Smart Biomaterials for Targeted Cancer Therapy

Anisha Parida and Ansheed Raheem

Centre for Biomaterials, Cellular and Molecular Theranostics (CBCMT), Vellore Institute of Technology, Vellore, India

Correspondence to: Ansheed Raheem, ansheed@gmail.com

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ABSTRACT

Cancer is one of the most formidable challenges in medicine, often constrained by the limitations of conventional treatments like chemotherapy and radiotherapy, which may induce severe side effects and lead to drug resistance. The emergence of smart biomaterials offers a revolutionary approach to targeted cancer therapy through precise drug delivery, minimizing systemic toxicity, and enhancing therapeutic outcomes. These biomaterials are engineered to respond to specific internal stimuli such as pH, temperature, or enzymes, and external triggers like light or magnetism provide unparalleled versatility in addressing the complex tumor microenvironment. Recent innovations encompass stimuli-responsive hydrogels, nanoparticle-based systems, and oxygen-releasing scaffolds, which overcome barriers such as tumor hypoxia and multidrug resistance. Nanogels, metal-organic frameworks, and biomolecule-functionalized materials exemplify the potential for multifunctional platforms that combine diagnosis and therapy. Moreover, innovations such as DNA-based nanorobots and AI (artificial intelligence)-driven biomaterial design facilitate highly personalized and adaptive treatments. Despite significant advancements in the past decades, challenges persist in translating these materials from laboratory research to clinical application due to biocompatibility, scalability, and regulatory constraints. This review explores the state-of-the-art advancements in smart biomaterials for cancer treatment, their mechanisms of action, and the potential to transform oncology.

Keywords: Cancer treatment, Smart biomaterials, Targeted drug delivery, Stimuli-responsive biomaterials

Introduction

Cancer remains one of the most intricate and devastating diseases despite decades of advancements in medical science. Traditional treatment modalities such as chemotherapy, radiotherapy, and surgery are often associated with significant limitations, including severe side effects, drug resistance, and logistical challenges. These limitations emphasize the need for novel solutions to improve therapeutic specificity and efficacy.[1,2] Targeted drug release has been anticipated for decades to improve therapeutic efficacy. Targeted therapy is crucial in cancer treatment because it focuses on specific molecular changes that propel cancer growth and progression. Unlike traditional chemotherapy, which affects both cancerous and healthy rapidly dividing cells, targeted therapy aims to interfere directly with cancer cell mechanisms, thereby minimizing damage to normal cells.[3]

These therapies focus on specific molecules that promote cancer growth, sparing healthy cells from harm. This focused strategy sharply contrasts with the wide-reaching effects of traditional chemotherapy, which can impact both cancerous and healthy cells alike. This accuracy diminishes side effects and enhances patients' quality of life, allowing them to endure treatment comfortably.[4] One of the most promising aspects of this approach is its tailored design, consistent with the genetic profile of a patient's tumor. This customization significantly improves the likelihood of treatment success, addressing the diverse nature of cancer across individuals.[5] Furthermore, targeted therapies showed potential in overcoming resistance, offering hope to patients whose cancers have become unresponsive to standard treatments.[6] The versatility of targeted treatment is further evident by its ability to complement other therapies, such as immunotherapy, creating powerful combination regimens. This integrative potential boosts overall efficacy, opening new opportunities in cancer care.[7]

Biomaterials represent a paradigm shift in addressing these challenges. Smart biomaterials have revolutionized targeted cancer therapy by facilitating precise drug delivery and improving therapeutic outcomes while minimizing side effects. These materials, engineered to respond to internal stimuli such as pH, enzymes, or hypoxia or external triggers like temperature and light, offer dynamic solutions to address the limitations of conventional therapies.[8–10] An important application is addressing tumor hypoxia, a condition often found in solid tumors with low oxygen levels, which render treatments like chemotherapy and radiotherapy less effective. Biomaterials that facilitate oxygen generation or delivery, such as calcium peroxide or hydrogen peroxide-based systems, offer sustained oxygen release, thereby enhancing treatment response.[8]

Furthermore, nanoparticle-based systems facilitate targeted drug delivery via surface functionalization with tumor-specific ligands, such as antibodies or peptides, improving drug bioavailability and reducing systemic toxicity.[9] Moreover, smart materials integrated into drug delivery systems are tailored to the tumor microenvironment. For instance, pH-sensitive polymers selectively release drugs in the acidic tumor milieu, ensuring localized therapeutic action while sparing healthy tissues.[10] Other advancements, like dendrimers and liposomes, enhance precision by offering multifunctional platforms for simultaneous diagnosis and therapy.[11] These innovations address critical challenges in oncology and facilitate personalized medicine, offering patients targeted, efficient, and safer treatment options.

This review highlights recent advancements in smart biomaterials for targeted cancer therapy, focusing on their design principles, therapeutic mechanisms, and potential to transform cancer treatment by offering specificity, efficacy, and reduced side effects.

Smart biomaterials are set to redefine cancer therapy and improve patient outcomes by addressing these critical gaps.

