International Journal of Radiation Oncology biology • physics

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Critical Review

Smart Radiation Therapy Biomaterials

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Received Aug 10, 2016, and in revised form Sep 21, 2016. Accepted for publication Oct 24, 2016.

Radiation therapy (RT) is a crucial component of cancer care, used in the treatment of over 50% of cancer patients. Patients undergoing image guided RT or brachytherapy routinely have inert RT biomaterials implanted into their tumors. The single function of these RT biomaterials is to ensure geometric accuracy during treatment. Recent studies have proposed that the inert biomaterials could be upgraded to "smart" RT biomaterials, designed to do more than 1 function. Such smart biomaterials include next-generation fiducial markers, brachytherapy spacers, and balloon applicators, designed to respond to stimuli and perform additional desirable functions like controlled delivery of therapy-enhancing payloads directly into the tumor subvolume while minimizing normal tissue toxicities. More broadly, smart RT biomaterials may include functionalized nanoparticles that can be activated to boost RT efficacy. This work reviews the rationale for smart RT biomaterials, the state of the art in this emerging cross-disciplinary research area, challenges and opportunities for further research and development, and a purview of potential clinical applications. Applications covered include using smart RT biomaterials for boosting cancer therapy with minimal side effects, combining RT with immunotherapy or chemotherapy, reducing treatment time or health care costs, and other incipient applications.

Introduction

Radiation therapy (RT) is used in the treatment of more than 50% of cancer patients either alone or in combination with other treatments such as surgery or chemotherapy (1). The ultimate goal of RT is to maximize damage to the cancer cells while minimizing toxicities to healthy tissue. Major advances have been made over the past decades

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Conflict of interest: none.

Int J Radiation Oncol Biol Phys, Vol. 97, No. 3, pp. 624–637, 2017
0360-3016/$ - see front matter
http://dx.doi.org/10.1016/j.ijrobp.2016.10.034

because improvements in engineering and computing have enabled RT modalities such as intensity modulated RT (IMRT), stereotactic ablative RT (SABR), and image guided RT (IGRT) to be used in routine clinical practice.

Currently, many patients undergoing IGRT or brachytherapy routinely have inert RT biomaterials implanted into their tumors. These inert RT biomaterials can include fiducial markers, spacers, beacons, and balloon applicators, engineered to be used in RT of patients with lung, pancreatic, breast, prostate, liver cancer, and other tumors exhibiting motion or deformation during RT (2-6). Currently, these inert RT biomaterials have only a single function: to ensure geometric accuracy during the treatment and enhance therapeutic efficacy (7-11).

With these RT biomaterials already having such unfettered access to the tumor subvolume, there is a compelling rationale for upgrading those single-function inert biomaterials to multifunctional or "smart" biomaterials that can deliver additional therapeutic or treatment-enhancing benefits. In general, biomaterials (other than foods or drugs) are designed for specific medical uses that interrelate with biological systems (12). Smart biomaterials (13-16) are specifically designed to be sensitive to a specific stimulus, such as those present in the tumor microenvironment (eg, temperature, pH, the wavelength or intensity of incident light or an electrical or magnetic field) and to then respond in active ways including changing their structure for drug delivery, radioprotection, priming an immune response, or other functions that have the potential to cogently enhance therapy.

In 2010, Cormack et al (11) proposed the use of smart RT biomaterials (SRBs): brachytherapy spacers or fiducials loaded with radiosensitizing drugs that could be activated by the tumor microenvironment, in the postimplantation period, to sustainably deliver the specific drug directly into the tumor subvolume. The authors concluded that drug loading of implantable devices routinely used in IGRT provides new opportunities for therapy modulation through biological in-situ dose painting. Later, Kumar et al (8) reported on such brachytherapy spacers for the delivery of localized chemoradiation therapy. Their results demonstrated that such spacers with customizable release profiles have potential for improving the combined therapeutic efficacy of chemoradiation treatment. High atomic number nanoparticles such as gold nanoparticles (GNPs) can also act as radiosensitizers (17). Recently, such nanoparticles have been investigated as payloads loaded into smart polymers in spacers, fiducial markers, or balloon applicators to boost RT efficacy (6, 7, 10, 18). Combining RT and immunotherapy using such smart RT biomaterials in treating metastatic disease, with minimal toxicities to healthy tissue is also being investigated (19).

Major advantages of using SRBs (Table 1) include the fact that sustained in situ delivery of drugs, nanoparticles, or other payloads directly into the tumor subvolume may overcome physiological barriers, allowing direct delivery of sufficiently potent payload into the tumor. Standard intravenous delivery approaches typically result in less than 5% of payloads, like drugs, reaching the tumor (15), whereas SRBs will enable direct delivery into tumors. The SRB delivery approach would therefore also significantly minimize any systemic or overlapping toxicities. This takes into account the fact that nanoparticles such as GNPs are relatively nontoxic (20) and that controlled in-situ release of payloads leads to minimal systemic toxicities (21, 22). Another advantage is that SRBs could simply replace currently used inert RT biomaterials and so can be used at no additional inconvenience to cancer patients. Furthermore, the sustained or controlled release and intratumor biodistribution of payloads from the SRBs can be customized or controlled by varying design parameters such as payload concentration, polymer type or weight, or nanoparticle size, allowing for optimization to RT schedules and for superior therapeutic efficacy.

Table 1 Advantages of smart radiation therapy biomaterials (SRBs)

1. Direct delivery of therapy-enhancing payloads into the tumor subvolume from SRBs overcomes physiological barriers, allowing direct delivery of sufficiently potent payload into the tumor compared with intravenous approaches, where less than 5% of payload arrives at the tumor even with the enhanced permeability and retention effect.
2. Local delivery of payload from SRBs allows for subvolume radiation therapy boosting with minimal toxicity to healthy tissue. Hence this could minimize systemic/overlapping toxicities, especially when radiation therapy is combined with other treatment modalities like chemotherapy.
3. SRBs can be designed/programmed for sustained release of the payload compared with repeated injections. Sustained in-situ delivery has also been shown to be more effective for certain applications and should be advantageous when radiation therapy and immunotherapy are combined.
4. SRBs could simply replace currently used inert radiation therapy biomaterials and thus can be used at no additional inconvenience to cancer patients.
5. SRBs could be multifunctional, including payloads with image contrast for theranostic applications or other therapy-enhancing agents in combining radiation therapy with other approaches like chemotherapy or immunotherapy.

Given this rationale and these advantages, SRBs represent a promising area of research and development. This should lead to a new generation of RT biomaterials, designed to perform their primary functions as inert RT biomaterials but also to controllably deliver therapy-enhancing payloads in situ, among other potential functions for optimal diagnostic and therapeutic efficacy.

