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Exploiting the Oxidative Landscape of the Tumor Microenvironment: ROS-Responsive Nanocarriers as Precision Platforms for Selective Cancer Therapy

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Abstract : Conventional chemotherapy continues to impose systemic toxicity and dose-limiting resistance on cancer patients because free drugs cannot biochemically distinguish malignant cells from healthy tissue. Reactive oxygen species, particularly hydrogen peroxide, accumulate in tumor tissue at concentrations approaching 100 µM orders of magnitude above the 20 nM levels characteristic of normal tissue creating a biochemical selectivity window that ROS-responsive nanocarriers are specifically engineered to exploit. This review examines the scientific foundation and translational trajectory of these platforms, beginning with the molecular biology of ROS generation in the tumor microenvironment, including the roles of mitochondrial electron transport chain dysfunction, oncogene-driven NADPH oxidase upregulation, and the dual pro-tumorigenic and cytotoxic functions of sustained oxidative stress. The principal ROS-responsive chemistries thioether, thioketal, aryl boronate ester, selenium-containing polymers, and polyprodrug architectures are evaluated mechanistically alongside the nanoplatform classes that deploy them, from polymeric nanoparticles and self-assembled micelles to mesoporous silica, metal-organic frameworks, and Fenton-active nanozymes. Hierarchical targeting strategies, multi-modal therapeutic combinations with photodynamic, chemodynamic, and immunotherapy modalities, and preclinical pharmacokinetic evidence are critically assessed. Translation barriers including ROS heterogeneity, manufacturing scalability, and regulatory gaps are addressed alongside emerging directions in multi-stimuli responsive design, artificial intelligence-guided formulation optimization, and theranostic integration. Collectively, the evidence positions ROS-responsive nanomedicine as a scientifically mature platform whose clinical realization depends on disciplined translation rather than further discovery.

***IndexTerms* - chemodynamic therapy, drug delivery systems, nanocarriers, reactive oxygen species, stimuli-responsive drug release, tumor microenvironment**

INTRODUCTION

Despite cancer being one of the most common causes of death in the world, its true impact is far more than just a biomedical problem and reflects the inadequacies of therapeutic systems created to tackle it. Chemotherapy is the mainstay of therapy for most solid tumors and haematological malignancies; it is based on a pharmacological principle that is fundamentally contradictory as the therapies used are designed to destroy rapidly growing cells and therefore will have a profound impact on the bone marrow, gastrointestinal mucosa and other healthy rapidly proliferating tissues [1]. These are the inevitable side effects of drugs which have no molecular "language" to tell the difference between a tumor cell and a normal cell. In addition to acute toxicity, the lasting effect of chemotherapy is also compromised by acquiring multidrug resistance, where cancer cells develop strategies to avoid the death of the cytotoxic drug with the over-expression of efflux transporters, such as P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP), both of which belong to the ATP-binding cassette superfamily [2].

Data available in the literature reveals that P-gp is over-expressed in about 50% of all human cancers and even initially sensitive tumor populations, under selective drug pressure, evolve towards resistant phenotypes, in effect making directed cancer therapy irreversible in failure. When treatment is inadequate in the context of advanced disease, a fact highlighted by statistical analysis, drug resistance is responsible for more than 90% of the cancer deaths [3]. These pharmacological restrictions led to the development of the nanomedicine field. This idea, which was used to create the two drugs mentioned above liposomal doxorubicin (Doxil) and albumin-bound paclitaxel (Abraxane) was that by using a passive tumor accumulation strategy (the enhanced permeability and retention, or EPR effect), researchers could increase the amount of drug available to the tumor while reducing the side effects in the rest of the body [4]. As experience with those platforms grew, however, it was evident that passively collecting is not enough to get the selectivity that precision oncology requires [5].

Most first-generation nanomedicines are still releasing drugs too early in the bloodstream, which reduces their therapeutic index, and, unless the nanocarrier is programmed to recognize a tumor-specific signal, the systemically injected nanocarriers are either inactive when they reach the tumor or release their drugs prematurely in off-target organs [6]. The most intellectually stimulating answer to this limitation is a biological phenomenon that tumors create and maintain as part of their own disease processes: a tumor microenvironment with high levels of reactive oxygen species (ROS) present at all times [7]. Reactive oxygen species (ROS) are metabolic byproducts of all aerobic cells, but are generated mainly at the mitochondrial electron transport chain and by NADPH oxidases at the plasma membrane, and include hydrogen peroxide (H_2O_2), superoxide anion ($O_2^{\bullet-}$), hydroxyl radical ($\bullet OH$), singlet oxygen ($^1O_2$), and hypochlorous acid (HOCl). Tumor microenvironment is defined not by the presence of these species, but by the amount of them accumulated: ROS levels in tumor tissues are as high as 100 µM, whereas levels in normal tissue are near 20 nM [8]. The biochemical contrast, about 5,000-fold between malignant and healthy tissue is unmatched in terms of the sharpness and consistency of the trigger, a property that no receptor-targeting ligand or pH difference can attain. Such an oxidative difference has led to the development of a new family of smart nanocarriers, ROS-responsive nanoplatforms, which capitalize on the chemical environment of the tumor to trigger spatiotemporally controlled drug release [9]. Such systems are designed to be chemically linked or polymer backbone capable of maintaining structure in the physiological ROS levels but undergo oxidative cleavage, phase transition, or degradation with the high concentration of H_2O_2 found in the tumor microenvironment. The therapeutic potential is huge: drug delivery is restricted only to the tumor area, external triggering (light, ultrasound, magnetic fields) is not required, and systemic drug exposure is reduced [10].

This review focuses on the scientific underpinnings and translation potential of ROS responsive nanocarriers as targeted cancer therapeutic platforms. It starts with the molecular biology of ROS in the tumor microenvironment, then it progresses to the chemistry of responsive linkers and the architectural variety of nanoplatforms based on them, and it comes to the targeting at tissue and organelle level and the assessment of the performance of these systems in combination therapeutic modalities and in preclinical tumor models. The last chapters critically address the translational challenges between pre-clinical promise and clinical reality and the future trajectory of the field multi-stimuli responsiveness, AI-directed design, and theranostic integration that will be the hallmarks of the next decade.

