantity of relevance is not necessarily the macroscopic absorbed dose but rather the amount of energy deposited locally around individual nanoparticles.

Nano-Dosimetry

So, the following should be taken into account when considering the nano-dosimetry:

- Concentration of nanoparticles in the tumor;
- spatial distribution in relation to tumor cells;
- intracellular and extracellular localization;
- type of radiation energy and particles;
- secondary-electron production;
- Auger-electron generation;
- local ROS production;
- the ratio of nanoparticles in tumor to those in normal tissue; and
- heterogeneous radiation exposure.

This makes an important conceptual difference between physical dose enhancement and biological dose enhancement. If the localization of nanoparticles and nanoscale energy deposition into two tumors differs for the same macroscopic radiation dose, different biological responses can be expected.

It is therefore important that future dosimetric models link up with:

The movement of nanoparticles through the body, followed by the interaction with radiation, leads to deposition at the nanoscale, which results in molecular damage and subsequently a biological response. These models have the potential to significantly enhance patient-specific radiation planning and offer a quantitative framework for evaluating the effectiveness of various nanomaterials used to enhance the sensitivity of radiotherapy ^[4, 12].

Artificial Intelligence and Computational Nanomedicine

Artificial Intelligence (AI) offers a new opportunity to deal with the complexity of radiation nanomedicine from multiple perspectives. A number of factors such as particle size, morphology, composition, surface charge, targeting ligands, drug loading, radiation energy, tumor biology, pharmacokinetics, and immunity influence the performance of nanoplatforms. This is a very large number of combinations to explore using the conventional experimental methods.

Thus, AI and machine-learning techniques could be used in:

- biomarker discovery or identification; and
- Size and surface chemistry optimization of particles; and
- forecasting of the accumulation of tumors;
- identification of radiosensitization mechanisms;
- radiation-dose optimization;
- prediction of toxicity;
- molecular-profile-based nanoplatform selection;
- radiomic prediction of treatment response; and
- adaptive treatment planning.

The incorporation of AI with radiomics might be especially potent. Imaging-derived features can describe the tumor heterogeneity, different vascularization, hypoxia-associated patterns, necrosis, and treatment response. Incorporating these data, along with molecular profiles and the properties of the nanoparticles, may enable computational systems to forecast the patient who is most likely to benefit from a given radiation-activated nanoplatform.

Sustainable and Biodegradable Nanoplatforms

Sustainability and lifecycle aspects should be increasingly integrated into the clinical development of radiation nanomedicine. If they are not easily broken down or removed from the environment, they can be a problem, causing environmental and biological issues. The future platforms could therefore consider biodegradable polymers, metabolizable organic materials, physiologically degradable linkers, or predictable clearance materials.

Green synthesis could also help to minimize the environmental impact of the production of nanoparticles. But “green” synthesis is not exclusively biological and using renewable materials. The development of a truly sustainable nanoplatform needs to be examined from the perspective of the whole life cycle, from raw material procurement, energy input in nanoplatform synthesis, purification and sterilization, packaging, clinical application, disposal, and degradation.

With the creation of biodegradable, radiation-responsive materials, this could then offer a compromise between high therapeutic function and lower long-term persistence.

Smart, Self-Regulating Nanoplatfoms

The next generation of radiation-activated nanoplatfoms will be moving towards self-regulating and feedback-controlled systems. Currently available nanoplatfoms typically only react to one stimulus, while tumors have multiple dynamic features.

The following elements might be included in future systems:

- radiation sensing;
- hypoxia sensing;
- ROS sensing;
- pH sensing;
- enzyme recognition;
- controlled drug release;
- feedback-regulated therapeutic activation;
- imaging-based monitoring; and
- adaptive treatment adjustment.

The concept of closed-loop radiation nanomedicine, where the nanoplatform reacts to radiation and cancer conditions, emits a quantifiable signal and gives information that can then be used to direct therapy, is particularly innovative.

Toward Clinical-Grade Radiation-Activated Nanomedicine

Making the transition from proof-of-concept experimentation to standardized development is the first step towards successful clinical translation. The composition, size distribution, morphology, surface chemistry, drug loading, aggregation state, radiation response, degradation, and impurities of nanoparticles need to be carefully controlled.