Fundamentals of Smart Biomaterials

Smart biomaterial is largely associated with regulating responses based on external factors, such as the mechanics of its interaction with the microenvironment inside the body or triggers from an external stimulus.[12] Advancements in smart biomaterials emphasize improving adaptability, allowing them to sense, process, and adjust their responses without external control. A major engineering challenge in determining the smartness of a biomaterial is the predictability of its response, which aids researchers in engineering precise outcomes.[13] This responsiveness allows smart biomaterials to execute specific functions, such as releasing therapeutic agents at targeted sites or altering their physical properties in response to physiological conditions. Figure 1 illustrates the varying degrees of biomaterial smartness that have been engineered to date. The integration of these responsive features distinguishes smart biomaterials from their conventional counterparts.

Salient Features for Smart Biomaterials

One of the key features of smart biomaterials is their stimuli-responsive behavior, which allows them to undergo physical or chemical transformations in response to external stimuli such as pH, temperature, light, magnetic fields, or redox conditions. This responsiveness is crucial in applications requiring precise control over material behavior, particularly in the biomedical field.[14] Ting et al. developed a pullulan-polydopamine hydrogel that facilitates pH-responsive drug release, attaining 87% at pH 5.0 due to polydopamine protonation, offering targeted cancer therapy with reduced impact on healthy tissues. Biocompatibility is a crucial factor in developing these materials, defined as the capacity to interact with biological systems without triggering adverse reactions or immune responses. Li et al. comprehensively discussed zwitterionic hydrogels, encompassing both anionic and cationic groups. These hydrogels are remarkable for their sensitivity to ions and temperature, their water-loving nature, and, most importantly, their excellent compatibility with biological systems. These attributes render them ideal for biomedical applications such as drug delivery and tissue engineering.[15] Zwitterions also possess immunomodulatory properties, preventing the formation of foreign body encapsulation. These features enable the materials to interact with the immune system in a controlled manner, avoiding unnecessary activation while supporting therapeutic goals.[16] The most transformative characteristic of smart biomaterials is their high specificity, which allows them to target specific cells or tissues, significantly enhancing the efficacy of applications such as targeted drug delivery.[17] A 2022 study found that RGD-functionalized VitroGel® hydrogels, particularly at a 1:2 concentration, effectively promoted chondrogenic differentiation of human adipose mesenchymal stromal cells, enhancing cartilage tissue engineering applications.[18] Moreover, these materials minimize systemic side effects and improve treatment outcomes by directing therapeutic agents to the desired location.

Types of Smart Biomaterials

Stimuli-responsive smart biomaterials are designed to modify their physical or chemical properties in response to specific triggers, such as variations in pH or temperature within the body or external cues like light or

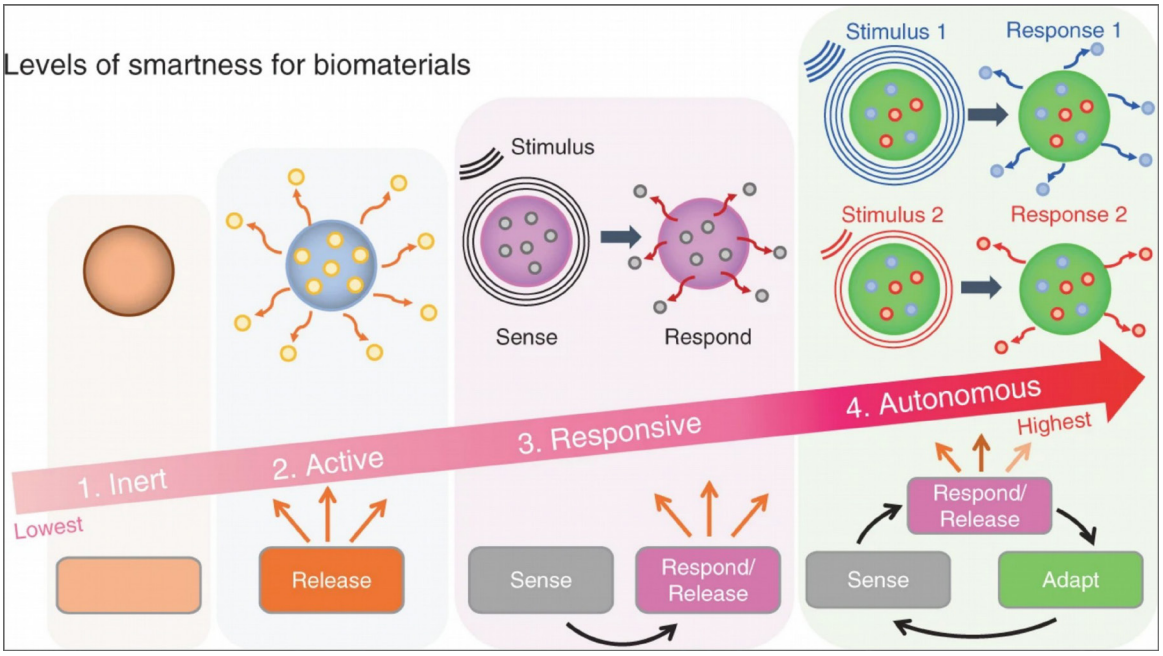

Fig 1 | Various levels of biomaterial smartness. Reproduced from Montoya, C., Du, Y., Gianforcaro, A.L. et al., On the road to smart biomaterials for bone research: definitions, concepts, advances, and outlook, Bone Res 9, 12 (2021), under the terms of a Creative Commons (CC BY) license