2. ROS Biology in the Tumor Microenvironment: The Case for Redox-Triggered Targeting

The oxidative nature of the tumor microenvironment is not a random by-product of the process of malignant transformation, but a carefully orchestrated biochemical condition that is created and required for tumor survival. Knowledge of the molecular organization of this redox environment is critical to understanding the unique and potentially more selective mechanism of tumor-targeted drug delivery that is afforded by ROS-triggered delivery systems in comparison to pH- and enzyme-based delivery systems [11]. In normal cells, the mitochondria are the major source of endogenous ROS, which are produced as byproducts of electron leakage from complexes I and III of the inner mitochondrial membrane from the process of oxidative phosphorylation [12]. The most abundant ROS species in the TME are H_2O_2, which is formed via dismutation of superoxide species by the action of superoxide dismutase enzymes, SOD1 in the intermembrane space and SOD2 in the matrix [13]. The second major source is membrane-associated NADPH oxidase (NOX) enzymes that are abnormally expressed in malignant cells and catalytically reduce molecular oxygen (O2) to produce extracellular superoxide. The NOX family (especially NOX1, NOX2 and NOX4) are functionally associated with oncogenic signaling in various cancers: NOX1 is constitutively active in colorectal and prostate cancers, NOX2 is activated downstream of the K-RAS oncogene in these cancers, and NOX4 is regulated by STAT3 signaling in several carcinomas [14].

In addition to these enzymatic sources, there are also non-enzymatic sources of H_2O_2 flux, such as dysregulation of protein folding in the endoplasmic reticulum and increased catabolism of polyamines through spermine oxidase (SMOX). In total, high production of ROS and inadequate antioxidant enzyme activity, due to the loss of activity of tumor suppressors, including TP53 which regulates the transcription of genes encoding antioxidants, and to the acetylation of SOD2 which makes it pro-oxidant, establishes a chronically oxidized intracellular environment that is not characteristic of normal differentiated tissues. Leading from this is the oncogenic drivers of ROS elevation [14]. Published data also validate that oncogenes, such as K-RAS, c-MYC, BCL-2, and Rac1 each by themselves induce ROS production; K-RAS by modifying mitochondrial metabolism and inducing NOX2 and NOX4, c-MYC by downregulating PGC-1α and reducing mitochondrial volume, and Rac1 by directly activating NOX1 [15]. The combination of these signaling cascades gives rise to a cancer cell that generates ROS at a rate higher than the antioxidant removal ability; this leads to a buildup of H_2O_2 in the cell, which creates the biochemical basis of the activation of nanocarriers. The duality of the role of ROS in tumor biology is an important aspect to be considered, as it is directly related to the therapeutic rationale of delivery systems based on ROS [16].

At moderate, sustained concentrations, ROS initiate mitogen-activated protein kinase (MAPK) pathways which include ERK1/2, JNK, and p38; all of which promote the proliferation, survival, epithelial-to-mesenchymal transition (EMT) and angiogenesis of cancer cells through the activation of PI3K/Akt/mTOR and NF-κB signaling. At these concentrations, ROS also impact the tumor immune microenvironment by inhibiting tumor-killing T cells and promoting immunosuppressive M2 macrophages [17]. Upon reaching the level that cancer cells are able to buffer by upregulating adaptive antioxidants, however, the role of ROS becomes pathological: they trigger cytochrome c release from mitochondria, activate the apoptosis pathways via caspase-9 and caspase-3/7 cascades, activate the pro-apoptotic transcription of BAX and PUMA by p53, and induce ferroptosis by inactivating GPX4 and accumulating lipid peroxides. A threshold-dependent cytotoxicity indicates that the same oxidative condition that promotes the growth of tumors is lethal when oxidative stress is increased a concept which is the basis for both ROS-responsive release systems and ROS-augmenting combination treatments [18].

The targeting aspect for H_2O_2-triggered and pH- or GSH-triggered drug release is that the latter is more selective. The acidic pH gradients of both endosomal compartments of normal cells and tumour extracellular space make pH responsive systems vulnerable to off-target activation. When used alone, disulfide-based systems are not specific enough because the concentration of GSH is high in many cancer cells as well as in healthy hepatic and intestinal tissues [19]. In contrast, published values show that the H_2O_2 level in tumor tissue can be as high as 100 µM, whereas the level in normal tissue is close to 20 nM, providing a selectivity window that is orders of magnitude larger than what is possible with pH or redox potential. This quantitative difference lends a mechanistic rationale to precision nanocarrier design using chemistries that are sensitive to H_2O_2, and also to the architectures of the linkers and polymer platforms that are discussed in the following sections of this review. Table 1 shows comparative information for the key ROS species of interest for the tumor microenvironment, including their identity, major cellular sources, approximate tumor to normal tissue ratios, half life and also therapeutic relevance for nanocarrier activation [20].

Table 1. Comparative overview of key reactive oxygen species in the tumor microenvironment and their relevance to ROS-responsive nanocarrier activation

ROS Species	Chemical Identity	Primary Tumor Source	Tumor Concentration	Normal Tissue Concentration	Half-Life	Nanocarrier Triggering Relevance
Hydrogen peroxide (H_2O_2)	Non-radical oxidant	SOD-catalyzed $O_2^{\bullet -}$ dismutation (mitochondrial ETC); NADPH oxidase	Up to 100 µM	~20 nM	Minutes	Primary trigger for aryl boronate, thioketal, thioether, and peroxalate systems; highest selectivity window for tumor-specific release
Superoxide anion ($O_2^{\bullet -}$)	Free radical	Complex I/III electron leakage; NOX1, NOX2, NOX4	µM range (subcellular)	Low nM	Milliseconds–seconds	Indirect trigger; SOD-dismutated to H_2O_2; precursor to downstream ROS cascade; directly cleaves TK bonds
Hydroxyl radical (•OH)	Free radical	Fenton/Haber-Weiss reaction (Fe^{2+}/Cu^{2+} + H_2O_2); Mn/Cu nanozyme catalysis	Locally generated at metal–H_2O_2 sites	Negligible	Nanoseconds	Not a release trigger; generated therapeutically by Fe, Cu, Mn CDT nanoplatforms for direct cytotoxicity
Singlet oxygen ($^1O_2$)	Excited-state oxygen	Photosensitizer activation (PDT); lipid peroxidation	Exogenously produced during PDT	Not endogenously significant	Microseconds	Drives self-amplified release in PDT–chemotherapy platforms; cleaves vinyl ether and aminoacrylate linkers
Hypochlorous acid (HOCl)	Non-radical oxidant	Myeloperoxidase in tumor-infiltrating neutrophils	Locally elevated at neutrophil-rich sites	Low	Short	Selectively oxidizes thioether bonds at low concentrations; relevant for sulfide-functionalized carrier activation
Peroxynitrite ($ONOO^-$)	Reactive nitrogen species	$O_2^{\bullet -}$ + NO from iNOS-expressing tumor-associated macrophages	Elevated under nitrosative stress	Negligible	Milliseconds	Co-activates boronate ester hydrolysis; exploited in dual ROS/RNS-responsive bimodal nanoplatforms