In fact, manufacturing reproducibility is especially critical, as it was observed that seemingly small differences in nanoparticle characteristics can have an impact on pharmacokinetics and biological activity. In recent years, translational investigations of nanomedicines have highlighted the importance of formulation optimization, scalable production, quality by design, and proper characterization as key to nanomedicine clinical success ^[8].

The future clinical-grade platforms should therefore focus on:

1. standardized physicochemical characterization;
2. reproducible and scalable synthesis;

3. clinically relevant radiation conditions;
4. quantitative pharmacokinetic and biodistribution studies;
5. long-term toxicity assessment;
6. Patient stratification using biomarkers;
7. validated nanoparticle dosimetry;
8. GMP-compatible manufacturing;
9. standardized clinical endpoints; and
10. Harmonized regulatory frameworks.

The regulatory route should also take into consideration the complexity of multifunctional systems. The potential of combining a radiosensitizer, targeting ligand, imaging component, drug, and immunomodulator together might offer better biological performance and also add to characterization and regulatory complexity. Based on this, the principle of functional simplicity and biological sophistication (achieving several therapeutic effects while using as few clinically required components as possible) should be followed during future development.

Emerging Research Opportunities

There are several research directions that can significantly redefine radiation-activated nanomedicine in the next decade.

Patient-Specific Nanodosimetry

If imaging technologies are able to determine the concentration and spatial distribution of nanoparticles within tumors, then radiation dose calculations can be made on an individual basis.

AI-Driven Nanopatform Design

Machine learning could be used to establish correlations among the structure of the nanomaterials, radiation response, biodistribution, toxicity, and therapeutic efficacy, thereby minimizing the need for trial-and-error material optimization.

Adaptive Radiation Nanotherapy

The ability to adjust radiation delivery based on the changing characteristics of the tumor may be achieved by the incorporation of real-time imaging and nanoparticle-mediated radiosensitization.

Immune-Responsive Nanoplatfroms

Future systems may also be used to improve radiation-induced immunogenic cell death and simultaneously deliver immune-modulating agents, which would link the local radiation effects and systemic antitumor immunity ^[13].

Biodegradable and Sustainable Platforms

The material development with the function of the intended therapy and predictable degradation after the function would reduce concerns of persistent accumulation of nanoparticles.

Digital Twins for Radiation Nanomedicine

A novel long-term possibility is to develop patient-specific computational “digital twins” that combine imaging, molecular data, radiation dosimetry, nanoparticle biodistribution, and treatment response. The models could be used to simulate alternative combinations of nanoplatform and radiation prior to clinical administration.

Table 4. Current Challenges and Emerging Solutions in Radiation-Activated Nanomedicine

Challenge	Underlying Problem	Emerging Solution	Expected Impact
Limited tumor penetration	Dense ECM and high interstitial pressure	Tumor-penetrating peptides and ECM-responsive systems	Improved intratumoral distribution
Heterogeneous nanoparticle accumulation	Variable tumor vasculature	Image-guided and biomarker-guided delivery	Improved treatment precision
Hypoxia	Reduced radiation effectiveness	O ₂ -generating and hypoxia-responsive systems	Increased radiosensitivity
Immune clearance	Rapid nanoparticle removal	Surface engineering and biomimetic strategies	Longer circulation
Off-target accumulation	RES uptake and nonspecific distribution	Active targeting and optimized surface chemistry	Reduced toxicity
Long-term persistence	Poor degradation/clearance	Biodegradable nanomaterials	Improved safety
Uncertain nano-dosimetry	Macroscopic dose does not capture nanoscale effects	Multiscale radiation modeling	More accurate treatment planning
Patient heterogeneity	Variable tumor biology	Biomarker-guided nanoplatform selection	Personalized therapy
Manufacturing variability	Batch-to-batch differences	Quality-by-design and GMP production	Reproducible clinical products
Complex regulatory pathway	Multifunctional composition	Standardized characterization and regulatory harmonization	Faster translation
Limited predictive models	Incomplete understanding of nanoparticle behavior	AI and machine learning	Better material selection
Static therapeutic systems	Changing tumor microenvironment	Self-regulating nanoplatforms	Adaptive treatment
Limited sustainability	Persistent materials and resource-intensive synthesis	Green synthesis and biodegradable systems	Reduced environmental burden