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magnetic fields. Their adaptability makes them exceptional for biomedical applications, encompassing targeted drug delivery, tissue engineering, and diagnostics.[19]

The pH-responsive biomaterials are extensively researched biomaterials engineered to alter their behavior in response to the acidity or alkalinity of their surroundings. This functionality significantly impacts drug delivery systems, as different tissues and pathological conditions, such as tumors or inflamed regions, exhibit distinct pH environments.[19] Hu et al. developed a pH-responsive hydrogel combining tobramycin and an ornidazole-conjugated dendrimer to target aerobic and anaerobic pathogens. This hydrogel is injectable, self-healing, and biocompatible, with acid-triggered antibiotic release. It demonstrated potent antibacterial activity against mixed bacterial infections, offering a promising approach for treating complex wounds and infections.[20]

Temperature-responsive biomaterials are designed to undergo predictable physical or chemical transitions when exposed to temperature changes. Their applications are particularly relevant in controlled drug delivery and tissue engineering, where variations in physiological temperature can stimulate therapeutic actions.[21] Parvaneh et al. developed nanocomposite hydrogels combining gelatin and poly(*N*–isopropylacrylamide) (PNIPAM) for advanced drug delivery applications. The drug-loaded PNIPAM nanoparticles synthesized via the photopolymerization technique were incorporated into the gelatin matrix, yielding a hybrid material with enhanced properties. This hydrogel composition demonstrated antibacterial activity and controlled drug release, especially at a lower PNIPAM-to-gelatin ratio, ensuring uniform and delayed drug delivery.[22]

Light-responsive biomaterials use light as a non-invasive, precisely controllable stimulus to modulate their properties. The ability to spatially and temporally control material behavior makes them appropriate for applications such as phototherapy and on-demand drug delivery. In this regard, Varun et al. used poly(heptazine imide) (PHI) carbon nitride microparticles as light-driven microswimmers capable of propulsion in various ionic and biological media. These microswimmers demonstrated high-speed movement without dedicated fuels, overcoming the limitations of previous light-driven microswimmers. The nanoporous structure of PHI facilitated the efficient loading of therapeutic agents, such as the cancer drug doxorubicin (DOX), with a high loading