3. Chemistry of ROS-Responsive Linkers and Polymer Architectures

The specificity of any ROS-triggered drug delivery system is ultimately defined by the chemistry of the ROS-responsive element that is incorporated into the structure of the nanocarrier; its sensitivity threshold, its fidelity in responding to the tumor-specific oxidant, the nature and toxicity of its cleavage products, and the rate at which structural changes lead to the release of the payload. The field now has a well-defined palette of oxidation-responsive chemical functionalities with different mechanistic behavior, and appropriate for different architectures of formulations and payloads [21]. These functionalities can be categorized according to the main action they take during oxidation to either change from hydrophobic to hydrophilic or to break the bond of the conjugated drug or to depolymerize the carrier matrix. Thioether systems take advantage of the oxidation of hydrophobic sulfide groups to hydrophilic sulfoxides and sulfones with H_2O_2 [22].

This conversion leads to the disruption of the amphiphilic balance of the polymer, thereby breakup of the micelle or vesicle and releasing the encapsulated payload. The most studied thioether containing polymer for this use is poly(propylene sulfide) (PPS) and amphiphilic block copolymers of PEG and PPS form micellar or vesicular nanostructures that are stable under physiological conditions but progressively destabilized as thioether oxidation proceeds [23]. The major drawback of the thioether systems is their moderate activation threshold; they work best in high ROS malignancies (e.g., glioblastoma and esophageal squamous cell carcinoma) but may not be fully activated without ROS-enhancing co-formulations in moderate ROS malignancies [24]. Thioketal (TK) linkers are a chemically different type of linkages where the drug or polymer backbone incorporates a 1,3-dithioketone structure that is cleaved by H_2O_2, •OH and $O_2^{\bullet -}$ through an oxidative mechanism in which a proton is abstracted, releasing acetone and two thiol-containing fragments as degradation products, which are metabolized without significant side effects [25]. In contrast to thioethers, the thioketal function undergoes direct chain scission, an unprecedented feature that makes a thioketal-based polyprodrug architecture with covalent incorporation of the drug highly accessible. A well characterized backbone polymer of this class is Poly(1,4-phenyleneacetone dimethylene thioketal) (PPADT); and doxorubicin, camptothecin and paclitaxel have been successfully linked to PEG-based carriers with H_2O_2 concentration-dependent release profiles demonstrated in the 10–100 μM range corresponding to ROS level in tumor tissue [26].

Most significantly, the rate of degradation of the TK bond can be controlled by changing the substituents next to the reactive dithioketone carbon, whereas the rate of degradation of a boronate system is fixed by the geometry of the complex. Among ROS-responsive chemistries, aryl boronic acid and boronate ester linkages provide the highest selectivity specifically towards H_2O_2, with the oxidation of the boron center to the boronic acid and aryl phenol being exclusively nucleophilic attack of H_2O_2 [27]. The reaction kinetics are second-order and concentration-dependent, that is, the rate of boronate hydrolysis is proportional to the H_2O_2 concentration, and thus is intrinsically amplified in high ROS environments. A closely related approach is the aryl oxalate ester (AOE) systems which, via an autocatalytic reaction, generate CO_2 as a harmless byproduct of reaction, and are sensitive to concentrations of ROS as low as 250 nM, making them suitable for early cancer detection and drug delivery in lower ROS microenvironments. These systems have excellent biocompatibility profiles as the phenol and boronic acid products of boronate cleavage are biodegradable. Both the Se–Se diselenide bond and the C–Se selenoether bond are responsive to both oxidative and reductive stimuli, and selenium- and tellurium-containing polymers are in a unique position in the ROS-responsive chemistry landscape because they exhibit dual-responsiveness from a single functional group through oxidation to the selenosulfone form and reduction to the selenoether form by H_2O_2 and GSH, respectively, as well as by thiol-selenide exchange [28].

The responsive micelles of the block copolymers with selenium-containing hydrophobic segments self-assemble in response to oxidative or reductive stimuli, and the bond dissociation energy of Se–Se is lower than that of S–S, which allows the selenium to respond to lower concentrations of oxidants than the S analogue. The polymers containing tellurium, for example PEG-PUTe-PEG, show similar properties: oxidation of the tellurium produces C=Te groups, which disrupts the block copolymer structure, thus releasing the encapsulated payloads. The ideal or the "edict" of ROS-responsive linker chemistry is the polyprodrug architecture. Polyprodrug systems are not loaded with a free molecule in a responding carrier matrix, but rather polymerize the drug molecule directly into the polymer's backbone with ROS-cleavable linkages (usually TK or boronate linkages), yielding theoretical drug loading efficiencies of up to 99% and avoiding phase separation and burst release issues typical of physically loaded systems [29]. These nanoparticles are kinetically stable under normal circulation conditions and the active drug molecule is released from the polymer chain in a one-to-one ratio with the amount of ROS exposure, thus conferring well-predictable dose-response behavior. Self-assembled nanoparticles of polyprodrug amphiphiles have been shown for the anti-cancer agents mitoxantrone, camptothecin, paclitaxel and doxorubicin with near zero premature release under physiological conditions and rapid and complete drug release in the presence of H_2O_2 in concentrations relevant to tumor tissue [30].