CONCLUSION

Radiation-activated nanoplatforms are an innovative strategy in precision oncology that combines advances in nanomaterials science, radiation physics, molecular biology, and immunotherapeutic treatments. While traditional radiotherapy is often constrained by the heterogeneity of the tumor, its

hypoxic nature, and the radiation resistance of surrounding healthy tissues, the engineered nanoplatfroms offer possibilities for spatial and biological control of radiation effects inside the tumor. Radiation-responsive nanoplatfroms can harness the energy of radiation to generate amplified intracellular effects through high-Z element-mediated radiation enhancement, catalytic ROS amplification, oxygen modulation, controlled therapeutic release, and immune activation to overcome major mechanisms of therapeutic resistance in the destruction of tumors.

The ongoing development of this field is a paradigm change from conventional radiosensitizers to multifunctional and intelligent nanotherapeutic systems with the ability to target tumors, enhance radiation, conduct molecular imaging, deliver drugs, and regulate immune responses. These platforms can be used as a scaffolding for the creation of personalized radiation treatments that match the properties of the nanomaterials with specific tumor characteristics, such as oxygen levels, metabolic activity, immune profile, and molecular vulnerabilities. In addition to the radiation-induced cellular damage, these systems' immunogenic signaling further underscores the promise of these systems for providing therapeutic activity beyond the immediate tumor control environment. Although significant progress has been made, there are a number of limitations that are encountered in the clinical translation of nanoparticles, including biological complexity, nanoparticle distribution, tumor penetration, long-term safety, manufacturing reproducibility, and regulatory requirements. Future studies should, however, go beyond proof-of-concept studies and focus on clinically relevant models, standardized evaluation protocols, biodegradable materials, precise nanodosimetry, and detailed pharmacological evaluation. These challenges need to be solved to enable safe and reproducible nanoplatfrom-based radiotherapy strategies. Assembling and applying these technologies in combination AI, computational modelling, molecular diagnostics, advanced imaging, and patient-specific treatment planning will likely be a crucial factor in the success of radiation-activated nanomedicine in the future. These technologies can facilitate rational choices of nanoplatfroms, forecasting therapeutic effects and optimizing radiation response in real time. In summary, future radiation-activated nanoplatfroms should be adaptive, multifunctional, and clinically translatable and integrate nanoscale engineering with tumor biology and personalized oncology. These developments could revolutionize radiotherapy, turning it into a more individualized, intelligent, and precise therapy platform.

REFERENCES

1. Bray, F., Laversanne, M., Sung, H., Ferlay, J., Siegel, R. L., Soerjomataram, I., & Jemal, A. (2024). Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: A Cancer Journal for Clinicians*, 74(3), 229–263. <https://doi.org/10.3322/caac.21834>
2. Shen, H., Huang, H., & Jiang, Z. (2023). Nanoparticle-based radiosensitization strategies for improving radiation therapy. *Frontiers in Pharmacology*, 14, 1145551. <https://doi.org/10.3389/fphar.2023.1145551>
3. He, M., Chen, S., Yu, H., Fan, X., Wu, H., Wang, Y., Wang, H., & Yin, X. (2025). Advances in nanoparticle-based radiotherapy for cancer treatment. *iScience*, 28(1), 111602. <https://doi.org/10.1016/j.isci.2024.111602>
4. Reilly, R. M., Georgiou, C. J., Brown, M. K., & Cai, Z. (2024). Radiation nanomedicines for cancer treatment: A scientific journey and view of the landscape. *EJNMMI Radiopharmacy and Chemistry*, 9, 37. <https://doi.org/10.1186/s41181-024-00266-y>
5. Penninckx, S., Thariat, J., & Mirjolet, C. (2023). Radiation therapy-activated nanoparticle and immunotherapy: The next milestone in oncology? *International Review of Cell and Molecular Biology*, 378, 157–200. <https://doi.org/10.1016/bs.ircmb.2023.03.005>
6. Zhu, Y., et al. (2023). Radiation-induced immunogenic cell death for cancer radioimmunotherapy. *Advanced Therapeutics*.