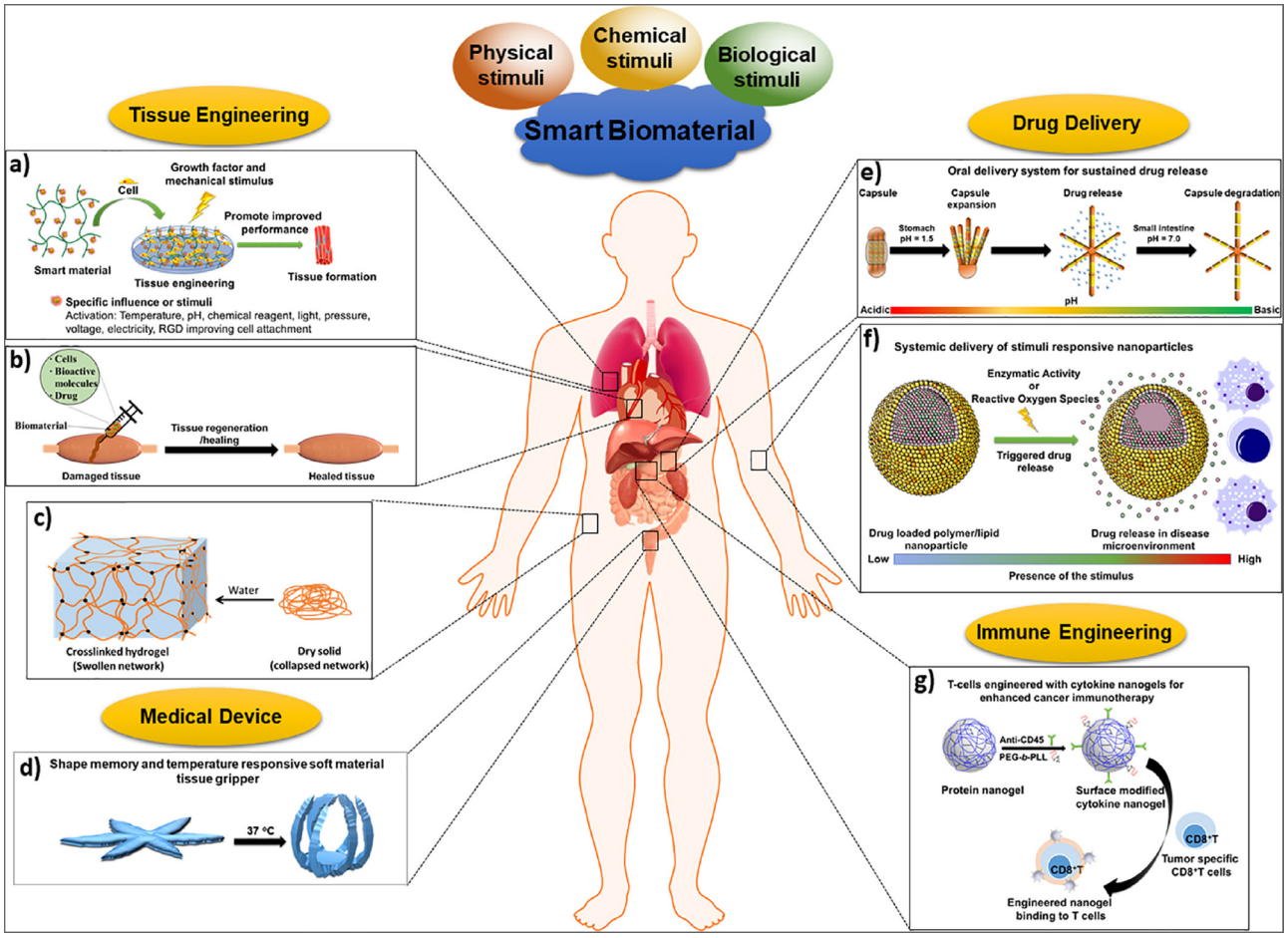

Fig 2 | Smart biomaterials and their stimuli responses. (a) Stimuli-responsive materials, (b) Injectable biomaterials, (c) Hydrogels with three-dimensional networks, (d) Shape-memory and temperature-sensitive materials, (e) Star-shaped systems, (f) Nanoparticle-based drug delivery systems, (g) Targeted delivery strategies using CAR T cells. Reprinted (adapted) with permission from P. S. Kowalski, C. Bhattacharya, S. Afewerki, and R. Langer, "Smart Biomaterials: Recent Advances and Future Directions," ACS Biomaterials Science & Engineering, 2018, 4 (11), 3809–3817. Copyright 2018 American Chemical Society[12]

efficiency of 185% and no passive release. Controlled drug release was achieved under different pH conditions and could be activated on-demand by illumination.[23]

Magnetism-responsive biomaterials are smart biomaterials that respond to external magnetic fields, enabling remote control over their behavior. These materials are particularly valuable in high-precision applications, such as targeted drug delivery and minimally invasive procedures. Kilian et al. developed magneto-active composites with locally adjustable stiffness using a laser bed fusion-based 3D printing technique. By tailoring laser parameters, they achieved stiffness variations ranging from 2–22 MPa, allowing advanced designs such as bio-inspired actuators and customizable medical stents.[24]

Smart biomaterials, modified with biomolecules, are specially designed to interact with the tissue microenvironment, facilitating precise biological functions. These advanced materials can adapt to environmental or biological triggers, making them highly effective for medical applications like targeted drug delivery and tissue engineering.[25,26] One such development is Targeting ligands, molecules engineered to bind specific cellular receptors, facilitating targeted delivery of therapeutics. Saini et al. showed the conjugation of cyclic RGD (cRGD) peptides to PEGylated titanium dioxide (TiO_2) nanoparticles. Molecular dynamics simulations have demonstrated that an optimal density of cRGD ligands on these nanoparticles enhances their binding efficiency to α_vβ_3 integrin receptors, which are overexpressed in tumor cells, improving targeted photodynamic therapy.[27] Figure 2 highlights some of the recently developed stimuli-responsive smart biomaterials, along with their smart properties and intended areas of application.

Table 1 | Various smart biomaterials features and their role in cancer mitigation

Smart Feature Used in Biomaterial Designing	Description	Examples/Applications	Ref.
Stimuli-Responsive Drug Delivery Systems	Release drugs in response to specific internal or external stimuli.	pH-sensitive hydrogels, redox-responsive nanocarriers, thermo-responsive hydrogels, ultrasound-triggered drug release.	[49]
Nanogels	Nanoscale, highly crosslinked polymer networks for drug encapsulation.	Targeted delivery to cancer cell receptors, stimuli-responsive drug release (e.g., pH, temperature).	[50]
Metal–Organic Biohybrids (MOBs)	Combine metal ions with biological molecules for therapeutic effects.	Generation of therapeutic agents like nitric oxide, tumor immunity modulation.	[51]
Synthetic Exosomes	Engineered vesicles mimicking natural exosomes for delivery.	Biocompatible platforms delivering drugs, RNA, or DNA with minimal immune response.	[52]
Biohybrid Microswimmers	Microscopic devices combining biological and synthetic elements.	Active targeting to tumor sites using biological propulsion mechanisms.	[53]
Cytokine Delivery Systems	Biomaterials designed for cytokine delivery.	Nanoparticle-based cytokine delivery, protection from degradation, sustained release at tumor sites.	[54]
Smart Polymers	Polymers that respond to environmental changes for therapeutic applications.	Cell carriers for releasing therapeutic cells in tumor microenvironments.	[55]
Photothermal Therapy (PTT) Agents	Materials converting light into heat to ablate cancer cells.	Gold nanoparticles, thermoplasmonic polymersomes for localized heat generation.	[56]
Photodynamic Therapy (PDT) Agents	Materials producing reactive oxygen species upon light activation.	Smart photosensitizers improving solubility, targeting, and activation under specific wavelengths.	[57]
Nanorobots	Molecular machines for specific tasks like targeted drug delivery.	DNA origami-based nanorobots carrying therapeutic agents, triggered release by tumor-specific stimuli.	[58]
Mesoporous Silica Nanoparticles (MSNs)	Porous nanoparticles for drug loading and controlled release.	Anti-fouling surface properties to prevent protein adsorption, enhancing circulation and targeting.	[59]
Lectin-Conjugated Nanoparticles	Nanoparticles targeting carbohydrate markers on cancer cells.	pH-responsive drug release in acidic tumor microenvironments.	[60]
Engineered CAR T Cell Delivery Systems	Platforms enhancing CAR T cell therapy delivery and efficacy.	Injectable hydrogels supporting CAR T cells' survival and activity in tumor microenvironments.	[61]
Biomaterials for Overcoming Tumor Hypoxia	Materials addressing hypoxia to improve therapy efficacy.	Oxygen-releasing biomaterials supplying oxygen to hypoxic tumor regions, enhancing radiotherapy and photodynamic therapy.	[62]