Figure 1. ROS-Responsive Linker Chemistry in Nanocarrier Design

4. Nanoplatform Architectures for ROS-Responsive Drug Delivery

All the various types of linker chemistry outlined in the previous section become clinically relevant only when applied to create functional nanocarriers at large scale, systemically distributed, biologically stable in circulation and capable of delivering their payloads with spatial fidelity. Each major nanoplatform class used for ROS-responsive delivery has unique physicochemical characteristics that can affect the loading capacity, ROS responsiveness and drug release characteristics, as well as stealth properties, biodistribution and compatibility with co-therapies that induce ROS. These platforms are well characterized in preclinical models in various types of cancers and type of architecture is still a formulation design decision, as summarized in Table 2. The most popular class of polymeric nanoparticles are those made from PLGA, PEG-b-PPS, poly(thioketal) derivatives and related matrices [31].

PLGA-based ROS-responsive systems have been developed by embedding TK-conjugated drugs in the PLGA matrix to achieve drug release upon exposure to H_2O_2 as well as through PLGA hydrolysis. One major benefit of PLGA-based systems is their FDA regulatory history and the fact that they have been scaled up to receive by two preparation methods: nanoprecipitation or emulsification-solvent evaporation, making the translation process less daunting than it is for more exotic polymer systems [32]. Since the initial work that showed that PEG-b-PPS nanoparticles and polymersome vesicles are disassembled in the presence of H_2O_2, they have been studied extensively and have been shown to be effective for the encapsulation of hydrophobic payloads and hydrophilic payloads in the hydrophobic PPS core and aqueous interior, respectively, with release occurring upon oxidative destabilization of the PPS segment in the presence of H_2O_2 in tumors. By tuning the hydrophilic/hydrophobic mass ratio, multiple nanoarchitectures can be obtained from the same chemical motif, such as nanospheres, polymersomes, and nanocapsules by using amphiphilic block copolymers that contain ROS-sensitive blocks. Another structurally simpler but equally effective platform are self-assembled micelles of amphiphilic block copolymers with TK, boronate ester or selenium-containing hydrophobic blocks [33].

A key benefit of their approach is their ability to use self-assembly as a thermodynamic driving force to achieve a narrow size distribution of nanostructures in the 20–100 nm range, without the need for high-energy emulsification processes, thus minimizing the need for batch-to-batch reproducibility. The rate of the conversion of the hydrophobic core to a hydrophilic counterpart can be tuned with the polymer molecular weight, block ratio and the nature of the linker chemistry, and the resulting micelle disassembly and drug release is very fast once the tumor H_2O_2 is encountered. In addition, micellar systems can be employed to prepare polyprodrug amphiphiles, nanostructures that are self-assembling in water, where the drug-TK-polymer conjugate is itself used to provide the amphiphiles with this property, avoiding the need for a carrier polymer and dictating the drug loading capacity structurally rather than through the processing conditions. ROS-responsive liposomes and lipid-based systems take advantage of the use of thioether phospholipid analogues, mainly thioether phosphatidylcholine (S-PC) derivatives, in bilayer membranes [34].

The hydrophobic S-PC lipids are oxidized to the sulfoxide and sulfone forms, which are more hydrophilic, are less well-packed in the bilayers, and cause permeabilization and corresponding release of the drugs. These systems have the biocompatibility benefits of the liposomal scaffold, including the known safety profile, PEGylation for prolonged circulation and the ability to co-encapsulate both hydrophilic and hydrophobic drugs in the hydrophilic internal compartment and the lipophilic layer, respectively, and the tumor selectivity of the oxidation-triggered release. The lipid-polymer hybrid nanoparticles, which consist of a polymeric ROS-responsive core surrounded by a lipid bilayer shell, have also been investigated as a means to "stealth" biocompatibility of lipid shell and structural stability of polymeric core. The gatekeeper strategy for ROS-responsive drug delivery involves the engineering of MSNs with ROS-cleavable linkers that are covalently bonded to molecular gates such as β-cyclodextrin, PEG chains or lipid caps that are immobilized on the pore openings. In the presence of H_2O_2, a linker is cleaved removing the gatekeeper and allowing the drug to be released in a concentration dependent manner [35].

The high drug loading of small-molecule chemotherapeutics is achieved due to the large surface area and tunable pore size of MSNs (typical range 2–10 nm pore diameters with a BET surface area of 700–1000 m^2/g) and the ability to protect the drug from enzymatic degradation during circulation by the rigid silica matrix. The ROS-responsive nanocarriers functionalized with a TK gatekeeper and co-loaded with DOX and ROS-producing agent (T/D@RSMSNs) showed that simultaneous release of DOX and ROS amplifier resulted in a significantly higher in vitro drug killing efficacy against the MCF-7 breast cancer cells compared to the ROS-responsive nanocarriers loaded with DOX without ROS amplifier [36].

A different type of mechanistically distinct systems involving the carrier material in the therapeutic chemistry is represented by metal-organic-frameworks (MOFs) and inorganic nanozyme platforms. The ZIF-8-based MOF nanoparticles are made of zinc ions and 2-methylimidazole linker, which can be degraded in the tumor microenvironment in mildly acidic and oxidative conditions to achieve pH/ROS dual-responsive drug release. Transition metal based nanozymes containing Fe, Cu, or Mn centers that are able to catalyze the Fenton or Fenton-like reaction ($H_2O_2 \rightarrow$ •OH) have the triple role of being able to carry drugs, to respond to the presence of H_2O_2 in the tumor, and to enhance the local oxidizing flux by producing •OH from H_2O_2. The physicochemical parameters of any ROS-responsive nanoplatform (including both particle size and surface charge neutrality, which are necessary for effective EPR-mediated tumor accumulation, PEGylation density to avoid MPS clearance while still allowing cellular uptake, and hydrophilic to lipophilic balance depending on the payload) must be optimized together with the responsive chemistry because they all contribute to the therapeutic window between the time of tumor accumulation and the time of premature systemic release [37].