More broadly, SRBs may also include functionalized stimulus-responsive nanoparticles that can be targeted and activated to boost RT (7, 23). These and other smart nanomaterials (15, 16) could themselves be incorporated into the traditional RT biomaterials (8). Targeting the nanoparticles is desirable because once nanoparticles are

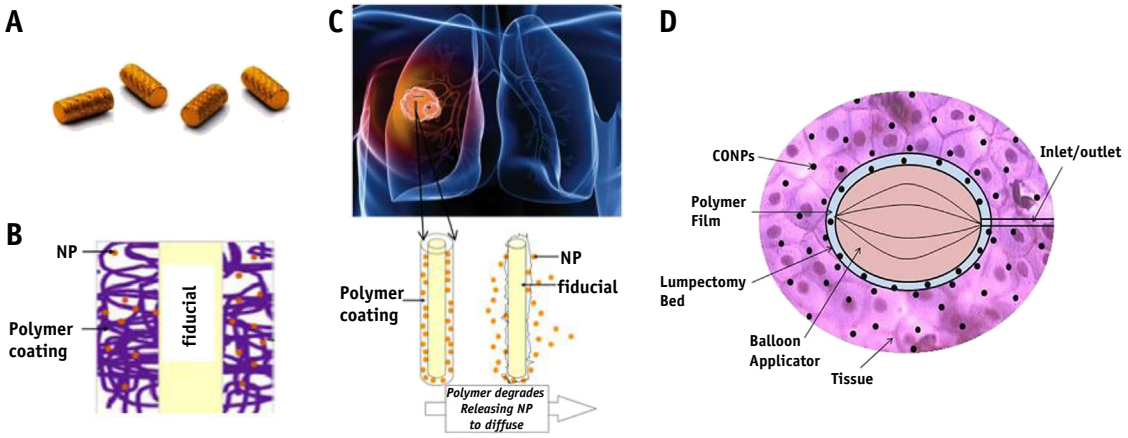

Fig. 1. (A) Currently used commercially available inert radiation therapy biomaterials (eg, fiducials) (CIVCO Medical). (B) One design (not to scale) of the smart radiation therapy biomaterial (SRBs). (C) SRBs could simply replace the inert biomaterials used for image guided radiation therapy (eg, for lung cancer). (D) Accelerated partial breast irradiation with balloon applicator (loaded here with cerium oxide nanoparticles [CONPs]) for selective protection of healthy breast tissue; once in place the SRB can be activated to sustainably release the payload in situ directly into the planning target volume. The release and distribution of payload could be customized or optimized to radiation therapy schedules (6, 10, 18). *Abbreviation:* NP = nanoparticles.

released into the tumor microenvironment, their uptake and retention in cells is important, as is their functionalization to reach subcellular targets like the nucleus (24) or mitochondria (25) to have maximal effect.

Research and development in SRBs is still at an early stage; yet, many lessons can be adapted from previous work on smart biomaterials developed for other in-vivo applications as well. Research in this area demands for cross-disciplinary collaborations and may even leverage international collaborations, given some of the applications being considered. This review examines the potential and state of the art in this exciting and procedure-changing area. It begins with coverage of the design of SRBs and how they can be customized or programmed for different functions. Potential applications of SRBs in overcoming current RT limitations, and emerging opportunities for research and development, are discussed.

Design and Structure of Smart Radiation Therapy Biomaterials

Design

An SRB is designed or structured to perform sensing and actuation during RT procedures. One design of an SRB is illustrated in Figure 1.

This simple design integrates a commercially available RT biomaterial (eg, fiducials) (Fig. 1A) into a smart polymer (16) coating that can sense and actuate or change structure to release a payload incorporated in its polymer matrix (Fig. 1B). The choice of smart polymer depends on the nature of the stimulus that will be used to initiate a response. Several studies (7-9, 26) have favored the use of biodegradable synthetic polymers such as poly(lactic-co-glycolic acid) (PLGA), natural biological polymers such as chitosan, or both. PLGA is a polymer that is used in a host of therapeutic devices approved by the US Food and Drug Administration because of its biodegradability and biocompatibility, whereas chitosan is also widely used in several biological applications.

Once in place, the SRB can be activated by stimulus (eg, tumor microenvironment, heat, sound, or electromagnetic wave) to controllably release the payload in situ, directly into the tumor (Fig. 1C). In an example reported in recent studies (9, 26) it was shown how gold fiducial markers can be coated with nanoporous polymer matrices incorporating nanoparticles. Different polymer types were investigated, including PLGA nanoparticles loaded with fluorescent coumarin-6, serving as a model for a hydrophobic drug, in a biodegradable chitosan matrix. A free drug release system consisting of doxorubicin, a hydrophilic drug, loaded into a nondegradable polymer poly(methyl methacrylate) (PMMA) coating was also demonstrated (9).

Other designs for SRBs that have been developed include those in which instead of coating commercially available SRBs, a completely new SRB is developed loaded with the payload. This latter approach has the advantage of higher loading capacity. In an example of such a newly designed SRB (8, 27), the authors fabricated implantable chemoradiation therapy (INCeRT) spacers loaded with silica nanoparticles (SNPs) containing a drug, to act as a slow-release drug depot for simultaneous localized chemoradiation therapy. The spacers were made of PLGA as matrix and are physically identical in size to the commercially available brachytherapy spacers (5 mm × 0.8 mm). The silica nanoparticles were conjugated with near-infrared fluorophore Cy7.5 as a model drug. The INCeRT spacers

were further doped with an anticancer drug, docetaxel. Studies considering the use of other chemotherapy drugs like cisplatin and carboplatin nanoparticles have also been reported (28-30).

Another design being investigated is that of hollow SRBs and a hybrid of the above design models to program or customize for different loading and release rates. These approaches could also be used for any RT biomaterials, including balloon applicators (Fig. 1D). Researchers are considering the coating of such balloon applicators with different nanoparticle types, such as targeted GNP for boosting of dose to residual tumor cells during accelerated partial breast irradiation (6) or cerium oxide nanoparticles to selectively protect healthy breast tissue during the same (18) or intraoperative RT.

Smart nanoparticles for radiation therapy

The potent component of SRBs is the payload, which could be nanoparticles or so-called nanocarriers/drones also carrying a payload. Several excellent recent review articles have covered the field of nanoparticle-aided RT, including high atomic number nanoparticles of gold/gadolinium, hafnium oxide, and others (7, 31-37). A growing consensus remains that a major challenge is how to selectively deliver nanoparticles to cancer cells. Functionalizing nanoparticles is a widely used technique that allows for conjugation of the nanoparticles with targeting ligands, which possess inherent ability to direct selective binding to cell types or states and therefore confer "smartness" to nanoparticles. Friedman et al (38) recently published an article, "The Smart Targeting of Nanoparticles," which described the methods of ligand-nanoparticle functionalization, and a cross-section of various ligand classes used, including small molecules, peptides, antibodies, engineered proteins, and nucleic acid aptamers. PEGylation adds stealth, and multifunctionalization could include imaging moieties for different applications (39-45). Biomaterials scientists (46) have also developed targeted, biodegradable nano "drones" to deliver drugs that could be adapted for RT applications. Using prostate cancer as a model, Fredman et al (46), Dhar et al (47, 48), and Farokhzad et al (49) have reported significant work on such smart targeted nanoparticles, including nanoparticles conferred with stealth. In 1 study, docetaxel-encapsulated nanoparticles were formulated with biocompatible and biodegradable poly(D,L-lactic-co-glycolic acid)-block-poly(ethylene glycol) (PLGA-b-PEG) copolymer and surface functionalized with RNA aptamers that recognize the extracellular domain of the prostate-specific membrane antigen (PSMA). The approach highlights the potential of using such nanocarriers to deliver payloads that could also enhance RT.

