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Designing Hydrogels for On-Demand Therapy

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CONSPECTUS:

Systemic administration of therapeutic agents has been the preferred approach to treat most pathological conditions, in particular for cancer therapy. This treatment modality is associated with side effects, off-target accumulation, toxicity, and rapid renal and hepatic clearance. Multiple efforts have focused on incorporating targeting moieties into systemic therapeutic vehicles to enhance retention and minimize clearance and side effects. However, only a small percentage of the nanoparticles administered systemically accumulate at the tumor site, leading to poor therapeutic effcacy. This has prompted researchers to call the status quo treatment regimen into question and to leverage new delivery materials and alternative administration routes to improve therapeutic outcomes. Recent approaches rely on the use of local delivery platforms that circumvent the hurdles of systemic delivery. Local administration allows delivery of higher "effective" doses while enhancing therapeutic molecules' stability, minimizing side effects, clearance, and accumulation in the liver and kidneys following systemic administration. Hydrogels have proven to be highly biocompatible materials that allow for versatile design to afford sensing and therapy at the same time. Hydrogels' chemical and physical versatility can be exploited to attain disease-triggered in situ assembly and hydrogel programmed degradation and consequent drug release, and hydrogels can also serve as a biocompatible depot for local delivery of stimuli-responsive therapeutic cargo. We will focus this Account on the hydrogel platform that we have developed in our lab, based on dendrimer amine and dextran aldehyde. This hydrogel is disease-responsive and capable of sensing the microenvironment and reacting in a graded manner to diverse pathologies to render different properties, including tissue adhesion, biocompatibility, hydrogel degradation, and embedded drug release profile. We also studied the degradation kinetics of our stimuli-responsive materials in vivo and analyzed the in vitro conditions under which in vitro−in vivo correlation is attained. Identifying key parameters in the in vivo microenvironment under healthy and disease conditions was key to attaining that correlation. The adhesive capacity

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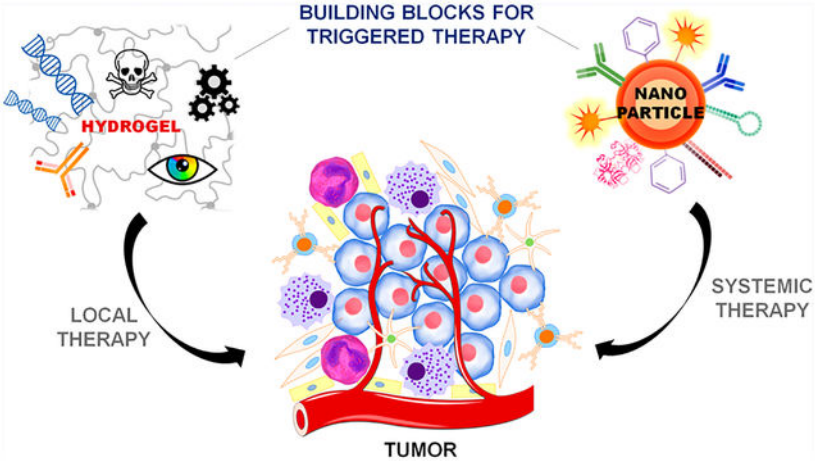
of our dendrimer−dextran hydrogel makes it optimal for localized and sustained release of embedded drugs. We demonstrated that it affords the delivery of a range of therapeutics to combat cancer, including nucleic acids, small molecules, and antibody drugs. As a depot for local delivery, it allows a high dose of active biomolecules to be delivered directly at the tumor site. Immunotherapy, a recently blooming area in cancer therapy, may exploit stimuli-responsive hydrogels to impart systemic effects following localized therapy. Local delivery would enable release of the proper drug dose and improve drug bioavailability where needed at the same time creating memory and exerting the therapeutic effect systemically. This Account highlights our perspective on how local and systemic therapies provided by stimuli-responsive hydrogels should be used to impart more precise, long-lasting, and potent therapeutic outcomes.

Graphical Abstract



INTRODUCTION

Drugs or drug combinations are systemically administered to inhibit tumor growth and induce cancer cell death. Never- theless, only a small portion of the intravenously administered drugs can reach their parenchymal target in vivo,[1] while the remaining circulating drug may harm normal tissues and result in undesired toxicity. To raise the effcacy per dose and reduce the side effects, drug carriers are used to surmount biological barriers and achieve enhanced uptake in cancer cells. Despite the advances in nanotechnology, systemic delivery of nano-particles still confronts challenges such as potential side effects, low drug dose at the target site, and low circulation time, which limit the translational potential of nanomedicine to the clinic. Therefore, it is imperative to re-examine the available delivery platforms and determine the optimal administration route on a case-by-case basis.

Hydrogels are cross-linked three-dimensional networks that can serve as effective drug depots to afford local drug delivery and respond to endogenous or exogenous triggers. Stimuli-responsive hydrogels can effciently overcome the hurdles of systemic delivery described above. Furthermore, they can be engineered to evoke both systemic and localized therapeutic responses, empowering them with great translational potential (Figure 1). This

Account will focus on recent endeavors in studying the role of hydrogels in generating localized therapeutic effects and our perspective on their use as local therapeutic platforms to elicit systemic effects.