Various Smart Biomaterials and Their Cancer Mitigation Abilities

Despite significant progress in cancer therapy, numerous challenges remain, including the complexity of tumor heterogeneity, resistance to treatment, and the adverse side effects associated with conventional medications.[28] Even after successful cancer therapy, a notable concern is the compromised quality of life experienced by a considerable number of patients. Thus, smart biomaterials represent a novel platform to improve cancer therapeutic efficacy in various ways. Table 1 lists various smart biomaterial features and how they aid cancer mitigation.

Targeted therapy has emerged as a promising innovation, complementing other strategic approaches like immunotherapy and early-stage detection, which are key areas of focus. Among these advancements, smart biomaterials stand out for their potential to revolutionize targeted drug delivery.[29] These materials are meticulously engineered to release therapeutic agents directly at the tumor site, thereby minimizing systemic side effects and enhancing overall treatment efficacy. Marina et al. demonstrated the use of smart biomaterials in cancer therapy by developing a multifunctional nanodevice based on MSNs. These nanoparticles are engineered with a pH-responsive polyacrylic acid (PAA) capping layer and a targeting ligand, concanavalin A (ConA), allowing selective binding to cancer cells overexpressing sialic acid. The system DOX is specifically designed for osteosarcoma cells, where the acidic tumor microenvironment triggers drug release. This innovative approach significantly enhances antitumor efficacy, achieving up to eightfold greater cytotoxicity against cancer cells than free DOX while sparing healthy cells, exemplifying the potential of smart biomaterials for targeted and efficient cancer therapy.

A notable characteristic of smart biomaterials is their ability to react to specific triggers, such as changes in pH, temperature, or the presence of enzymes typical of the tumor microenvironment.[30] This responsiveness facilitates controlled and sustained drug release, which reduces the frequency and dosage of treatments, facilitating significant benefits for patient compliance and comfort. Zahra et al. developed a pH-responsive biomaterial for cancer therapy, a magnetic metal-organic framework system incorporating Fe_3O_4 nanoparticles.

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This composite leverages the structural characteristics of the Cu-BTC framework as a drug carrier, while Fe_3O_4 nanoparticles serve as imaging agents, creating a multifunctional theranostic platform. The material is designed to release the anticancer DOX in response to pH changes, allowing for controlled delivery directly within the acidic environment of tumors. This targeted approach reduces side effects throughout the body and improves the effectiveness of the treatment. Furthermore, the system boasts a high drug-loading capacity of 40.5% for DOX and offers the potential for combined pH, glutathione (GSH), and photo-responsive drug delivery. Its multifunctionality extends to photoactive antibacterial applications, making it a versatile tool in cancer treatment. The integration of therapeutic and diagnostic capabilities emphasizes the promise of stimuli-responsive biomaterials in improving precision and outcomes in cancer therapy.[31]

Tumor hypoxia, a condition of low oxygen levels in tumor tissues, can reduce the effectiveness of certain therapies.[32] Smart biomaterials have been engineered to enhance oxygen distribution within tumors, thereby improving the efficacy of treatments like chemotherapy and photodynamic therapy. Shiekh et al. developed an oxygen-releasing antioxidant cryogel scaffold (PUAO-CPO) to address tumor hypoxia and tissue regeneration challenges. Combining antioxidant polyurethane (PUAO) with calcium peroxide (CPO), the scaffold delivered sustained oxygen for up to 10 days while minimizing harmful ROS production, as demonstrated in figure 3. It supported cell survival under hypoxic conditions *in vitro* and prevented tissue necrosis *in vivo* for up to 9 days, preserving tissue structure and collagen. This smart biomaterial shows promise to mitigate tumor hypoxia and treat ischemic conditions like myocardial infarction and chronic wounds, effectively delivering oxygen with reduced oxidative stress.[33]

Nanogels represent a distinct category of smart biomaterials, specifically designed as hydrogels engineered for targeted cancer therapy. Their unique properties, such as high water content, biocompatibility,