For RT, there is also a growing consensus that delivery of nanoparticles within the tumor subvolume may be necessary but not sufficient to enhance therapy and that subcellular targeting may be crucial in maximizing therapeutic efficacy. This may be particularly important for high atomic number nanoparticles like GNP, which can boost RT by emission of short-range photo/Auger electrons with subcellular range. For example, Burger et al (24) developed an approach to enhance the uptake of small GNP functionalized with DNA, allowing for strong perinuclear focal accumulation (Fig. 2). These authors reported that only the GNP functionalized with DNA showed a significant radiosensitizing effect ($P = .005$) on clonogenic survival using clinically relevant megavolt X rays. Recently, other third-generation (23) and fourth-generation (7) nanoparticles have been optimized for targeted RT applications functionalized with other moieties like Arg-Gly-Asp (RGD).

In combination therapy approaches, smart or stimuli-responsive nanocarriers (15) loaded, for example, with

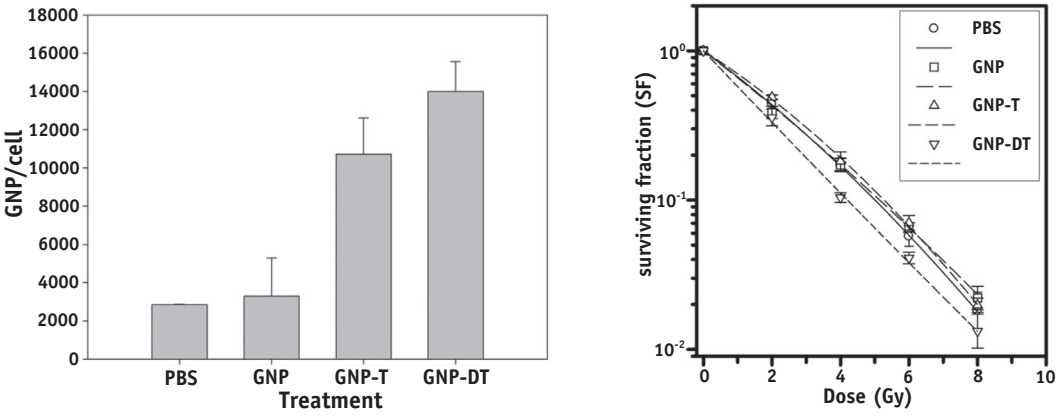

Fig. 2. Left, localization microscopy-assisted quantification of gold nanoparticles (GNPs) in HeLa cells after treatment shows that functionalizing the GNPs through the addition of transfection (GNP-T and GNP-DT) results in a significantly increased number of GNPs/cell. The GNPs linked to DNA and transferred into HeLa cells by transient transfection GNP-DT showed the most efficiency. Right, clonogenic survival of HeLa cells after 6-MV x-ray irradiation showing significant decrease in SF for GNP-DT compared with nonfunctionalized GNPs (figure from Burger et al, Nanomedicine 2014;10:1365-1373). *Abbreviations*: SF = Surviving fraction; PBS = phosphate-buffered saline.

chemotherapy drugs or immunoadjuvants have also been reported (50). Gold nanoshells are currently being investigated as nanocarriers with both diagnostic and therapeutic applications, including photothermal ablation, hyperthermia, drug delivery, and diagnostic imaging, particularly in oncology (51, 52). These gold nanoshells are valuable for their localized surface plasmon resonance, biocompatibility, and easy functionalization; hence, they can be readily adapted to RT applications leveraging the cross-section for the photoelectric effect. Recently, studies have demonstrated that gold nanoshells are able to deliver antitumor drugs into cancer cells, which enhances the efficacy of treatment (51, 52). It is now well established that GNPs have the advantage of being easily functionalized with active targeting ligands such as antibodies, aptamers, and peptides to increase the particles' specific binding to the desired targets.

Nanoparticles loaded with immunoadjuvants (53, 54) are particularly attractive because the use of nanoparticles may allow improved antigen stability and immunogenicity, but also targeted delivery and slow release. Several nanoparticle vaccines varying in composition, size, shape, and surface properties have been approved for use in human beings, and the number of candidates is increasing (55). However, challenges remain because of a lack of fundamental understanding of the in-vivo behavior of nanoparticles that could operate either as a delivery system to enhance antigen processing or as an immunostimulant adjuvant to activate or enhance immunity. In-situ delivery of such nanoparticles or immunoadjuvants to prime the abscopal effect (56) during RT is appealing. Besides nanoparticles, other nanocarriers such as micelles, carbon nanotubes, water-soluble polymers, liposomes, and dendrimers have been engineered as agents for targeted delivery to benefit tumor diagnosis and therapy (33, 37, 57) and could be adapted for enhancing RT.

Song et al (58) have reported on smart GNPs designed for photoacoustic imaging, an image contrast agent responsive to the tumor microenvironment. Such nanoparticles could be used to enhance RT treatment by means of the photoelectric effect while providing the imaging function. From this perspective, GNPs stand out as suitable multifunctional platforms for the development of efficient delivery, imaging, and therapy enhancement systems. However, other nanoparticles are also being considered, such as gadolinium nanoparticles designed as smart molecular magnetic resonance imaging contrast agents (59).

Figure 3 shows the development of amphiphilic gold nanoparticles by the Irvine group at MIT, composed of gold cores surrounded by an amphiphilic mixed organic ligand shell, capable of embedding within and traversing lipid membranes (60). A strategy has been developed to transport such membrane-penetrating particles into tumor cells and promote their transfer to intracellular membranes for enhanced RT of cancer (60). Microneedles have also been developed (Figs. 3B and 3C), designed as warheads that can be loaded with a therapeutic payload for sustained in-vivo release (Fig. 3D) (61, 62). Although these microneedles were originally designed for delivery of immunomodulators through the skin, similar structures might be adapted as