SYSTEMIC DELIVERY TO ELICIT LOCAL EFFECTS: THE CURRENT GOLD STANDARD

Potent chemotherapeutic drugs are effective cancer cytotoxic agents but are distributed nonspecifically throughout the body, affecting both normal and cancer cells. This lack of cell and tissue specificity reduces drug bioavailability and effcacy.[2,3] Nanotechnology has enabled more effective drug delivery and targeting. Appropriate particle design[4] ffmaterial type, particle size, charge, functional groups, and targeting moietiesff

provides “nanomedicines” that can circulate longer in the blood, passively overcome biological barriers, accumulate in tumors, actively target cancer cells, and sense biomolecules for triggered cargo release.[5,6] Passive targeting exploits the leaky vasculature and the poor lymphatic drainage of the tumor microenvironment, leading to the enhanced permeability and retention (EPR) effect.[7,8] Alternatively, active targetingffin which targeting ligands (i.e., antibodies, peptides) are conjugated to the surface of nanoparticles[4] ffis used to recognize and bind to tumor tissue through cellular surface receptors that are overexpressed on the tumor cells (Figure 2).[9] A variety of ligands, such as antibody therapeutics,[10,11] aptamers, DNA or RNA oligonucleotides with receptor-binding capabilities,[12–14] folic acid, [15,16] EGF,[17,18] and transferrin,[19] have demonstrated increased accumulation in the tumor milieu, greater intracellular accumulation, and enhanced therapeutic potency.[20] While these targeting ligands may help in improving uptake in cancer cells, the challenge of low accumulation at the tumor site remains because of rapid clearance of nanoparticles when they are administered systemically. In fact, recent evidence points to less than 1% tumor accumulation of systemically administered nanoparticles.[21] While systemic treatment is necessary to eliminate metastasis, this approach is suboptimal for treating primary tumors. Eliminating the primary tumor that serves as the “source” for metastasis using chemotherapy drugs, as well as preventing metastasis before its spread by genetically modifying the tumor, [22] can revolutionize patients’ point of care. Local application of a cargo-containing vehicle at the target site might be the method of choice for a multitude of pathologies, as it enables the delivery of a higher “effective” dose while enhancing therapeutic molecules’ stability and minimizing side effects and clearance. In fact, a local therapeutic vehicle opens up new vistas for effective neo-adjuvant therapy, for the treatment of unresectable tumors, and for washout procedure following tumor resection to prevent recurrence.[22–25]

HYDROGELS AS A DEPOT FOR LOCALIZED DRUG DELIVERY

The use of hydrogels as a depot for local delivery of drugs is an approach that has gained momentum in the past decade, particularly when pathology is contained and localized. We have developed a novel class of biodegradable and biocompatible adhesive hydrogels based on amine−aldehyde chemistry.[26]

Aldehydes, provided by dextran macromolecules, react with tissue amines to impart adhesion, while unreacted aldehydes react with the amines on the dendrimer to form the cohesive bulk of the material (Figure 3). The excess, nonreactive dextran aldehyde groups cross-link with the dendrimer amines to reduce the free aldehyde concentration, prevent adhesions to other organs, and form the cohesive bulk of the hydrogel. We have studied how various endogenous triggers affect the hydrogel's morphology and properties in vitro and in vivo.[26,27] We have also investigated the use of this scaffold as a nanoparticle depot for triggered cargo release.[23,24]

Rational hydrogel design that enables sensing of specific cues in the microenvironment can provide in situ hydrogel assembly, triggered hydrogel degradation driving drug release, and triggered drug release from embedded cargo nanoparticles to yield on-demand therapeutic effects (Figure 4). This section will focus on describing our work on tissue- and disease-responsive dendrimer−dextran hydrogels and provide insights as to how to design materials to impart on-demand local therapeutic effects.

Stimuli-Responsive in Situ Cross-Linking of Hydrogels

Multiple efforts have been carried out in the past decade to achieve hydrogels that are responsive to a variety of triggers, such as light[28] and electric fields.[29] However, these triggers rely on external sources and can pose translational limitations. A more clinically relevant approach for in situ material gelation consists of utilizing physiological conditions such as temperature or disease-specific microenvironmental cues as triggers, avoiding additional external steps to trigger their in vivo assembly or disassembly. A novel thermogelling PLGA−PEG− PLGA triblock copolymer exhibited a sol−gel transition with an increase of temperature.[30,31] This temperature-responsive hydrogel was thoroughly studied and optimized to respond to clinically relevant conditions through modification of the molecular weight and the molar mass distribution of the block copolymers[32,33] and the addition of PEG homopolymers.[34] This approach can become even more specific by the design of disease-triggered hydrogels. Recently, Zhang et al.[35] developed a drug delivery hydrogel based on negatively charged ascorbyl palmitate that is capable of spontaneous self-assembly when applied to positively charged inflamed colon tissues and release of drug upon enzymatic degradation. This approach allowed higher drug delivery efficacy and reduced side effects.