Table 2. Comparative summary of ROS-responsive nanoplatform architectures for cancer drug delivery [38–40]

Nanoplatform Class	**Representative System**	**ROS-Responsive Element**	**Drug Payload**	**H_2O_2 Trigger Range**	**Key In Vivo Outcome**	**Primary Limitation**
Polymeric nanoparticles	PEG-b-PPS polymersomes; PPADT NPs; PLGA-TK hybrids	Thioether oxidation (PPS); thioketal backbone scission	Doxorubicin; paclitaxel; dexamethasone	100 μM–1 mM	Significant tumor growth inhibition; improved tumor-to-organ drug ratio in xenograft models	High ROS threshold for PPS disassembly; polymer synthesis batch variability
Polymeric micelles	PEG-poly(Se); PEG-b-PPS;	Se→selenoxide phase transition;	Camptothecin; cisplatin;	10–500 μM (ROS/GSH	Enhanced tumor accumulation;	Colloidal stability during

	TK-CPT prodrug micelles	thioether oxidation; TK scission	doxorubicin	dual-responsive)	significant tumor volume reduction in 4T1 and MCF-7 models	scale-up; critical micelle concentration sensitivity
Liposomes/Lipid hybrids	S-PC thioether bilayer liposomes; lipid-polymer core-shell NPs	S-PC oxidation (→sulfoxide/sulfone); bilayer permeabilization	Doxorubicin; hydrophilic small molecules	~100 µM–1 mM	Improved pharmacokinetics; reduced cardiac drug accumulation vs. free DOX	Incomplete activation at low H_2O_2; risk of premature membrane oxidation
Mesoporous silica NPs	TK-gated MSNs (T/D@RSMSNs); β-CD-TK capped MSNs	TK linker cleavage releasing pore gatekeeper	Doxorubicin; ROS co-producers; gene cargo	50–500 µM	Superior antitumor efficacy vs. single-agent DOX MSNs in MCF-7 breast cancer model	Incomplete in vivo silica degradation characterization; renal clearance concerns
Metal-organic frameworks	ZIF-8 with TK/ROS-cleavable linkers	Acid/ROS-triggered zinc-imidazolate degradation; TK cleavage	ICG; doxorubicin	pH 5.0–6.5 + H_2O_2 >50 µM	>81% cancer cell eradication in CDT/PDT combination models	Metal ion leakage; complex scale-up; unpredictable biodegradation
Inorganic nanozymes	Fe_3O_4, Cu_2O, MnO_2 Fenton-active NPs; $Ru_xCu_{1-x}O_2$ nanodots	Fenton/Fenton-like $H_2O_2 \rightarrow {\bullet}OH$ catalysis; simultaneous CDT + drug release	DOX + Fenton metal pair; camptothecin + Cu	Endogenous TME H_2O_2 (self-amplifying)	Multitherapeutic tumor eradication with minimal systemic toxicity	Heavy-metal toxicity risk; low Fenton efficiency at physiological pH
Polyprodrug nanoparticles	PolyMTO (mitoxantrone-TK backbone); PEG-PCPT micelles	TK backbone scission directly liberating active drug	Mitoxantrone; camptothecin; doxorubicin	Tumor-relevant $H_2O_2/O_2^{\bullet-}$	Near-zero premature release; complete drug liberation within 4–6 h; significant in vivo antitumor efficacy	Multi-step synthesis complexity; strict drug-loading stoichiometry control required

5. Tumor Targeting Strategies: Passive, Active, and Organelle-Level Precision

The difference between drug accumulation and delivering drugs to the tumor cells is a conceptual one that is assuming increasing significance as the field advances. The preceding, such as survival in circulation, release in the tumor vasculature, passage through the tumor stroma, and internalization into the tumor cell, require spatial targeting strategies which need to be developed independently and in a complementary manner to ROS responsive chemistry. To date, the model of how nanocarriers move from the injection site to deliver their contents to the intracellular environment involves three levels of targeting: the passive accumulation at the tissue level by exploiting the enhanced permeability and retention (EPR) effect, the targeting of cells by exploiting the surface ligand–receptor interactions, and subcellular precision by targeting the organelles for organelle-targeted delivery. The EPR effect is the most frequently cited passive targeting mechanism and is based on the fact that tumor neovasculature has structural defects such as wide fenestrations in the endothelial cells, defects in the basement membrane, and poor lymphatic drainage that allow nanoparticles from the size range of 20–200 nm to extravasate and then to become trapped within tumor tissue due to the lack of effective lymphatic drainage. In 1986, the first systematic proof of this principle was given by Matsumura and Maeda, laying the conceptual groundwork for the development of tumor-targeted nanomedicine, which has since been followed by the design of virtually all cancer nanocarrier platforms [41].

The field has, however, come to a more sophisticated, and empirically honest, evaluation of EPR in human oncology. However, there are already a number of pieces of clinical and preclinical evidence showing that the accumulation of nanoparticles in human tumors is much more variable than in subcutaneous mouse xenografts, and varies among different types of tumors, among patient groups, at different stages of disease, and even within different regions of the same tumor. Published data on tumor delivery of nanoparticles by injection has been subjected to meta-analysis and the median percentage of injected dose that is accumulated at the tumor level has been reported to be low. EPR-based accumulation alone has been reported as not enough to reach therapeutic doses at the level of the tumor cells [42]. In pancreatic ductal adenocarcinoma and desmoplastic breast cancer, dense collagenrich stromal barriers generate high interstitial fluid pressure that result in steep diffusion gradients and restrict the diffusion of extravasated nanoparticles to perivascular regions, limiting their penetration depth. To overcome these constraints, active targeting has been suggested to be combined with receptor-mediated, precision targeting of EPR-based accumulation, resulting in a dual targeting approach: nonspecific extravasation plus specific cellular targeting. In particular, hyaluronic acid (HA) has proved to be a very versatile ligand, satisfying the requirements for coating of surfaces to enhance circulation time, but also acting as a targeting agent for CD44, a transmembrane adhesion glycoprotein that is overexpressed in many solid tumors as well as in cancer stem cells such as breast, colorectal and lung cancer [43].

The addition of HA-based endocytosis mechanisms to ROS-responsive payload release is provided by the receptor-ligand interaction at T-cell surface and the HA's natural susceptibility to hyaluronidase, which is abundant in the TME. Folate receptor-mediated targeting is also well known; ovarian, lung, renal and head and neck cancers overexpress folate receptors, and folate-decorated ROS-responsive nanoparticles exhibit significantly improved cellular uptake in comparison with folate-undecorated nanoparticles, especially in the case of RGD peptide-mediated targeting systems [44]. The nanocarriers are functionalized with transferrin to take advantage of the enhanced uptake of iron by metabolically hyperactive cancer cells, while the effect is mediated by the binding of RGD (Arg-Gly-Asp) peptides to the αvβ3 integrins present on the cancer neovasculature and on metastatic cancer cells. Each kind of ligand/receptor pairing creates a receptor-mediated endocytosis pathway, which allows the nanocarrier to be delivered to endosomes/lysosomes and the ROS from the intracellular sources to be exposed to the complimentary receptor, allowing additional responsive activation to take place in these compartments, where the pH is mildly acidic [45].