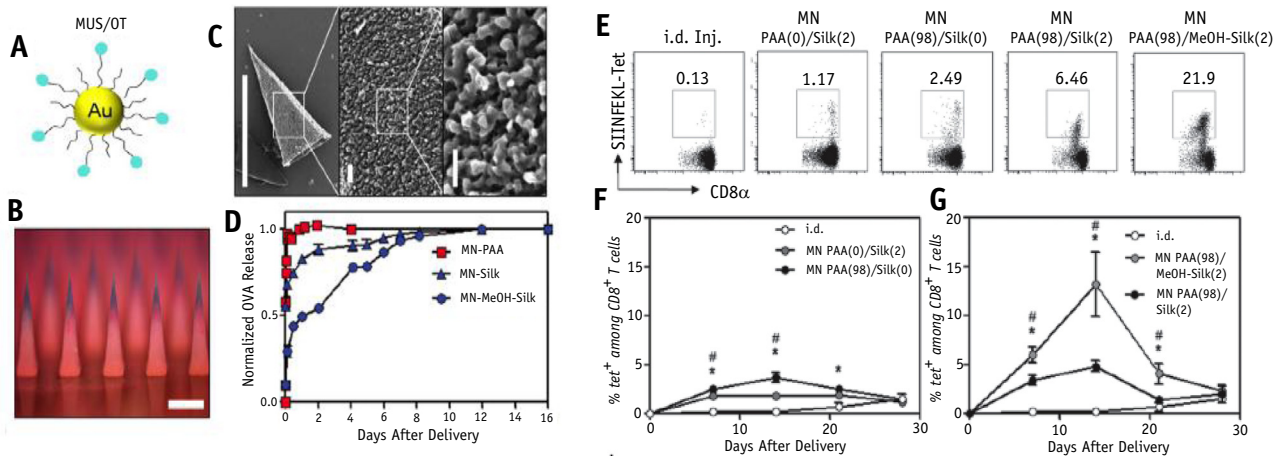

Fig. 3. (A) Amphiphilic gold nanoparticle. (B) Optical image of microneedles to load gold nanoparticles or other payloads. (C) Electron microscopic image of silk microneedle tip (left scale bar 500 μm). (D) Quantitative analysis of model protein (OVA) payload release from microneedle overtime in vivo for silk tips or methanol-treated silk tips that release entrapped protein more slowly. (E, F, G) Sustained/slow vaccine release profile elicits increased proliferation of antigen-specific $CD8^+$ T cells $*p < 0.05$, $^{\#}p < 0.05$ (reference *Advanced Healthcare Materials*, *3*(1), 47-58). *Abbreviations:* MN-PAA = Microneedle made of Polyacrylic Acid; MN-Silk = Microneedle made of silk; MN-MeOH-Silk = Microneedle made of silk pretreated with methanol (MeOH); OVA = ovalbumin; PAA(0)/Silk(2) = Vaccine dose split 0% in polyacrylic acid and 2% in silk; PAA(98)/Silk(0) = Vaccine dose split 98 percent in polyacrylic acid and 0% in silk; PAA(98)/Silk(2) = Vaccine dose split 98% in polyacrylic acid and 2% in silk; PAA(98)/MeOH-Silk(2) = Vaccine dose 98% in polyacrylic acid and 2% in silk and pretreated with methanol; i.d inj. = intradermal injection.

SRBs (eg, for cervical cancer treatment). Previous studies have shown that delivery of a vaccine using microneedles elicits major increase in proliferation of antigen-specific $CD8^+$ T cells in comparison with injections (61). The delivery of a payload sustainably over many days is expected to also be more effective, as envisaged for SRBs.

Programming SRBs

The design of SRBs with smart polymer components allows for programming these polymers to be activated at the appropriate time and site of action (63, 64). These polymers typically exhibit a nonlinear response to a small stimulus, leading to a macroscopic alteration in their structure or properties. Fascinating features of such smart polymers arise from their versatility or tunable sensitivity. The versatility of polymer types and their combinatorial synthesis make it possible to program the action or delivery of payloads. In general, the release kinetics and distribution of payloads from SRBs can be customized or programmed by varying the polymer type or weighting or crosslinking, and by payload concentration, size of nanoparticle, and other factors, improving treatment efficacy (7, 27, 60, 65-68).

Table 2 shows examples of smart polymers considered for SRBs and which stimuli they are responsive to. For some applications, sensitivity to more than 1 stimulus may be advantageous.

Whereas there are many smart polymers, the most commonly reported polymers being used to develop smart biomaterials are PLGA or chitosan, given their biocompatibility and biodegradability (23, 27, 31, 69). Some studies have reported the potential to use multiple polymer types, as highlighted by Yang et al (67). They designed a release system made of cross-linked chitosan containing both free drug molecules and drug-loaded PLGA nanoparticles. Before exposure to acid or pH stimulus, the chitosan polymers can keep their structural integrity without leakage of the encapsulated substances. Upon acid-triggering, there is first a burst release resulting from the acid-induced decomposition of the chitosan. The encapsulated free drug molecules and drug-loaded PLGA nanoparticles are rapidly released. Next, the drugs loaded in the PLGA nanoparticles are slowly released over many days to achieve sustained release based on the synergistic effect of drug diffusion and PLGA degradation. Such systems with programmed sequential release proffer more versatility for controlled release in biomedical applications and could be adapted for RT biomaterials. Adaptations of PLGA (PLGA−PEG−PLGA triblock copolymers) and chitosan are also thermosensitive polymers (70). In response to a small temperature change, such thermosensitive polymers undergo abrupt changes in their solubility to release payloads.

Another exciting class of smart polymers that can be used for SRBs are based on materials that respond when irradiated at particular wavelengths (68, 73). The features shared by photon-activated polymeric biomaterials involve photons interacting with the material, which triggers photochemical reactions that alter the structure of the cross-linked polymer network. Many such structural alterations result in an evolution of the polymer network and in subsequent macroscopic deformation, enabling release of the therapy-enhancing payload. Some authors have considered smart biomaterials that can be activated by a combination of pH and light (71). For RT, a range of wavelengths could be used to stimulate release, including ultraviolet light present in the form of Cerenkov radiation during external beam RT.

Table 2 Examples of stimuli-responsive polymers of interest in development of smart radiation therapy biomaterials

Polymer type	Stimulus type	Response	Reference example(s)
PLGA	Hydrolysis, tumor microenvironment	PLGA biodegrades into lactic and glycolic acid	(69, 70)
Chitosan	Temperature, Mg 2+, pH	Gelation through interactions, which involve electrostatic attraction with an inorganic ion	(9, 26, 67, 71, 72)
Azobenzene, polyacrylamide-tri-phenylmethane leuco derivatives, poly (N-vinyl carbazole) composite	UV, IR radiation	Photosensitiveness induces structural changes to deliver payload	(15, 73)
Dodecyl isocyanate-modified PEG-grafted poly (HEMA), Perfluorocarbon nanoemulsions	Ultrasound	Thermal or mechanical effects generated by cavitation or force	(15, 73)
PNIPAAm hydrogels containing ferromagnetic material, PNIPAAm-co-acrylamide	Magnetic field	Magnetic force or a temperature increase when an alternating magnetic field is applied	(15, 73)
Dendrimers, poly(ethacrylic acid)	pH	Acid sensitive bonds or polymers that undergo conformational or solubility changes in response to pH variation	(15, 73)

Abbreviations: PLGA = poly(lactic-co-glycolic acid); UV = ultraviolet; PEG = Pegelated; IR = infra-red; HEMA = hydroxyethyl methacrylate; PNIPAAm = Poly(N-isopropylacrylamide).