Similarly, we exploited the tumor microenvironment characteristics to allow for preferential assembly of our hydrogel to the surface of tumoral tissues.[27] Biochemical analysis of the surface of tumors showed increased amine density, which we correlated with increased collagen production (Figure 5a,b) owing to extracellular matrix (ECM) deposition by cancer cells supporting tumor growth. Because collagen is the most abundant protein in the ECM, comprising over 70% of the proteins present, we were able to correlate the surface amine density with the collagen content. As a result of this increase in ECM production and hence tissue surface amine density, the material−tissue interface was denser (Figure 5c), and the adhesion of dendrimer−dextran to tumoral tissues was 43% higher than that to healthy tissues (Figure 5d), leading to improved interactions at the tissue−material interface. Our hydrogel reacted in a graded manner with tissue surfaces as a function of their tissue

chemistry, as manifested by disease. We also investigated the interaction of our material with inflamed tissues in a colitis model. These tissues are characterized by excessive breakdown of the ECM to allow remodeling, and evidently collagen and amine contents were lower than in healthy tissues, leading to a 58% reduction in the adhesion of the same hydrogel formulation to colitic tissue compared with healthy tissue. By understanding the governing mechanisms associated with inflammation and their effect on tissue chemistry, we were able to tune the formulation of our material to attain comparable adhesion levels in healthy and inflamed tissues, improve tissue−material interactions, and maintain adequate mechanical properties. Understanding the impact of the microenvironment on the material post-implantation is crucial for attaining the desired outcome. It also highlights the importance of developing materials in light of the specific disease microenvironment in which they will be used, as different pathologies present with distinct biological cues to which a given material may respond, affecting its performance.

Stimuli-Responsive Hydrogel Degradation and Drug Release

Controlling the release kinetics of small bioactive molecules from hydrogels remains a challenge because of the high water content and large pore size of hydrogels, often resulting in rapid drug release, known as burst release. Burst release is associated with unpredictable and uncontrolled release kinetics,[36] typically in a much shorter time than the regimen required to treat most pathologies. Several approaches have been developed to minimize burst release and prolong drug delivery time frames. Inclusion of hydrophobic domains, charge interactions, or hydrogen bonds between the hydrogel and the cargo can slow the release, prolonging it to a few days. The injectable hydrogel using human serum albumin (HSA) and tartaric acid derivative (TAD) could deliver doxorubicin over approximately 4 days[37] as a result of electrostatic interactions between positively charged doxorubicin and the negatively charged hydrogel. However, there are still challenging issues regarding the inevitable initial burst release and the inability to control the release kinetics overtime. By chemical conjugation of the therapeutic cargo of interest to the hydrogel, the burst release can be eliminated, and the hydrogel degradation profile would drive the drug release kinetics. On-demand release based on triggered hydrogel degradation in response to pathological cues would afford a drug release profile that is titrated to pathological need. Gajanayake et al.[38] developed a hydrogel for triggered release of the immunosuppressive drug tacrolimus in response to proteolytic enzymes that are overexpressed in inflammation. Complete drug release occurred between 4 to 14 days without apparent burst release, compared with less than 10% drug release in phosphate-buffered saline over 28 days. The release of cross-linked cargo relies on hydrogel depot degradation, and hence, special attention must be placed on the mechanisms and triggers governing it.

We studied dendrimer−dextran degradation as a response to target tissue surface chemistry.[26] We found that the hydrogel microstructure and adhesion strength were altered as a result of interactions of the material with tissue surfaces of varied surface chemistry, as well as the hydrogel degradation profile. Dextran aldehyde reacts with tissue amines and dendrimer amines simultaneously in a competitive manner. For a given material formulation (dendrimer amine content), the higher the amine density on the surface of the tissues, the less material aldehydes will react internally to form a cross-linked network, resulting in more adhesive

chemical bonds and lower hydrogel cross-linking density. This in turn will affect the rate and mode of degradation of the adhesive hydrogel. Surface amine density studies of the three regions of the small intestineffjejunum, duodenum, and ileumffshowed that the ileum had higher amine density compared with the other two regions. When we applied the same fast-degrading formulation to the three regions of the small intestine ex vivo and measured the degradation kinetics, we observed that material degradation was slower upon application to the ileum compared with application to the jejunum and duodenum (Figure 6a). When we analyzed snapshots of the degradation process on the three regions, we observed that, indeed, the bulk of the material degraded faster in the case of the ileum compared with the jejunum and duodenum, while the interface degradation rate was lower (Figure 6b). Because the ileum provides more functional amines for the material, creating more points of interaction between them, the material stability at the interface is enhanced. As a result, embedded drug release profiles would be significantly different depending on the target organ.