7. Demuynck, R., Engelen, Y., Skirtach, A. G., De Smedt, S. C., Lentacker, I., & Krysko, D. V. (2024). Nanomedicine to aid immunogenic cell death-based anticancer therapy. *Trends in Cancer*, 10(6), 486–489. <https://doi.org/10.1016/j.trecan.2024.03.003>
8. Zhang, X., Chan, H. W., Shao, Z., Wang, Q., Chow, S., & Chow, S. F. (2025). Navigating translational research in nanomedicine: A strategic guide to formulation and manufacturing. *International Journal of Pharmaceutics*, 671, 125202. <https://doi.org/10.1016/j.ijpharm.2025.125202>
9. Mohammadi, M., et al. (2023). A review of bismuth-based nanoparticles and their applications in radiosensitising and dose enhancement for cancer radiation therapy. *Journal of Radiation Research and Applied Sciences*.
10. Xiao, W., Zhao, L., Sun, Y., Yang, X., & Fu, Q. (2024). Stimuli-responsive nanoradiosensitizers for enhanced cancer radiotherapy. *Small Methods*, 8(1), e2301131. <https://doi.org/10.1002/smt.202301131>
11. Mostafavi, M., Ghazi, F., Mehrabifard, M., Alivirdiloo, V., Hajiabbasi, M., Rahimi, F., et al. (2025). State-of-the-art application of nanoparticles in radiotherapy: A platform for synergistic effects in cancer treatment. *Strahlentherapie und Onkologie*, 201, 577–588. <https://doi.org/10.1007/s00066-024-02301-y>
12. Luobin, L., Wan, H., Guo, Y., Zheng, Q., Liang, Z., Wu, D., et al. (2024). Nanomedicine-induced programmed cell death in cancer therapy: Mechanisms and perspectives. *Cell Death Discovery*, 10, 386. <https://doi.org/10.1038/s41420-024-02121-0>
13. Linderman, S. W., DeRidder, L., Sanjurjo, L., Foote, M. B., Alonso, M. J., Kirtane, A. R., Langer, R., & Traverso, G. (2025). Enhancing immunotherapy with tumour-responsive nanomaterials. *Nature Reviews Clinical Oncology*, 22, 262–282. <https://doi.org/10.1038/s41571-025-01000-6>
14. Huang, et al. (2025). Tumor microenvironment-responsive nanomedicines for potentiating cancer immunotherapy. *Advanced Science*. <https://doi.org/10.1002/advs.202513567>
15. Galluzzi, L., Guilbaud, E., Schmidt, D., Kroemer, G., & Marincola, F. M. (2024). Targeting immunogenic cell stress and death for cancer therapy. *Nature Reviews Drug Discovery*, 23, 445–460. <https://doi.org/10.1038/s41573-024-00920-9>
16. Ma, C., Cheng, Z., Tan, H., et al. (2024). Nanomaterials: Leading immunogenic cell death-based cancer therapies. *Frontiers in Immunology*, 15, 1447817. <https://doi.org/10.3389/fimmu.2024.1447817>
17. Bhatt, J., Jain, S., Gupta, S., & Bhatia, D. D. (2025). Nanomedicine revolutionizing cancer immunotherapy: Recent advancements in nanotechnological strategies and applications. *Nanoscale Advances*, 7, 7086–7108. <https://doi.org/10.1039/D5NA00390C>
18. Gomerding, V. F., Nabar, N., & Hammond, P. T. (2025). Advancing engineering design strategies for targeted cancer nanomedicine. *Nature Reviews Cancer*, 25, 657–683. <https://doi.org/10.1038/s41568-025-00847-2>
19. Sabit, H., Pawlik, T. M., Radwan, F., Abdel-Hakeem, M., Abdel-Ghany, S., Wadan, A.-H. S., Elzawahri, M., et al. (2025). Precision nanomedicine: Navigating the tumor microenvironment for enhanced cancer immunotherapy and targeted drug delivery. *Molecular Cancer*, 24, 160.
20. Ahsan, W., Aggarwal, G., et al. (2025). Regulating nanomedicines: Challenges, opportunities, and the path forward. *Nanomedicine*, 20(15), 1911–1927. <https://doi.org/10.1080/17435889.2025.2533107>