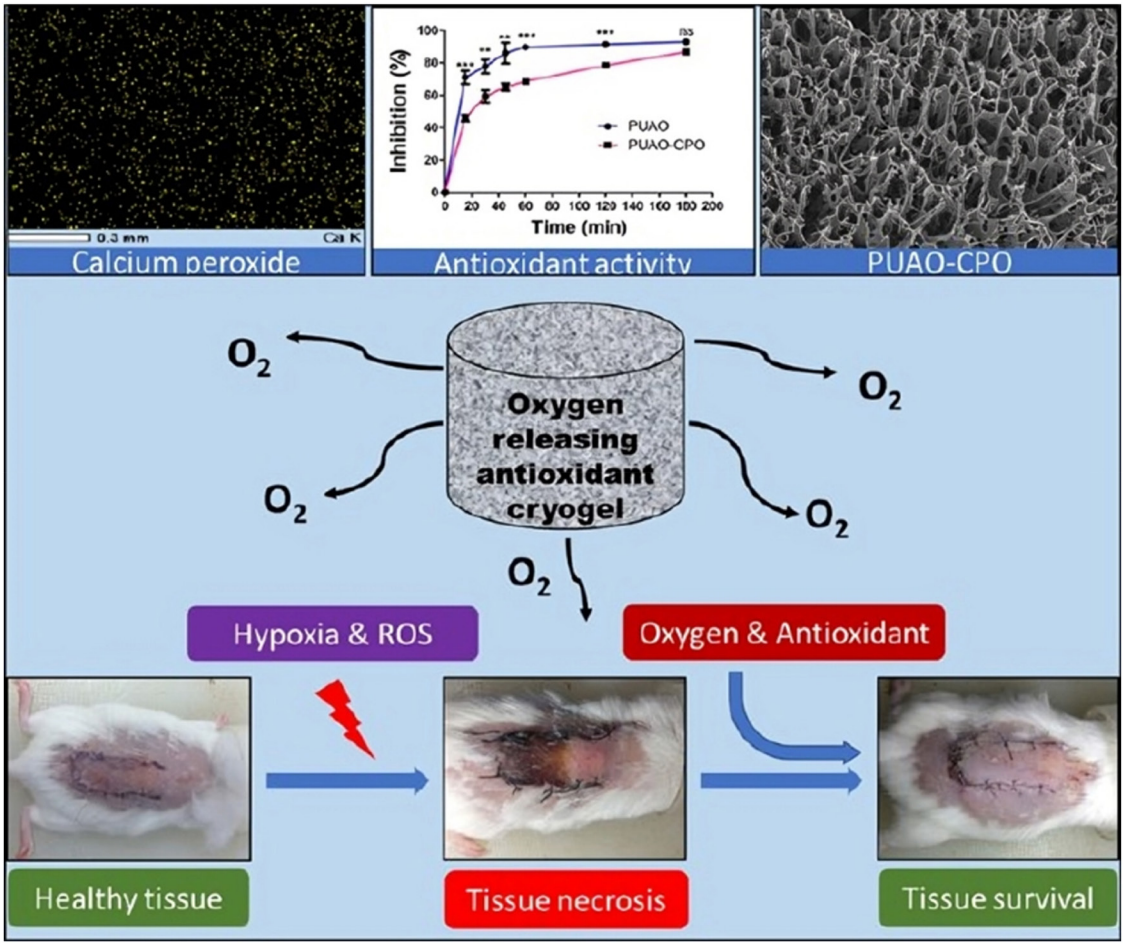

Fig 3 | Schematic overview and supporting data for the oxygen-releasing antioxidant cryogel scaffold (PUAO-CPO). (Top left) Distribution of CPO within the cryogel. (Top center) Antioxidant activity assay demonstrates the sustained ability of PUAO-CPO to reduce ROS. (Top right) Scanning electron microscopy (SEM) image shows the porous architecture of the PUAO-CPO scaffold. (Center) Illustration of oxygen release from PUAO-CPO, addressing hypoxia and preventing excessive ROS generation. (Bottom row) In an *in vivo* ischemic flap model, the oxygen-releasing cryogel prevents tissue necrosis and preserves tissue structure, underscoring its potential for treating ischemic injuries. Reprinted (adapted) with permission from P. A. Shiekh, A. Singh, and A. Kumar, "Oxygen-Releasing Antioxidant Cryogel Scaffolds with Sustained Oxygen Delivery for Tissue Engineering Applications," ACS Applied Materials & Interfaces, 2018, 10 (22), 18458–18469. Copyright 2018 American Chemical Society[33]

and tunable responsiveness to specific stimuli, render them ideal carriers for delivering therapeutic agents directly to tumor sites. This targeted approach enhances the effectiveness of cancer treatments while minimizing the damage to healthy tissues. One of the defining features of smart nanogels is their stimuli-responsive behavior. They can be designed to respond to various internal or external triggers, such as pH changes, temperature variations, redox conditions, or enzymatic activity, often characteristic of the tumor microenvironment. For instance, pH-sensitive nanogels can exploit the acidic environment of tumors to trigger drug release precisely at the desired location.[34,35] Zhang et al. developed a system that involves a bioreducible cross-linked dextrin nanogel (DNG) system coated with the FDA-approved CXCR4 antagonist AMD3100 designed to target CXCR4 chemokine activity and inhibit tumor metastasis as shown in Figure 4. This system allows for the reduction-responsive intracellular release of doxorubicin (DOX) to suppress cancer cell proliferation. The DOX-loaded AMD3100-coated nanogels (DOX-AMD-DNG) demonstrated enhanced cellular uptake and cytotoxicity against breast cancer cells compared to non-coated variants. *In vivo* studies revealed stronger tumor targeting and significant antimetastatic effects, reducing cell invasion and cancer progression. These findings emphasize the dual functionality of nanogel in improving anticancer efficacy and combating metastasis.[36]