The effect of the target organ on material degradation was also investigated in another study involving an enzymatically triggered biodegradable hydrogel composed of cross-linked gelatin.[39] We explored the degradation profile of these hydrogels after subcutaneous, intramuscular, or intraperitoneal implantation in a mouse model. The results showed remarkable differences in degradation profile among these three locations (Figure 7A), which did not correlate with varying concentrations of enzyme (the degradation trigger) in vitro but with the total volume of enzyme solution (Figure 7B,C). Indeed, materials implanted in the intraperitoneal or intramuscular spaces are exposed to higher fluid volumes than those in the subcutaneous space.

Both examples highlighted in this section emphasize the importance of examining target microenvironmental triggers(i.e., tissue type, location, or pathology) affecting in situ assembly, hydrogel degradation, and drug release and taking them into consideration in the design of stimuli-responsive hydrogel depots.

Hydrogel-Embedded Stimuli-Responsive Cargo

An alternative to stimuli-responsive hydrogels would be the use of composite hydrogels doped with stimuli-responsive cargo. We doped the dendrimer−dextran hydrogel with gold nanoparticles decorated with 5-fluorouracil (5-FU)-intercalated hairpin DNA to silence the multidrug resistance protein-1 (MRP1) and reverse the resistance to chemotherapy prior to 5-FU treatment.[24] This approach takes advantage of the ability of certain chemotherapeutic drugs, such as 5-FU, to intercalate into DNA through moderate interaction (binding constant of9.7×10^4) with the nitrogenous bases of the nucleic acid.[40] This interaction becomes weaker when the hairpin opens through hybridization with the complementary target (MRP1 mRNA), allowing simultaneous release of the drug and knockdown of the mRNA encoding the protein responsible for drug resistance. We also incorporated diagnostic capabilities to the system by means of triggered fluorescence emission in response to hybridization with the target MRP1 mRNA. A fluorescence marker, Quasar 705, was conjugated to the end of the hairpin sequence, and a black hole quencher (BHQ2) was conjugated to the surface of the nanoparticle. Without the trigger, the DNA remains in a hairpin conformation and the

BHQ2 quenches the fluorescence of Quasar 705 because of their proximity. When the complementary target is present and the hairpin opens up, the fluorescence tag resides outside the quenching radius of BHQ2 and thus emits fluorescence (Figure 8a). While the hydrogel itself did not exhibit disease-triggered response, the nanobeacons responded to a biological trigger–MRP1–to provide both therapy (drug release and mRNA knockdown leading to tumor size reduction; Figure 8b) and diagnosis (fluorescence signal; Figure 8c). An approximately 90% decrease in luciferase activity (tumor size; Figure 8d) was observed exclusively for the nanobeacons anti-MRP1-loaded with 5-FU-treated tumors compared with nanobeacons nonsense with 5-FU ($n = 5$, $P < 0.005$). Moreover, fluorescence images of the implanted hydrogels revealed, as expected, that the fluorescence signal was OFF at day 0 (2 h after surgery) and turned ON at day 1 (24 h), reaching a maximum intensity for MRP1 and luciferase detection at day 2 (48 h), only for nanobeacons anti-MRP1 with 5-FU (Figure 8e). We also leveraged gold-nanorod-embedded dendrimer− dextran hydrogel to impart thermally triggered release of the antibody drug Avastin from the gold nanorods.[23] The nanorods can convert near-IR radiation into heat and cleave the PEGylated linker that was used to conjugate Avastin to the rods. Avastin release increased with laser exposure duration, suggesting that the release was thermally driven. We elucidated the Avastin release mechanism following irradiation by quantifying the antibody drug and PEG concentrations in the supernatant after nanorod centrifugation and showed that PEG and Avastin remained bound to each other after laser exposure, proving that the drug is released following the cleavage of the PEG−nanorod bond.

These nanoparticles were part of a triple therapy (chemo-, gene, and phototherapy) platform (Figure 9a) using both gold nanorods and nanospheres as carriers to deliver therapeutic molecules, such as antibody drugs (with thermal activation) and siRNAs. The ability to provide multimodal therapy locally in a controlled and triggered manner led to almost complete inhibition of colon tumors that was more pronounced than with either systemic (tail-vein injection) or intratumoral delivery (Figure 9b–d). The local administration of the hydrogel patch doped with the triple-therapy combination resulted in more than 90% tumor shrinkage (Figure 9c), while only 60% and 40% tumor reductions were attained following intratumoral and systemic administration of the same therapy combination, respectively, leading to poor survival increments (Figure 9d). Moreover, systemic nanoparticle administration resulted in nonspecific accumulation in the kidneys, spleen, and liver (Figure 9b). These results provide convincing evidence that the hydrogel patch is instrumental for the achievement of superior therapeutic performance due to high bioavailability of the therapeutic molecules and prolonged cargo release over time.

The field of stimuli-responsive hydrogels has evolved dramatically over the past decade, and multiple novel and original approaches have been proposed to attain local delivery of bioactive molecules for the treatment of local pathology. A question remains as to whether we can use the advantages of local rather than systemic delivery (i.e., sustained and triggered release) to elicit prolonged systemic effects.