A new light-sensitive polymer containing multiple light-sensitive triggering groups along the backbone and incorporating a quinone-methide self-immolative moiety was recently developed and formulated into nanoparticles encapsulating a model dye Nile Red (72). Triggered burst-release of the payload upon irradiation and subsequent degradation of the nanoparticles was observed. This system is designed to be versatile, whereby the triggering group can be sensitive to several wavelengths (72). At the nano-scale, studies show that smart gold nanoshells can also be spatially and temporally triggered to release controlled quantities of drugs inside target cells when illuminated with photons (51, 52). In general, photon-responsive polymers are very attractive for triggering payload release because of the ability to control the spatial and temporal triggering of the release. The encapsulated payload can be released after irradiation with a photon source from outside the body. Visible and infrared (64) photon-sensitive polymers are traditionally preferred over ultraviolet-sensitive polymers because of the deeper penetration of photons at higher wavelengths, safety, and ease of use. However, an area worth exploring in RT applications is if the ultraviolet-range Cerenkov radiation present in the tumor during RT could be exploited for activating SRBs. Such Cerenkov radiation is currently being considered for quality assurance (74-76) and therapy applications (77, 78). Other researchers have also been investigating the use of targeted upconversion nanoparticles that emit high-energy photons upon excitation by near-infrared light to boost tumor cell kill (79). The results suggest that such a targeted nanoplatform has potential to serve not only as an imaging reagent but also as a therapeutic agent for the treatment of large or deeply seated tumors.

Besides varying the polymer type, another approach to program or customize the release kinetics of nanoparticles or drug payloads from SRBs is by varying the smart polymer weight or cross-linking (9, 80). The structure of some smart polymers can be readily tuned by controlling the density of cross-links. For polymers activated by the tumor microenvironment, their affinity or interaction with the environment could also be customized by varying the cross-links. The porosity of the polymer matrix enables subsequent drug release at a rate dependent on the diffusion coefficient of the nanoparticle or macromolecule through the polymer matrix. Indeed, the benefits of polymers for drug delivery may be largely pharmacokinetic. This is specifically useful with a depot formulation created in the matrix from which the payload can slowly elute, maintaining a high local concentration of the payload over an extended period (70).

The sustained release of payload from the SRBs is important in determining success. The release of the payload can be tuned based on the composition of SRBs and the encapsulated payload. Studies already show that the release kinetics of nanoparticles or drugs from SRBs can be programmed or customized to RT schedules (7). Figure 4A shows an electron microscopic image of a prototype new design SRB. In-vitro release of payload can be customized for rapid release (Fig. 4B) or relatively more sustained release over many days (Fig. 4C).

In-vivo release of a payload with fluorescent label to track distribution has also been investigated, with representative results illustrated in Figure 5. Live animal in-vivo optical fluorescence imaging with mice implanted with prototype SRB is shown in Figure 5A.

Figure 5B shows a 2-dimensional view of increased intensity (in more image pixels) over time as the fluorescent payload is gradually released in mouse tumor. Figure 5C highlights quantification of the fluorescence intensity. The results demonstrate the potential for customizing the release. In 1 case with the use of nanoparticles, there is a constant increase in intensity for 14 days, as opposed to the second case, where there is rapid release and then decrease over the same time frame. Several publications have reported on efforts to model the distribution of released payload from SRBs (10, 11). Conclusions include the fact that ultrasmall nanoparticles may be more appropriate for RT application. More experimental work is needed to validate some of these models and to develop optimized algorithms based on experimental data that can benefit further research and the development of treatment planning tools in preparation for potential clinical translation. Such

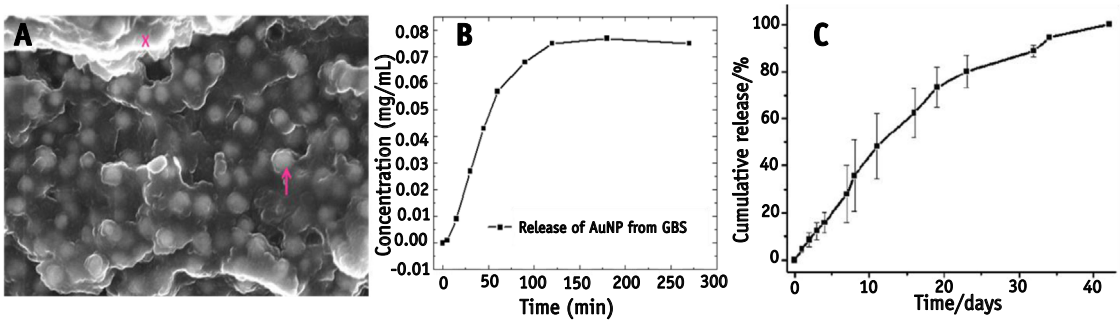

Fig. 4. (A) Electron microscopic image (1 μm^2) of prototype smart radiation therapy biomaterial (SRB). X, polymer matrix; arrow, payload. (B, C) Customizable in-vitro release of payload from the prototype SRB showing the ability for (B) rapid release or (C) sustained release (reference Physics in medicine and biology 2010;55:6039-52). *Abbreviation:* GBS = gold nanoparticle-loaded biomaterial/spacer.