Quantum dots represent a cutting-edge class of smart biomaterials recently employed in cancer therapy due to their exceptional tissue penetration capabilities and ease of functionalization. Seyyed et al. explored the potential of MXene quantum dots (MQDs) in cancer treatment and immunomodulation. These nanosystems, derived from MXene nanosheets, exhibit remarkable biocompatibility, photoluminescence, and tunable properties, facilitating their application in targeted drug delivery, photothermal therapy, and cancer diagnostics. Advanced synthesis techniques further enhance their functionality and safety, while their immunomodulatory properties allow precise regulation of immune responses and tissue regeneration. MQDs are particularly promising in personalized cancer therapies, providing targeted tumor action with minimal side effects. However, challenges remain, such as long-term toxicity, biodistribution, and scalability. The study emphasizes MQDs as a groundbreaking innovation in theranostics, encouraging further research to optimize their clinical potential and applications.[37]

Translational Challenges of Smart Biomaterial in Cancer Treatment

While smart biomaterials hold significant potential in cancer therapeutics, they present numerous challenges. As an emerging field within materials science, smart biomaterials have yet to establish a stable presence in clinical practice. Most published studies

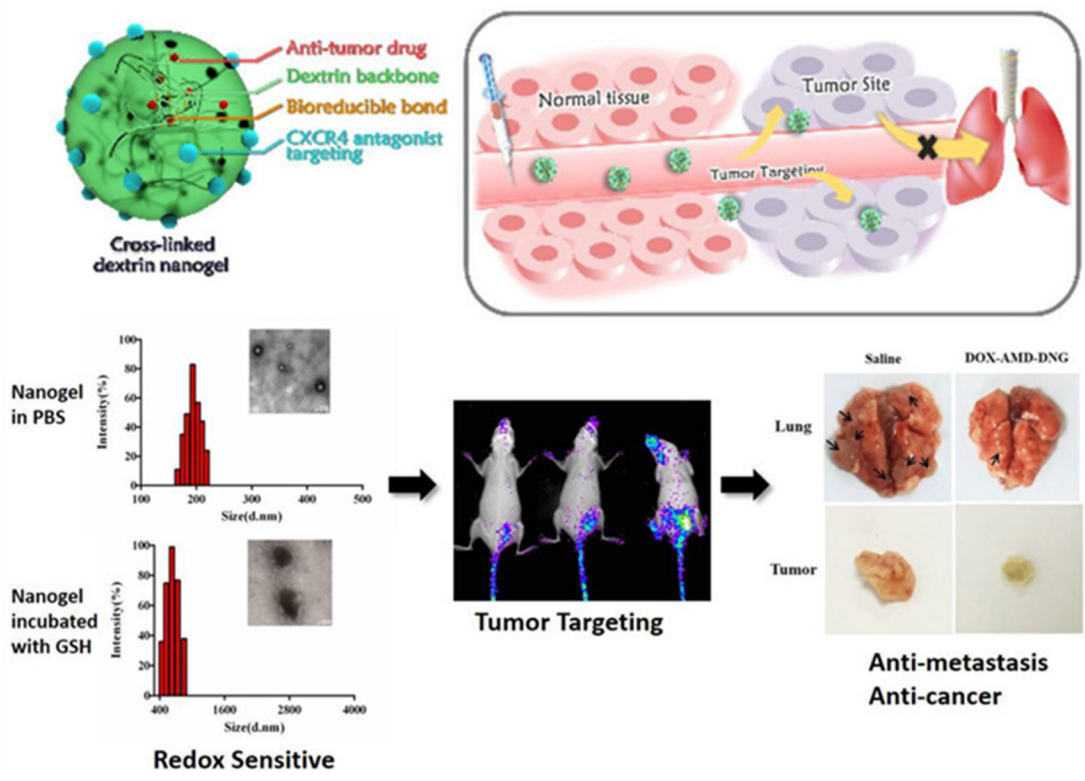

Fig 4 | Bioreducible dextrin nanogel loaded with doxorubicin and AMD3100 demonstrates tumor-specific targeting, enhanced cellular uptake, redox-responsive drug release, and anti-metastatic effects in 4T1 breast cancer models alongside *in-vivo* results. Reprinted (adapted) with permission from F. Zhang, S. Gong, J. Wu, H. Li, D. Oupicky, and M. Sun, "CXCR4-Targeted and Redox Responsive Dextrin Nanogel for Metastatic Breast Cancer Therapy," Biomacromolecules, 2017, 18 (6), 1793–1802. Copyright 2017 American Chemical Society[36]

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remain confined to laboratory settings, with only a few advancing from the bench to the bedside. A notable exception is NovaCaps, an encapsulated cell therapy product designed to treat inoperable pancreatic cancer. This approach involves encapsulating genetically modified cells within a semi-permeable membrane made of cellulose sulfate, allowing for the localized production and release of therapeutic agents directly at the tumor site.[38] Ensuring biocompatibility and safety is critical, as these materials must be non-toxic and avoid triggering adverse immune responses. For instance, some polymers used in pH-responsive drug delivery systems may not degrade efficiently in the body, potentially leading to accumulation and toxicity.[39] Achieving precise targeting of cancer cells while sparing healthy tissues is another significant hurdle. The heterogeneity of tumor environments—such as varying pH levels within different tumor regions—can compromise the performance of pH-responsive systems and result in off-target effects.[40]

Furthermore, the scalability and manufacturing of smart biomaterials present technical challenges. The complexity of synthesis and functionalization can drive up production costs, hindering widespread clinical adoption. Regulatory hurdles further complicate the landscape, as rigorous safety and efficacy testing and the lack of standardized evaluation protocols for novel biomaterials can delay clinical translation.