HYDROGELS WITH SYSTEMIC EFFECTS: IMMUNOTHERAPY

Localized delivery using hydrogels has become popular in the field of immunotherapy, as hydrogels can provide controlled cell microenvironments for immune cells, enabling the recruitment, expansion, and activation of immune cells ex vivo and in vivo.[41] The choice of materials is dictated by the end use, including biocompatibility, immunogenicity, site of implantation, types of stimuli, and release kinetics. Currently, hydrogels have been utilized in both active and passive immunotherapies (Figure 10).

Active immunotherapy using cancer vaccines is a robust tool that has gained significant research attention. The therapeutic benefit of active immunotherapy lies in the engagement of the host immune system by stimulating immune cells using cancer vaccines to actively recognize and diminish cancer cells. Nanoengineered hydrogels represent an innovative platform for the delivery of antigens to dendritic cells (DCs), which induce T-cell stimulation and B-cell-mediated antibody response, because the mild synthesis conditions required to make these hydrogels and the tunable physicochemical properties allow for effcient encapsulation of immunomodulatory molecules as well as immune cells. DCs can be activated either ex vivo in hydrogels prior to implantation or in vivo by immobilizing stimuli within the gels. Verbeke and Mooney[42] described the development of an injectable alginate hydrogel system to locally enrich DCs in vivo without inducing their maturation or activation. Using the same material, Hori et al.[43] developed self-gelling alginate hydrogels that are capable of carrying and releasing antigen-loaded DCs when injected subcutaneously in mice. Besides DCs, researchers have been seeking to target macrophages because studies have revealed that macrophages may also play a major role as antigen-presenting cells in tumor vaccination.[44] Muraoka et al. developed a cholesteryl pullulan-based hydrogel to deliver peptide antigens to macrophages located in lymph nodes.[45] This hydrogel is immunologically inert and was able to travel to lymph nodes after subcutaneous administration because of its small size, and the antigens were successfully presented to CD8+ cytotoxic T cells.

Passive immunotherapy comprises immune system components having intrinsic antitumor activity. Since the first clinical trial initiated 28 years ago using tumor-infiltrating lymphocytes (TILs) for the treatment of metastatic melanoma,[46] remarkable research efforts have been invested on adoptive cell therapy (ACT), the curative potential of which heavily depends on the administration of allogeneic T cells. Besides TILs, genetically modified tumor-specific T cells, such as T-cell receptor (TCR)-or chimeric antigen receptor (CAR)-transduced T cells, have been developed to overcome the limitation of TIL expansion and augment ACT-mediated immunotherapeutic responses against various types of cancer.[47] Compared with systemic delivery of T cells, which can possibly cause their loss at noncancerous sites of inflammation, localized administration into tumor sites using hydrogels offers improved delivery effciency and release of T cells in a sustained manner. Elias et al.[48] investigated the feasibility of a thermosensitive, amine-reactive oligo(ethylene glycol) methacrylate-based hydrogel as a T-cell carrier. Monette et al.[49] developed an injectable thermogel based on chitosan, a widely used natural polymer, with the purpose of encapsulating, expanding, and delivering cytotoxic T cells.

THE FUTURE OF HYDROGELS IN CANCER THERAPY

Despite the rapid advances in nanotechnology and drug discovery, the effcacy of systemic cancer therapies in the clinic remains disappointing. Only a small dose of the systemically administered drugs reaches the tumor site, resulting in suboptimal primary tumor treatment, which is also the source for metastasis. The development of hydrogels as drug delivery platforms offers new opportunities for better therapeutic schemes. Hydrogels that can respond specifically to tumor cells can enhance cell selectively and further reduce side effects. Recently, researchers have begun to explore the potential of hydrogels in a wide range of immunotherapy applications, utilizing this local platform to elicit systemic effects. Safety issues related to the potential side effects and the lack of consistent durable responses highlight the complexity of the process of properly directing and activating immune cells in a predictive and controllable manner.

In the future, the combination of systemic and local therapeutic modalities that exploits triggered release by unique stimuli-responsive hydrogel platforms may act as a new paradigm of cancer therapy. Materials that act in a graded manner based on patient-need by responding to specific tumor cues that trigger drug release may permit the development of a “magic peel” that would be therapeutically silent unless triggered. In that way, the peel may contain different types of chemotherapy drugs and genes that may become active in one patient and not the other, providing the most appropriate therapy in each clinical scenario.

Biographies

Dr. Nuria Oliva received her Ph.D. in Medical Engineering and Medical Physics (MEMP) at the Harvard−MIT Division of Health Sciences and Technology (HST), focused on the development of a novel adhesive hydrogel and its use as a model platform to understand how disease microenvironment affects material performance and how to leverage those cues to attain tumor-cell-selective delivery of chemotherapy in a local and sustained manner. Currently she is a T32 postdoctoral fellow within the Organ Design and Engineering Training Program (ODET) at Brigham and Women’s Hospital (Harvard Medical School). Her current research interests lie in understanding patient-derived tumor microenvironments to improve translational capabilities of drug delivery platforms.