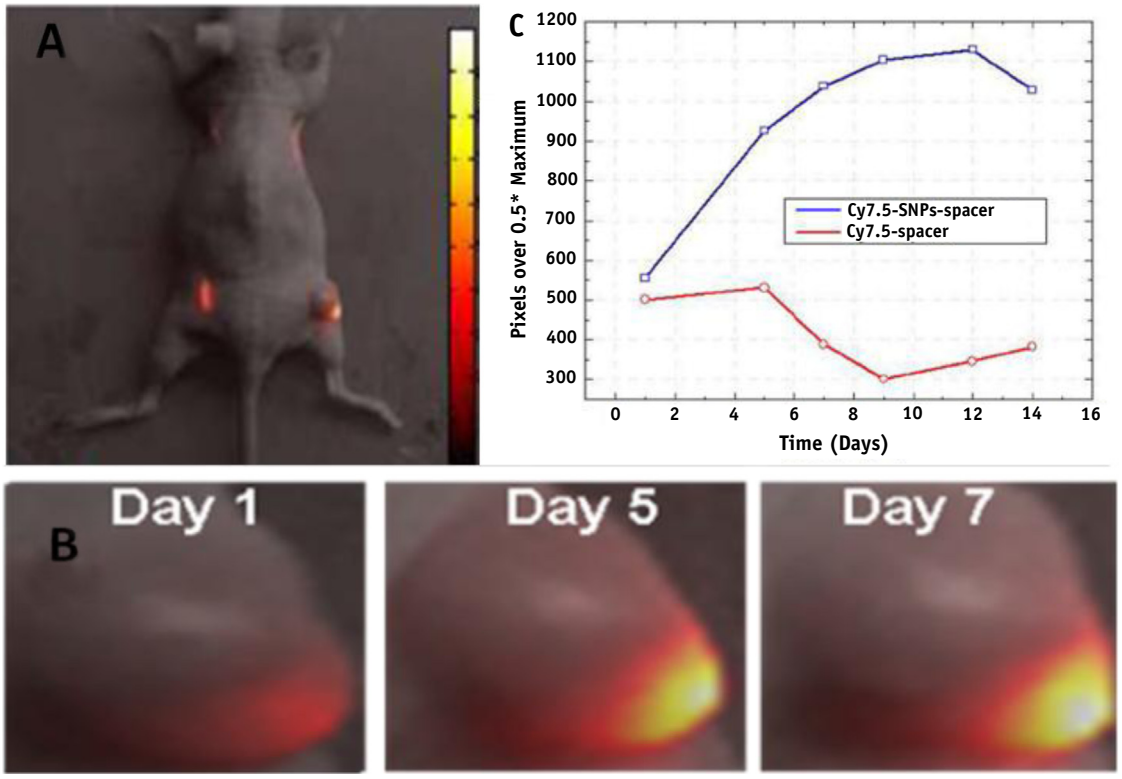

Fig. 5. (A) Live animal in vivo optical fluorescence imaging with mice implanted with prototype smart radiation therapy biomaterial. (B) Optical fluorescence (same intensity scale) of live mouse tumor over time. Day 1 represents image 1 day after implantation, and so on. (C) Quantification of the fluorescence intensity highlighting the ability to customize the release kinetics of the payload (reference Int J Radiat Oncol Biol Phys 2015;91:393-400). *Abbreviation:* SNPs = silica nanoparticles.

data could be in the form of look-up tables mapping design parameters to function.

Potential Applications for Smart Radiation Therapy Biomaterials

Despite remarkable advances in the development of RT modalities such as IMRT, SABR, and IGRT, major limitations remain in extending the benefits of RT to many more patients to increase their survival and quality of life. SRBs offer opportunities to address some of these limitations in potential clinical applications.

Dose painting or radiation boosting

In RT practice, a persisting limitation is obviously that of normal tissue toxicity (7, 37, 81). Clinical studies indicate that radiation boosting or dose painting leads to a significant increase in survival for cancer patients (82, 83). For example, it has been estimated that an increase in every 1-Gy boost of biologically effective dose could lead to a 4% relative improvement in survival (83). However, current modalities for radiation boosting are critically limited by normal tissue toxicity, compounded by respiratory or intrafraction/interfraction tumor motion (82). An American medical task group report notes that new treatment strategies that can overcome these limitations, allowing an enhanced dose to the tumor while sparing normal tissue, will significantly improve the balance between adverse events and cure (82).

Nanoparticle-aided RT (eg, using GNPs) is emerging as a promising new treatment strategy for overcoming these limitations, to enable substantial radiation boosting with minimal toxicity to neighboring healthy tissue (7). Such targeted nanoparticle-aided RT with GNPs involves first targeting the tumor cells with nanoparticles, and then targeting the nanoparticles during RT to enhance RT efficacy. In a study by Hainfeld et al (17), the use of GNP with 250-kVp X-rays/photons produced 86% long-term survival, in comparison with 20% when radiation was used alone, indicating major therapeutic enhancement resulting from the GNP. Other experimental work has also demonstrated the amplification of damage to tumor cells by GNP (7, 24, 60, 84, 85). However, the delivery of sufficiently potent concentrations of nanoparticles to the tumor to boost RT at clinical beam configurations (eg, 6 MV) is limited by physiological barriers, especially when administered intravenously (7). These physiological barriers in the tumor vasculature are a problem that is particularly pronounced in

cancers like pancreatic cancer (65). The use of SRBs could overcome these limitations and therefore is an active area of research for applications in radiation boosting with minimal toxicities to normal tissue.

Furthermore, some nanoparticles like GNPs or gadolinium nanoparticles can serve as multifunctional platforms or theranostic agents (ie, providing imaging contrast while also enhancing therapy). The potential of nanoparticles to provide imaging contrast may benefit treatment planning during nanoparticle-aided RT or in image-guided drug-delivery, inasmuch as nanoparticles could also selectively deliver therapeutic agents (86). The development of quantitative in vivo imaging methods for image-guided drug delivery is an area of research that could advance the ability to guide, monitor, and evaluate drug delivery across different physical and physiological scales so as to interrogate biodistribution and therapeutic response. There may also be utility in the combination of SRBs with radioisotopes for imaging and therapeutic delivery, as shown with some nanoparticles (87). Research in this direction could allow for noninvasive imaging during local delivery of the therapeutic payload loaded on nanoparticles to tumors while providing microanatomic and functional imaging feedback during treatment.

Leveraging the abscopal effect

Another intrinsic limitation to RT is that it is generally prescribed for treatment of localized disease. However, in 1953, Mole (88) described the abscopal effect whereby localized RT at 1 site may lead to regression of metastatic cancer at distant sites that were not irradiated. This potent effect could extend the use of RT from treating localized disease to treat metastatic or systemic disease. In 2004, Demaria et al (56) originally connected the abscopal effect with mechanisms involving the immune system.

More recent studies corroborate these findings that the abscopal effect is mediated by the immune system (89). However, the effect is rare because immune-tolerance mechanisms may hamper the development of therapeutically effective responses (88). A combination of RT and immunoadjuvants (Fig. 6) could overcome immune suppression and lead to vigorous antitumor T cell responses (89, 90). However, although such combinations of RT and immunoadjuvants are promising, their systemic and overlapping toxicities are a major obstacle reported in many studies (89). The use of SRBs proffers an innovative approach that would minimize such toxicities and enable slow/sustained in-situ delivery of nanoparticles with immunoadjuvants, which is expected to enable greater therapeutic efficacy (21). Early research and previous work from vaccine studies (Fig. 3) suggests that such an approach could indeed be more effective (68). Investigations in this area are therefore also ongoing for leveraging the abscopal effect more effectively.

The modus operandi for such an approach is illustrated in Figure 7 with potential for the SRB to be activated either by the tumor microenvironment, sound, heat, or electromagnetic waves or other stimuli for controlled in-situ release of the payload directly into the tumor. The release kinetics of the SRB can be customized or programmed for sustained release (blue curve) compared with repeated injections (9). The use of SRBs could thus be optimized to significantly enhance local and metastatic tumor cell kill during RT with minimal toxicity or side effects for patients. Such an innovative approach could transform RT practice extending the use of RT to treatment of metastatic disease and therefore to many more patients.