The most advanced development of targeting the tumor places the drug release at the subcellular level, targeting the organelle that is most likely to produce ROS and most likely to be disrupted by the oxidative amplification of drugs. Cellular ROS production in cancer cells occurs mostly in mitochondria and is under hyperactive oxidative phosphorylation, which gives a higher proton gradient thus causing a higher membrane potential (ΔΨm) in cancer cells as compared to normal cells (−180 to −200 mV). This differential in membrane potential serves as the driving force for the selective localization of triphenylphosphonium (TPP) cations; 100- to 1000-fold higher inside mitochondria than in the cytoplasm [46]. The efficacy of mitochondria-targeted systems to disrupt ROS homeostasis compared to the delivery of PS to the cytoplasm, via TPP-conjugated nanocarriers carrying PS together with chemotherapeutic drug camptothecin (CTX) and activated by TK cleavage, has been demonstrated, because such systems generate supraphysiological ROS levels in the target organ, which drives TK cleavage with high fidelity, whereas the delivery of PS to the cytoplasm does not affect the stress level of ROS. This self-amplifying loop happens when ROS-induced drug release at the mitochondria meets the most vulnerable mitochondria in the body; this is the conceptual "holy grail" of precision delivery in one nanocarrier architecture, in which all three levels of hierarchical targeting are achieved [47].

6. ROS-Responsive Nanocarriers in Combination Therapeutic Modalities

One of the most important conceptual advances has been the development of ROS-responsive nanocarriers that are multi-modal therapeutic systems. This was accomplished through a mechanism of great elegance: if a nanocarrier is designed to respond to ROS to release the drug, then if some therapeutic approaches release endogenous ROS at the tumor, then the responsivity to ROS and the therapeutic efficacy become one and the same where the same ROS that is produced to release the drug also is produced in large enough quantities to kill the tumor [48]. This self-amplifying, mutually reinforcing logic drives the rationale for pairing ROS-responsive systems with photodynamic therapy (PDT), chemodynamic therapy (CDT), sonodynamic therapy (SDT) and immunotherapy. The combination of ROS-responsive drug delivery and PDT is the best characterized among the many possible combinations. In PDT, the light of an appropriate wavelength is directed to the photosensitizers, such as chlorin e6 (Ce6), zinc phthalocyanine (ZnPc), and pheophoride A, which upon illumination with light of the proper wavelength, transfer excited-state energy to molecular oxygen, producing singlet oxygen ($^1O_2$) and other ROS that oxidize cellular membranes, impair mitochondrial function, and induce apoptosis or necrosis [49].

If the chemotherapeutic payload is co-encapsulated in the nanocarrier with a photosensitizer, then ROS generated during PDT acts as a two in one mechanism of action, delivering both killing of the tumor cells and simultaneous cutting of the TK linker, thereby releasing the chemotherapeutic payload. A polymer-lipid hybrid nanocarrier system (TKHNP-C/D) co-encapsulating Ce6 and doxorubicin in the poly(thioketal phosphoester) hydrophobic core was found to be able to achieve significantly higher tumor growth inhibition in vivo when administered upon 660 nm laser irradiation, due to the ability of Ce6-generated ROS to self-accelerate the drug release from the nanocarrier system through cleavage of the TK groups. Further, there is the development of natural polysaccharide based amphiphilic carriers incorporating hyaluronic acid and diselenide bonds that would simultaneously address PDT hypoxicity and ROS triggered release of the amphiphiles, where the diselenide bond would react with the oxidative environment of PDT, in addition to the reductive GSH present intracellularly, without the need for any additional structural complexity beyond a single chalcogen function [50]. Chemodynamic therapy offers a mechanistically complementary method for generating ROS that does not require light, allowing it to be used on deep-seated tumors that cannot be excited by light. The principle of CDT is based on the Fenton or Fenton-like reaction, which occurs in the tumor environment where transition metal ions such as Fe^{2+}, Cu^+ and Mn^{2+} catalyze the formation of •OH the most cytotoxic ROS species from endogenous H_2O_2. The great merit of the integration of CDT chemistry in the ROS-responsive nanocarriers is the establishment of a self-supplying loop: the Fe/Cu/Mn catalytic center would generate •OH from the H_2O_2 present in the tumor environment, the •OH would increase the local concentration of ROS, this would break the responsive linker, releasing the CDT agent, and the released CDT agent, such as doxorubicin, would generate H_2O_2 by redox cycling, thus providing a new substrate for the Fenton catalytic reaction. CDT has been shown to trigger immunogenic cell death (ICD) through ROS-mediated induction of ER stress that leads to the surface exposure of calreticulin (CRT), active secretion of ATP and passive release of high-mobility group box protein 1 (HMGB1), which constitute the DAMP signature that initiates activation of dendritic cells, their maturation and subsequent priming of antigen-specific $CD8^+$ T cells. The generation of ICD in the presence of the copper-COF nanoplatform (Cu@COF-TATB) in combination with anti-PD-1 checkpoint blockade resulted in a potent infiltration of $CD3^+$ and $CD8^+$ T-cells, well beyond what was achieved by PDT or CDT alone, and in the suppression of both primary and abscopal tumor growth in preclinical models [51].