Dr. João Conde received his Ph.D. in Biotechnology from the New University of Lisbon under the European Consortium NanoScieE^{+}–NANOTRUCK for the development of multifunctional gold nano-particles for in vivo gene silencing. Currently he is a Marie Curie Early-Stage Career Fellow at the Massachusetts Institute of Technology, Harvard−MIT Division for Health Sciences and Technology and in School of Engineering and Materials Science, Queen Mary University of London. His scientific interests are focused on creating smart and potent therapeutic and diagnosis platforms for cancer using multifunctional nanomaterials and scaffolds for tumor targeting, gene therapy, hyperthermia, and drug delivery.

Dr. Kui Wang received his dual Ph.D. in Materials Science and Engineering and Nanotechnology and Molecular Engineering from the University of Washington, where his

research focused on the design of multifunctional nanomaterials to improve cancer gene therapy. Currently he is a postdoctoral research fellow at Brigham and Women's Hospital (Harvard Medical School) and Massachusetts Institute of Technology, and his research interests lie in the design of smart multifunctional biomaterials for controlled drug delivery and cancer immunotherapy.

Prof. Natalie Artzi is an Assistant Professor of Medicine at Brigham and Women's Hospital, Harvard Medical School. She is a Principal Research Scientist at the Institute for Medical Engineering and Science at MIT and an Associate Member of the Broad Institute of Harvard and MIT. Leveraging materials science, chemistry, imaging, and biology, Dr. Artzi's group is dedicated to studying basic mechanisms that control materials' function postimplantation to enable the rational design of medical devices and therapies to improve human health. Her work has covered diverse areas of materials, including cell-seeded scaffolds for vascular healing, nanocomposite materials for orthopedic applications and cancer theranostics, and injectable materials for tissue regeneration. Dr. Artzi pioneered the basic understanding of tissue− biomaterial interactions that has enabled her lab to drive the design of a variety of tissue-responsive materials− materials that exploit specific tissue microenvironmental cues that are altered in the face of disease to provide triggered therapy when and where needed.

REFERENCES

(1). Li KCP; Pandit SD; Guccione S; Bednarski MD Molecular Imaging applications in nanomedicine. Biomed. Microdevices 2004, 6, 113–116. [PubMed: 15320632]

(2). Bae YH; Park K Targeted drug delivery to tumors: Myths, reality and possibility. J. Controlled Release 2011, 153, 198–205.

(3). Devadasu VR; Bhardwaj V; Kumar MNVR Can Controversial Nanotechnology Promise Drug Delivery? Chem. Rev 2013, 113, 1686–1735. [PubMed: 23276295]

(4). Conde J; Dias JT; Grazu V; Moros M; Baptista PV; de la Fuente JM Revisiting 30 years of biofunctionalization and surface chemistry of inorganic nanoparticles for nanomedicine. Front. Chem 2014, 2, 48. [PubMed: 25077142]

(5). Chithrani DB Nanoparticles for improved therapeutics and imaging in cancer therapy. Recent Pat. Nanotechnol 2010, 4, 171–180. [PubMed: 20618149]

(6). Nie S Biomedical nanotechnology for molecular imaging, diagnostics, and targeted therapy. Conf. Proc. IEEE Eng. Med. Biol. Soc 2009, 2009, 4578–4579. [PubMed: 19963842]

(7). Gil PR; Parak WJ Composite nanoparticles take aim at cancer. ACS Nano 2008, 2, 2200–2205. [PubMed: 19206383]

(8). Conde J; Doria G; Baptista P Noble metal nanoparticles applications in cancer. J. Drug Delivery 2012, 2012, 751075.

(9). Bao CC; Conde J; Polo E; del Pino P; Moros M; Baptista PV; Grazu V; Cui DX; de la Fuente JM A promising road with challenges: where are gold nanoparticles in translational research? Nanomedicine 2014, 9, 2353–2370. [PubMed: 25413854]

(10). Conde J; Bao CC; Cui DX; Baptista PV; Tian FR Antibody-drug gold nanoantennas with Raman spectroscopic fingerprints for in vivo tumour theranostics. J. Controlled Release 2014, 183, 87–93.

(11). Hughes B Monoclonal antibodies - Expanding the mAb pool. Nat. Rev. Drug Discovery 2008, 7, 561–561.