Reducing treatment time or health care costs

With increasing advances in RT from conformal to IGRT and proton therapy, RT is perceived by many as an

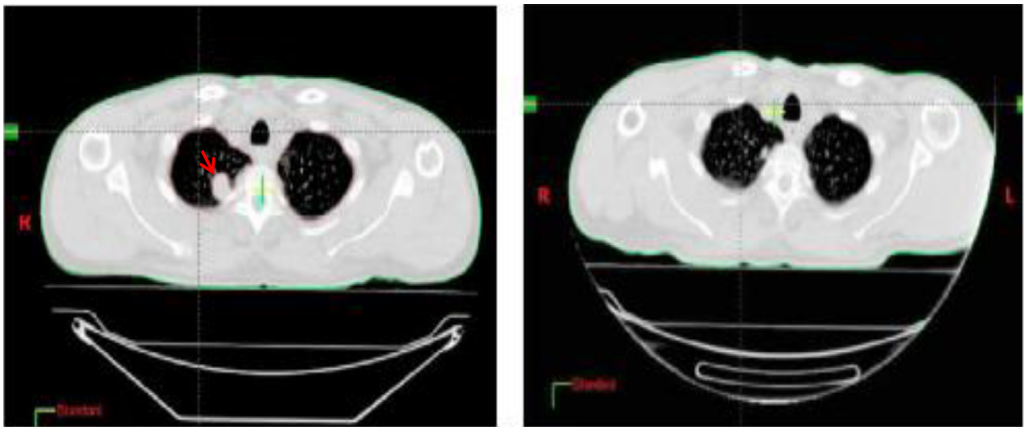

Fig. 6. Abscopal effect in cancer patient by use of immunoadjuvants. Left, computed tomographic view of an apical lesion (arrow) not included in the radiation field. Right, same lesion 2 months after treatment of a different, caudal metastasis with radiation and the immunoadjuvant Granulocyte macrophage colony-stimulating factor (GM-CSF) (reference Lancet Oncol. 2009 July; 10(7): 718-726).

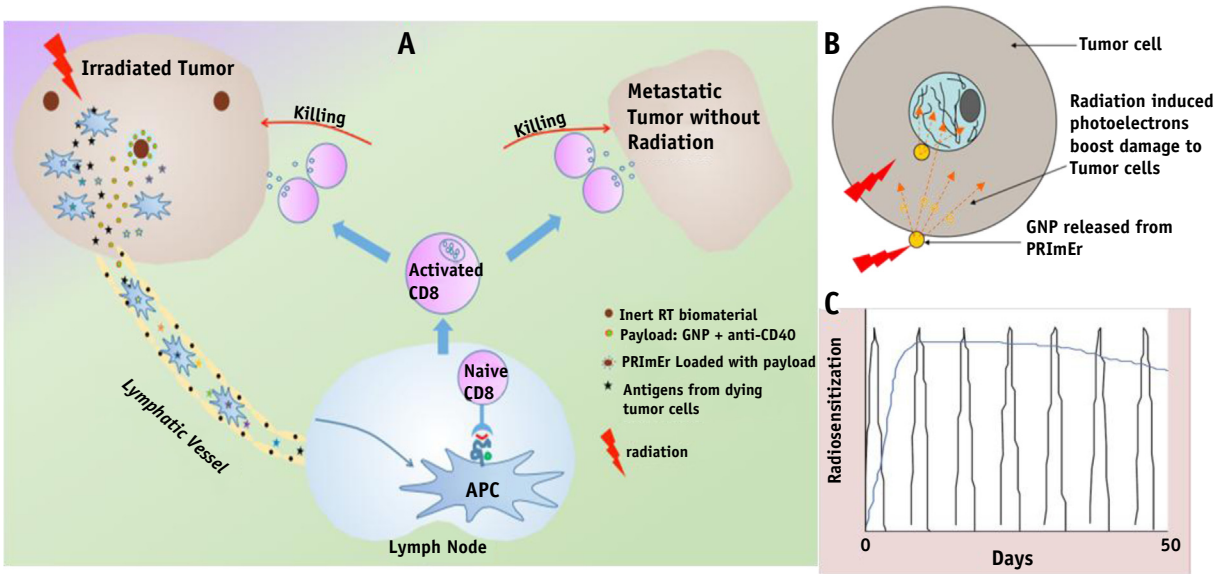

Fig. 7. (A) New radiation therapy approach using smart radiation therapy biomaterial (PRImEr) loaded with gold nanoparticles (GNPs) and immunoadjuvant. The SRB will simply replace current routinely used inert radiation therapy biomaterials. (B) GNPs amplify local damage to tumor cells during radiation therapy. (C) Sustained slow release of immunoadjuvant to prime metastatic cell kill expected to be more effective than repeated injections (black curve with multiple peaks). *Abbreviation:* APC = antigen presenting cells.

expensive treatment modality, especially in resource-poor settings with weak health care systems. Today, two-thirds of cancer deaths occur in low-income and middle-income countries (LMICs). A drastic shortage of RT infrastructure in LMICs means that up to 70% of cancer patients in LMICs who may benefit from radiation medicine do not receive this essential curative or pain-relieving treatment. The International Atomic Energy Agency has been working to bring together RT equipment suppliers and RT users in developing countries to help make RT infrastructure more affordable or accessible to LMIC populations.

Given the vast disparities in disease burden between developed countries and LMICs, researchers are also working to accelerate the production of new technologies that may help to bridge this gap. The National Cancer Institute Center for Global Health and other organizations are now also increasing funding mechanisms to promote the development of lower-cost technologies that can make treatments, including RT, more affordable in LMICs. Affordability is inextricably linked to value, quality, efficiency, equity, and accessibility. To this end, the use of SRBs, which could boost RT, is being considered as an approach to enable hypofractionation, which could in turn potentially reduce treatment times or health care costs. The use of SRBs to leverage the abscopal effect in treating metastatic disease is also an attractive approach that could benefit many more patients and increase survival, allowing for greater return on investment, especially for state-sponsored RT centers, common in LMICs (91). This would yield major benefits in developing countries, where patients often present with cancer that is already at the late stages. Partnerships or collaborations will be very important in this effort to develop lower cost-technologies or adaptations of them that are more affordable. Pioneering efforts developing the use of SRBs in this direction are currently in progress (19). Here, instead of treating patients with many fractions, these SRBs could replace currently used RT biomaterials (eg, fiducials and spacers) for highly localized radiation boosting with minimal toxicity to healthy tissues (7). The potential to hypofractionate or reduce treatment times could avail patients in LMIC countries because the wait times can be unacceptably long for many patients after they have trekked hundreds of miles to an RT center. Prolonged waiting times for receiving treatment can even affect the timing between the administration of RT doses, hence compromising clinical outcomes and treatment effectiveness. In carrying out research for SRB technology applications in lower-cost RT, collaborations with developing country partners could be highly beneficial.

Challenges and Opportunities for Future Research and Development

Despite the potential of SRBs, many challenges remain with opportunities for research and development. Overall, the challenges and opportunities for further research and development described in other reviews of nanoparticle-aided RT (7) also apply in the development of SRBs. A major advantage is that physiological barriers before

nanoparticles reach the tumor or penetrate the tumor subvolume could be obviated using SRBs.