The most clinically translatable of the combination therapies, which amplify ROS, is sonodynamic therapy, which is the use of ultrasound without depth limitation and without the need for a photosensitizer to be photo excited. The 1O2 and other ROS generated through activation of the sonosensitizers such as protoporphyrin IX (PpIX) or chlorin e6 by sonoluminescence energy transfer have been shown to cleave the responsive linker for drug release and to directly kill hypoxic tumor cells that cannot be reached by light, when these two components are co-loaded onto nanocarriers. The current cutting edge of the combination therapy scene includes ROS-responsive nanocarriers that co-deliver chemotherapeutics and immunomodulatory agents, such as Toll-like receptor agonists or IDO inhibitors, or TGF-β siRNA (siTGF-β)). At the same time, these systems release a cytotoxic agent that promotes ICD as well as an immunomodulator that rescues T cells from checkpoint-mediated exhaustion, transforming the so-called "cold" tumor defined by poor T-cell infiltration and active immune suppression into a "hot" tumor that can elicit systemic, long-lasting antitumor immunity. The current upper limit of the therapeutic ambition of this field is the combination of ROS-responsive delivery, ICD induction, and immunomodulatory co-payload, which places ROS-responsive nanomedicine at the crossroads of drug delivery science and cancer immunotherapy [52].

7. Preclinical Performance and Translational Evidence

There is a significant body of preclinical evidence supporting the scientific basis of ROS-responsiveness for nanocarriers, by any quantitative measure. In vivo studies have demonstrated that ROS-responsive systems, compared to their non-responsive counterpart, are more effective in cancer types and different nanocarrier architectures in terms of drug accumulation in tumor, pharmacokinetics and different antitumor efficacy parameters. The efficacy of such improved outcomes in the subcutaneous xenografts models can be reliably translated to the mechanistic logic that is, the activity of the nanocarriers is enhanced during circulation to the tumour and, therefore, the extent of accumulation and the magnitude of the effects on tumour growth are meaningful when compared to free drug and non-responsive nanocarriers [53]. To achieve pharmacokinetic separation between circulation stability and the tumor activated release of the drug at the formulation level, the drug release of the TK-linked camptothecin prodrug nanoparticles has been found to be near zero under physiological conditions (0 μM H_2O_2) and 63–80% after 72 hours under tumor tissue conditions (10–25 μM H_2O_2). In all published reports, PEGylated ROS-responsive polymeric nanoparticles have led to 2- to 4-fold longer plasma half-life than the free drug, corresponding to a longer circulation time and higher total exposure of tumors. For the responsive nanocarrier groups, the ratio of accumulation in tumour versus liver is lower than that of non-responsive nanocarriers with the same responsive property, as the initial accumulation of non-disassembled nanocarriers into the liver is limited by the ROS selective and PEG stealth properties. The NBTXR3 hafnium oxide nanoparticle (product of Nanobiotix) is one of the few nanomedicine candidates based on ROS that has advanced to clinical trials, and has been approved for clinical use in Europe as a radiotherapy enhancing agent and has shown activity in soft tissue sarcoma [54].

This is not a drug, but a radio inorganic sensitiser molecule and it highlights the fact that nanoplatforms that can make use of ROS can be well regulated when the mechanism is well understood and the manufacturing process is controlled. Although the enormous amount of preclinical literature, there is no ROS-responsive polymeric nanocarrier, with a cleavable linker mechanism, is in the phase III clinical evaluation yet, which means the translation gap between the preclinical studies and the clinical evaluation needs to be bridged by literature. The biological model is one of the major factors underlying this distinction. Indeed, subcutaneous xenograft tumors in immunocompromised mice are the predominant model system for nanomedicine preclinical research, and are far more uniform in space and have much stronger EPR characteristics than human solid tumors. The structure of tumor vascular density, permeability and stromal composition in subcutaneous xenografts differ dramatically from human primary cancers, especially highly desmoplastic cancers like pancreatic and breast cancer, in which collagen networks and interstitial fluid pressure actively prevent the infiltration of nanoparticles. Furthermore, the phagocytic kinetics of the immune system of mice differs from that of humans, and even in the case of xenografts, and even when body weight is taken into account, there are uncertainty factors in the dose transfer. Recently, patient derived xenograft (PDX) models and three dimensional (3D) organoid cultures are regarded as more predictive preclinical models and preliminary studies indicate that the passive accumulation of nanocarriers in PDX is significantly decreased compared to conventional cell-line xenografts, indicating that nanocarriers should be more actively targeted to overcome this low passive accumulation baseline in human-relevant tumor architecture [55].

8. Challenges, Limitations, and Barriers to Clinical Translation

While the preclinical potential of nanocarriers responsive to ROS is both real and well-established, there are a number of scientific, regulatory, and biological challenges that are interwoven that must be addressed to bring such nanocarriers to the clinic. While each challenge separately is not insurmountable with enough research effort, it is the combination of these challenges in the context of complex multicomponent nanomedicines that is causing the translational bottleneck that is currently facing the field. The basic biological questions are concerned with ROS heterogeneity, which is the non-uniform distribution of H_2O_2 and •OH within and between tumors at the spatial and temporal scales. Published data have shown that the ROS concentration in tumor tissues can increase to 100 μM, but this is an average for heterogeneous tissue with different parts in varying states of hypoxia and hyperoxia, and the efficiency of Fenton catalysis can be further reduced in hypoxic necrotic cores where oxygen levels are already low. Thioether-type carriers are especially susceptible to incomplete activation in regions of moderate ROS in tumor cells, with a portion of the drug payload remaining intact. Moreover, cancer cells often respond to therapeutic oxidative stress by up-regulating antioxidant mechanisms such as increase in glutathione synthesis through NRF2, and GPX4 expression, further diminishing the amount of ROS in cancer cells and diminishing the effectiveness of repeated treatment [56].