(12). Conde J; Ambrosone A; Sanz V; Hernandez Y; Marchesano V; Tian FR; Child H; Berry CC; Ibarra MR; Baptista PV; Tortiglione C; de la Fuente JM Design of Multifunctional Gold

Nanoparticles for In Vitro and In Vivo Gene Silencing. ACS Nano 2012, 6, 8316–8324. [PubMed: 22882598]

(13). Shangguan D; Li Y; Tang ZW; Cao ZHC; Chen HW; Mallikaratchy P; Sefah K; Yang CYJ; Tan WH Aptamers evolved from live cells as effective molecular probes for cancer study. Proc. Natl. Acad. Sci. U. S. A 2006, 103, 11838–11843. [PubMed: 16873550]

(14). Conde J; Rosa J; de la Fuente JM; Baptista PV Gold-nanobeacons for simultaneous gene specific silencing and intracellular tracking of the silencing events. Biomaterials 2013, 34, 2516–2523. [PubMed: 23312904]

(15). Yuan Y; Zhang J; An LN; Cao QJW; Deng Y; Liang GL Oligomeric nanoparticles functionalized with NIR-emitting CdTe/CdS QDs and folate for tumor-targeted imaging. Biomaterials 2014, 35, 7881–7886. [PubMed: 24952975]

(16). Low PS; Henne WA; Doorneweerd DD Discovery and development of folic-acid-based receptor targeting for Imaging and therapy of cancer and inflammatory diseases. Acc. Chem. Res 2008, 41, 120–129. [PubMed: 17655275]

(17). Shimada T; Ueda M; Jinno H; Chiba N; Wada M; Watanabe J; Ishihara K; Kitagawa Y Development of Targeted Therapy with Paclitaxel Incorporated into EGF-conjugated Nanoparticles. Anticancer Res 2009, 29, 1009–1014. [PubMed: 19414339]

(18). Gao J; Xia Y; Chen HW; Yu YS; Song JJ; Li W; Qian WZ; Wang H; Dai JX; Guo YJ Polymer-lipid hybrid nanoparticles conjugated with anti-EGF receptor antibody for targeted drug delivery to hepatocellular carcinoma. Nanomedicine 2014, 9, 279–294. [PubMed: 23721168]

(19). Dixit S; Novak T; Miller K; Zhu Y; Kenney ME; Broome AM Transferrin receptor-targeted theranostic gold nanoparticles for photosensitizer delivery in brain tumors. Nanoscale 2015, 7, 1782–1790. [PubMed: 25519743]

(20). Sakurai Y; Kajimoto K; Hatakeyama H; Harashima H Advances in an active and passive targeting to tumor and adipose tissues. Expert Opin. Drug Delivery 2015, 12, 41–52

(21). Wilhelm S; Tavares AJ; Dai Q; Ohta S; Audet J; Dvorak HF; Chan WCW Analysis of nanoparticle delivery to tumours. Nat. Rev. Mater 2016, 1, 16014.

(22). Gilam A; Conde J; Weissglas-Volkov D; Oliva N; Friedman E; Artzi N; Shomron N Local microRNA delivery targets Palladin and prevents metastatic breast cancer. Nat. Commun 2016, 7, 12868. [PubMed: 27641360]

(23). Conde J; Oliva N; Zhang Y; Artzi N Local triple-combination therapy results in tumour regression and prevents recurrence in a colon cancer model. Nat. Mater 2016, 15, 1128–1138. [PubMed: 27454043]

(24). Conde J; Oliva N; Artzi N Implantable hydrogel embedded dark-gold nanoswitch as a theranostic probe to sense and overcome cancer multidrug resistance. Proc. Natl. Acad. Sci. U. S. A 2015, 112, E1278–E1287. [PubMed: 25733851]

(25). Conde J; Oliva N; Atilano M; Song HS; Artzi N Self-assembled RNA-triple-helix hydrogel scaffold for microRNA modulation in the tumour microenvironment. Nat. Mater 2016, 15, 353–363. [PubMed: 26641016]

(26). Oliva N; Shitreet S; Abraham E; Stanley B; Edelman ER; Artzi N Natural tissue microenvironmental conditions modulate adhesive material performance. Langmuir 2012, 28, 15402–15409. [PubMed: 23046479]

(27). Oliva N; Carcole M; Beckerman M; Seliktar S; Hayward A; Stanley J; Parry NM; Edelman ER; Artzi N Regulation of dendrimer/dextran material performance by altered tissue micro-environment in inflammation and neoplasia. Sci. Transl. Med 2015, 7, 272ra11.

(28). Haines LA; Rajagopal K; Ozbas B; Salick DA; Pochan DJ; Schneider JP Light-activated hydrogel formation via the triggered folding and self-assembly of a designed peptide. J. Am. Chem. Soc 2005, 127, 17025–17029. [PubMed: 16316249]

(29). Lu Q; Bai S; Ding Z; Guo H; Shao Z; Zhu H; Kaplan DL Hydrogel Assembly with Hierarchical Alignment by Balancing Electrostaic Forces. Adv. Mater. Interfaces 2016, 3, 1500687.

(30). Yu L; Chang GT; Zhang H; Ding JD Injectable block copolymer hydrogels for sustained release of a PEGylated drug. Int. J. Pharm 2008, 348, 95–106. [PubMed: 17825508]

(31). Yu L; Zhang Z; Zhang H; Ding J Mixing a sol and a precipitate of block copolymers with different block ratios leads to an injectable hydrogel. Biomacromolecules 2009, 10, 1547–1553. [PubMed: 19385649]

(32). Chen L; Ci T; Li T; Yu L; Ding J Effects of Molecular Weight Distribution of Amphiphilic Block Copolymers on Their Solubility, Micellization, and Temperature-Induced Sol–Gel Transition in Water. Macromolecules 2014, 47, 5895–5903.