One area requiring more work includes optimizing current SRB prototypes. Work still needs to be done to optimize the release and space-time biodistribution profiles, interactions (cellular uptake and retention) of payloads (eg, of nanoparticles including at the subcellular level as a function of design parameters such as payload concentration, nanoparticle size and functionalization, polymer type or weight). Various experimental approaches such as nanoscopy (92), electron microscopy, cytometry by time-of-flight (CyTOF), magnetic resonance imaging, and computed tomographic imaging will avail such efforts. The establishment of space-time biodistribution profiles/look-up tables, optimized nanoparticle interaction, uptake, localization, and retention with cells would be a significant milestone. It is anticipated that the intratumoral distribution of the released payloads will not be uniform. However, it may be more important to have a sufficiently potent distribution of the released payload in the tumor subvolume for dose painting or for priming a robust T cell response. Detailed studies using different polymer types/weight or nanoparticle size and functionalization would allow optimization of distribution. The results of such work should provide more robust data or information on the optimal material parameters and the distribution and interaction of nanoparticles. This could also allow more effective modeling of the biodistribution, benefiting further research and treatment planning efforts toward clinical translation.

Another active area of research is to further elucidate the mechanisms of interactions of SRBs and associated payload with the tumor microenvironment and cells for optimizing therapeutic response. This could involve the use of different nanoparticle types, including those with chemotherapy or immunoadjuvant payloads. More research to optimize the synergistic interactions of nanoparticles with RT photons and dosing, and refining computer models to predict or maximize outcomes, is needed. Recent work (24), which shows that subcellular targeting increases the radiosensitization effect of nanoparticles, suggests the need to further optimize radiosensitization efficiency and enhanced understanding of mechanisms for maximizing therapeutic efficacy.

Another attractive area is the development of imaging and treatment planning software tools when using SRBs. Based on experimental findings and elucidation of mechanisms availing the clinical application of SRBs, such tools could include treatment algorithms that can be subsequently evaluated or optimized in a clinical setting. The tools could also be used for further research and education purposes.

Another challenge highlighted from previous work (15, 71) is that the clinical translation of smart biomaterials is not straightforward. This could be explained by the usual sophisticated designs of such biomaterials, which makes the development more complex, especially in terms of the manufacturing process, reproducibility, and quality control. Furthermore, nontrivial optimizations or improvements are often required to translate stimulus-responsive biomaterials from preclinical experimental models to the bedside. In particular, endogenous stimuli may be hard to control because they may vary from patient to patient (such as the pH of a tumor). Hence, systems responsive to external stimuli appear more feasible if issues resulting from tissue-penetration depth of the stimulus and its focusing to avoid damage to healthy tissues are addressed. RT biomaterials responsive to RT photons or ultraviolet light generated by Cerenkov radiation may also be worth investigating. Interestingly, smart polymeric biomaterials made of PLGA and chitosan are well known and characterized and therefore are a promising reason why most SRBs under development use these polymers. As a general rule, the simpler and easier the development of a smart biomaterial is, the better are its chances of reaching the clinic.

Going forward, the prospect of increased collaborations to extend RT to systemic therapy through the abscopal effect is exciting and attractive, and SRBs provide an opportunity for further research and development in combining RT and immunotherapy by such an approach. SRBs slowly eluting immunotherapy agents may provide a means of achieving greater effectiveness and of overcoming systematic toxicity resulting from intravenous administration, and also increasing accumulation of these agents at the tumor site or draining lymph nodes because the agents are delivered locally within tumor (93). Therefore, there will likely be a growth in the number of studies using different immunoadjuvants delivered with SRBs during RT. In general, an advantage of using SRBs for in-situ delivery of payloads is that it could minimize toxicity in comparison with intravenous or systemic delivery of such payloads. However, more studies are needed to cogently establish this possibility.

Irradiation of a volume of tissue leads to a change in the surface antigens of the blood vessels (several of the Intercellular Adhesion Molecules are upregulated). Targeting of nanoparticles may be improved when a tumor-containing volume of tissue is preirradiated, nanoparticles coupled to antibodies versus the upregulated surface antigens are injected intravenously, and these nanoparticles get (more or less) selectively attached to the preirradiated vessel walls close to the tumor. By this process, the local concentration is higher, and in addition to the enhanced permeability and retention effect, the interstitial/intracellular concentration of the nanoparticles is selectively increased.

Another potential direction of research in SRBs is in the in-situ labeling of cancer cells. SRBs could be used to label cancer cells in situ, right at the source tumor. A factor motivating research in this direction is cancer metastasis, which accounts for over 90% of cancer-associated suffering and death (94), involving circulating tumor cells (CTCs) shed by the primary tumor into the blood vessels or lymph nodes, especially after the start of fractionated RT (95). The detection of such CTCs is valued in cancer management to

monitor disease progression, tumor aggressiveness, and treatment response. However, current methods to detect CTCs are limited by the scarcity of the CTCs in blood (96). Only 1 to 10 CTCs are present in 1 mL of blood, which contains millions of white blood cells and almost a billion red blood cells (97). As such, the direct detection of metastatic or rare CTCs remains a formidable technological problem when currently available methods are used. For example, although the detection of CTCs in lymph nodes is an attractive approach in diagnosing the aggressiveness of a tumor, the methods to do so are mostly suboptimal and are accompanied by significant morbidities. The approach to labeling tumor cells in situ using SRBs has potential to significantly enhance labeling effectiveness, detection, and isolation efficiency of CTCs, and noninvasive nodal status assessment for cancer patients.

Some, like Baumann et al (98), suggest that with recent technological advances in RT, new research and development should focus less on improving the dose distribution and more on reducing treatment times (99). If the use of SRBs for radiation boosting or priming the abscopal effect can lead to hypofractionation, the anticipated benefit of reducing treatment times would resonate with this suggestion. Reducing the treatment times could also help with reducing costs. This is supported by recent studies (100) showing that use of hypofractionation results in a significant reduction in the financial costs associated with treating breast cancer patients. In general, lower-cost technologies have the potential to change the lives of millions of individuals living in LMICs and other resource-poor settings. With the emerging global radiation oncology movement, physicists, biologists, mathematicians, chemists, engineers, physicians, and other scientists will likely also now focus on developing lower-cost technologies or adaptations of current technologies that can make RT more affordable and accessible in such settings.

Indubitably, other potential applications will emerge from the development of SRBs. Those highlighted in these review may not be comprehensive, but they provide a useful reference, especially for cross-disciplinary collaborations toward the development and translation of such technologies. Creating opportunities and training programs for cross-disciplinary research for individuals engaged in these areas should also be encouraged to significantly accelerate work on SRBs, facilitate clinical translation, and create new applications.

In conclusion, biomaterials have already had an enormous impact on health care, as seen in myriad prosthetic and drug delivery device applications. Research on SRBs proffers a compelling rationale for upgrading the currently used inert RT biomaterials to smarter materials and for developing stimuli-responsive nanoparticles that can deliver additional therapy enhancement benefits during RT. The anticipated range of applications for such smart devices could lead to increased survival and quality of life for cancer patients, and extend the benefits of RT to many more patients, including those in LMICs. Cross-disciplinary and international collaborations could highly avail the development of SRBs for future applications.

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