The therapeutic implication is that if the tumor is high-ROS at the onset of treatment, the tumor may have become lower-ROS after the treatment, when the nanocarrier is introduced. Barrier number two is the manufacturing and scale up. The most promising polymer architectures for responsive drug delivery in preclinical models polyprodrug nanoparticles with stoichiometrically defined drug-TK conjugates, diselenide-containing block copolymers, and hafnium oxide nanodots – are produced by multi-step chemical synthesis in which the drug-to-polymer ratio has to be tightly controlled and the synthesis is not easily scalable. The molecular weight, polydispersity index, drug conjugation efficiency, and size distribution of nanoparticles created from different batches will result in variability in drug loading, release rate, and in vivo responses, which are not addressed by the current Good Manufacturing Practice (GMP) frameworks for stimuli-responsive materials. The manufacturing also has a high cost compared to conventional chemotherapeutics, because clinically relevant amounts of these materials need to be made [57]. A third systemic barrier is regulatory and characterization gaps. There is no validated standard method available to quantify the concentration threshold of H_2O_2 that triggers activation of nanocarriers in human tumor tissue and no consensus has been reached on how to define and measure the release-trigger specificty to be submitted to regulatory bodies. In vitro models of drug release based on hydrogen peroxide concentration of 100–1000 μM are analytically convenient but may not be representative of the spatiotemporal ROS exposure that occurs in human tumor tissue during a treatment cycle. Regulatory agencies have no predictive tools to evaluate the clinical pharmacology of formulation data alone, because there are no clinically validated in vitro–in vivo correlation (IVIVC) models for ROS-responsive systems. Adding to this, the concerns with nanotoxicology regarding the inorganic responsive components include the possibilities of liver, spleen, or other organ accumulation with repeated doses suggesting selenium, tellurium, manganese, and iron containing nanostructures may accumulate with time in humans; however, their long-term clearance profiles are not fully characterized. The long-term metabolic fate of the high molecular weight polymer degradation products containing chalcogen in humans is yet to be determined, and PEGylation has been shown to retard clearance in animal models. In addition, anti-PEG antibodies have been reported in a subset of patients who have received PEGylated therapeutics, and have been linked to rapid clearance from the blood and hypersensitivity reactions with repeat administration, which is important for any ROS-responsive PEG-based carrier, which may need multiple doses [57].

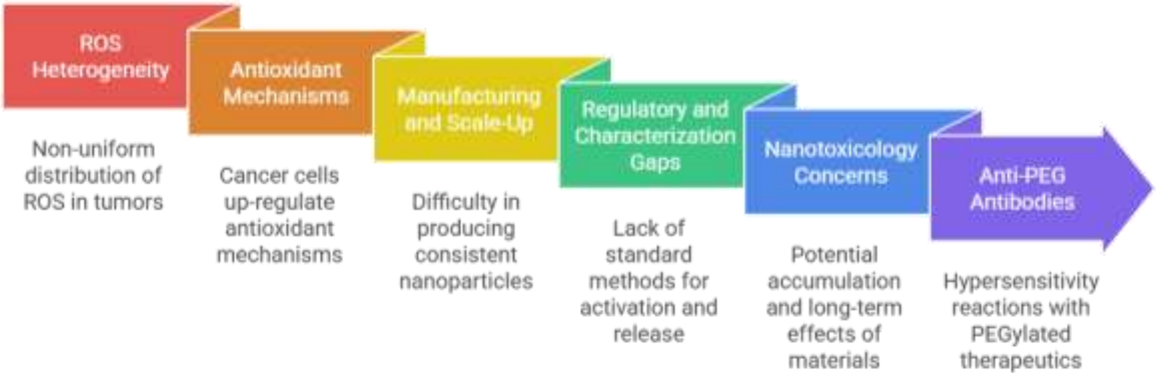

Figure 2: Challenges in Clinical Translation of ROS-Responsive Nsanocarriers

9. Future Perspectives and Conclusion

The future of ROS-responsive nanomedicine seems to be heading to platforms much more complex than the one-stimulus systems that have been used so far. It is expected in the coming decade that three converging directions will emerge and develop in this field. The first is multi-stimuli responsive design, where nanocarriers are required to release the payload only when they are also exposed to high levels of H_2O_2 and acidic pH and the presence of over-expressed enzymes like MMP-2. The fact that several tumor-specific signals occur in succession is more selective than any individual signal, resulting in low levels of premature systemic release, when the activation is done via a combination of pH-induced structural priming followed by ROS-induced bond cleavage. The introduction of ROS amplification agents like glucose oxidase, β-lapachone, or palmitoyl ascorbate as co-encapsulates further tackles the ROS heterogeneity by providing extra endogenous H_2O_2 levels inside tumor [58].

The second is the optimization of the formulation under the guidance of artificial intelligence. For the high-dimensional design space of polymer molecular weight, block ratio, linker density, PEGylation degree, and particle size, the experimental approach is not feasible. Machine learning models learned from current in vivo efficacy and pharmacokinetic data can uncover non-intuitive design principles for the generation of optimized formulations, with the molecular dynamics model of oxidative polymer cleavage and Monte Carlo model of intratumoral nanoparticle diffusion supporting nanoparticle design for tumor types where ROS profiles have been established. The third direction is theranostic integration a nanocarrier containing a fluorescent or photoacoustic probe which can provide real-time reporting of ROS-triggered drug release, creating the evidence-based platform for tumor oxidative profile patient stratification. In the pre-clinical models, the introduction of TK linked payloads to the Mn-based MRI contrast agents has already shown that MRI signal change can spatially map the activation of the carrier in the tumor tissue. Treatment with these agents is not a metabolic side effect, but a metabolically exploitable biochemical property of the tumour. The chemical backbone is developed, the preclinic is strong, the only thing left is the transition. Whether the clinical promise of two decades of ROS responsive nanomedicine will be fulfilled will depend on the field that emphasizes standardized ROS-trigger assays, patient-derived tumor models and patient selection based on oxidative biomarker [59].

10. Conclusion

The review of the body of evidence presented here makes one thing very clear, there is a very good and compelling biochemical solution to the therapeutic selectivity issue in oncology in the oxidative landscape of the tumor microenvironment. The difference in hydrogen peroxide levels between malignant and normal tissue is about five thousand-fold, which is sufficient to enable spatiotemporally controlled drug liberation with selectivity not provided by any physiological pH gradient or GSH elevation. The chemistry needed to convert this signal to payload release is now of multiple functional classes, ranging from thioketal scission to boronate ester hydrolysis to selenium-phase transition to polyprodrug depolymerization and is consistently shown to be more effective at inducing antitumor activity than active targeting and combination modality alone in pre-clinical studies. The clinical record, on the other hand, shows that this scientific maturity has yet to be translated into benefits for patients. The reasons are explicable: EPR-mediated accumulation is not uniform in human tumors, there is variation of ROS levels within individual tumors, and a validated biomarker framework for patient stratification by oxidative tumor profile does not exist. This science, which has earned the promise of a deep impact on the clinical landscape for 20 years, will be fulfilled by the field that designs nanocarriers to respond to the actual biochemistry of the patient's tumor and not an idealized version of it that exists in the mouse.

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