Stability during storage is another critical concern, as temperature sensitivity and environmental conditions can affect functionality. Finally, the high costs associated with developing and producing smart biomaterials pose accessibility challenges, requiring a careful balance between cost and therapeutic benefit to ensure these innovations become viable options for cancer therapy.[12,14,41]

Future of Smart Biomaterial Technology for Cancer Therapeutics

Technological improvements in the physical and chemical aspects of biomaterials have brought about significant innovations that have led to the development of smart biomaterials. When judiciously used in various aspects of cancer therapy, these materials have attained significant progress that was previously challenging to overcome. Targeted delivery is the most desired application of smart biomaterials in cancer therapeutics, primarily due to the lack of bioavailability in current drugs. The stimuli responsiveness and specificity of smart biomaterials are key features that will drive future improvements in this technology.[42]

Another approach involves modulating anti-tumor immunity with the help of smart biomaterials. Smart biomaterials enhance anti-tumor immunity using their sensitivity to the tumor microenvironment, controlled drug release, immune modulation, and support for multimodal therapies. Designed to react to specific tumor environments, such as changes in pH, temperature, or oxygen levels, these materials facilitate targeted drug delivery and safeguard healthy tissues from the impact of the drug. Furthermore, they facilitate sustained and targeted release of immunotherapeutic agents, such as checkpoint inhibitors, providing consistent immune stimulation with reduced dosing frequency. Moreover, these biomaterials enhance dendritic cell recruitment and antigen presentation, thereby boosting T-cell activity by incorporating immune stimulants such as CpG oligodeoxynucleotides or GM-CSF. Additionally, smart biomaterials facilitate combination therapies by integrating treatments like phototherapy and immunotherapy into a single platform, offering synergistic tumor suppression and systemic immune activation.[43]

A cutting-edge discovery under investigation using nanobots engineered using DNA origami-engineered nanobots offers a revolutionary approach to cancer treatment by precisely targeting tumor blood vessels. These rectangular DNA structures are programmed to deliver thrombin, a blood-clotting enzyme, to tumor sites via a DNA aptamer that binds to nucleolin, a protein overexpressed in tumor vasculature. Upon activation, thrombin induces localized clotting, effectively cutting off the tumor's blood supply and leading to its regression. This method has shown significant efficacy in animal models for various cancers, including breast cancer and melanoma, while preserving healthy tissues. This innovation is biodegradable and immune-compatible, signifying a secure, targeted, and versatile advancement in nanomedicine.[44,45]

Integrating AI and smart biomaterials can revolutionize cancer therapeutics by facilitating rapid design, optimization, and application of biomaterials for targeted, personalized, and effective treatments.[46] AI accelerates material discovery, enhances drug delivery precision, and facilitates real-time monitoring through biosensors.[47] It supports immune modulation, adaptive therapies, and personalized medicine by leveraging patient-specific data and multi-omics integration. Moreover, AI optimizes manufacturing processes, ensuring scalability and sustainability while advancing remote-controlled and non-invasive therapies.[48] Despite the challenges in data integration and regulations, AI is paving the way for next-generation hybrid therapies and digital twins for treatment planning, promising a future filled with adaptable and effective solutions for cancer management.

Conclusion

The advent of smart biomaterials signifies a transformative development in cancer therapy, offering innovative solutions that address the limitations of traditional treatments. These cutting-edge materials have demonstrated remarkable potential in preclinical studies, using advancements such as stimuli-responsive systems, multifunctional platforms, and AI-driven designs to redefine the scope of precision medicine. However, the path toward clinical implementation remains a complex and challenging endeavor.

It is essential to address significant challenges to unlock the full potential of smart biomaterials, ensuring their long-term biocompatibility, scaling up production for widespread use, and navigating the rigorous

requirements of regulatory approval processes. Collaborative research areas such as materials science, biology, and clinical medicine are essential to bridge the gap between laboratory research and practical patient care. Furthermore, integrating emerging technologies like AI and machine learning opens up exciting possibilities to improve biomaterial design. These advancements allow for real-time customization tailored to individual patients, helping to maximize the effectiveness of treatments.

In the future, smart biomaterials can revolutionize oncology by shifting the paradigm from generalized treatments to highly personalized, efficient, and minimally invasive approaches. Their adaptability also holds promise for handling other complex diseases, positioning these materials as a cornerstone of next-generation biomedical innovation. By continuing to advance the boundaries of science and technology, smart biomaterials are poised to transform cancer therapy and the broader medical landscape, ushering in a new era of healthcare innovation.

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