(33). Chen L; Ci T; Yu L; Ding J Effects of Molecular Weight and Its Distribution of PEG Block on Micellization and Thermogellability of PLGA–PEG–PLGA Copolymer Aqueous Solutions. Macro-molecules 2015, 48, 3662–3671.

(34). Zhang H; Yu L; Ding J Roles of Hydrophilic Homopolymers on the Hydrophobic-Association-Induced Physical Gelling of Amphiphilic Block Copolymers in Water. Macromolecules 2008, 41, 6493–6499.

(35). Zhang S; Ermann J; Succi MD; Zhou A; Hamilton MJ; Cao B; Korzenik JR; Glickman JN; Vemula PK; Glimcher LH; Traverso G; Langer R; Karp JM An inflammation-targeting hydrogel for local drug delivery in inflammatory bowel disease. Sci. Transl. Med 2015, 7, 300ra128.

(36). Huang X; Brazel CS On the importance and mechanisms of burst release in matrix-controlled drug delivery systems. J. Controlled Release 2001, 73, 121–136.

(37). Kakinoki S; Taguchi T; Saito H; Tanaka J; Tateishi T Injectable in situ forming drug delivery system for cancer chemotherapy using a novel tissue adhesive: characterization and in vitro evaluation. Eur. J. Pharm. Biopharm 2007, 66, 383–390. [PubMed: 17240124]

(38). Gajanayake T; Olariu R; Leclere FM; Dhayani A; Yang Z; Bongoni AK; Banz Y; Constantinescu MA; Karp JM; Vemula PK; Rieben R; Vogelin E A single localized dose of enzyme-responsive hydrogel improves long-term survival of a vascularized composite allograft. Sci. Transl. Med 2014, 6, 249ra110.

(39). Artzi N; Oliva N; Puron C; Shitreet S; Artzi S; bon Ramos A; Groothuis A; Sahagian G; Edelman ER In vivo and in vitro tracking of erosion in biodegradable materials using non-invasive fluorescence imaging. Nat. Mater 2011, 10, 704–709. [PubMed: 21857678]

(40). Jangir DK; Charak S; Mehrotra R; Kundu S FTIR and circular dichroism spectroscopic study of interaction of 5-fluorouracil with DNA. J. Photochem. Photobiol., B 2011, 105, 143–148. [PubMed: 21940176]

(41). Singh A; Peppas NA Hydrogels and scaffolds for immunomodulation. Adv. Mater 2014, 26, 6530–6541. [PubMed: 25155610]

(42). Verbeke CS; Mooney DJ Injectable, pore-forming hydrogels for in vivo enrichment of immature dendritic cells. Adv. Healthcare Mater 2015, 4, 2677–2687.

(43). Hori Y; Winans AM; Huang CC; Horrigan EM; Irvine DJ Injectable dendritic cell-carrying alginate gels for immunization and immunotherapy. Biomaterials 2008, 29, 3671–3682. [PubMed: 18565578]

(44). Hume DA Macrophages as APC and the dendritic cell myth.J. Immunol 2008, 181, 5829–5835. [PubMed: 18941170]

(45). Muraoka D; Harada N; Hayashi T; Tahara Y; Momose F;Sawada S.-i.; Mukai S.-a.; Akiyoshi K; Shiku H Nanogel-based immunologically stealth vaccine targets macrophages in the medulla of lymph node and induces potent antitumor immunity. ACS Nano 2014, 8, 9209–9218. [PubMed: 25180962]

(46). Rosenberg SA; Packard BS; Aebersold PM; Solomon D;Topalian SL; Toy ST; Simon P; Lotze MT; Yang JC; Seipp CA; Simpson C; Carter C; Bock S; Schwartzentruber D; Wei JP; White DE Use of tumor-infiltrating lymphocytes and interleukin-2 in the immunotherapy of patients with metastatic melanoma. N. Engl. J. Med 1988, 319, 1676–1680. [PubMed: 3264384]

(47). Restifo NP; Dudley ME; Rosenberg SA Adoptive immunotherapy for cancer: harnessing the T cell response. Nat. Rev. Immunol 2012, 12, 269–281. [PubMed: 22437939]

(48). Elias PZ; Liu GW; Wei H; Jensen MC; Horner PJ; Pun SH A functionalized, injectable hydrogel for localized drug delivery with tunable thermosensitivity: Synthesis and characterization of physical and toxicological properties. J. Controlled Release 2015, 208, 76–84.

(49). Monette A; Ceccaldi C; Assaad E; Lerouge S; Lapointe R Chitosan thermogels for local expansion and delivery of tumor-specific T lymphocytes towards enhanced cancer immunotherapies. Biomaterials 2016, 75, 237–249. [PubMed: 26513416]

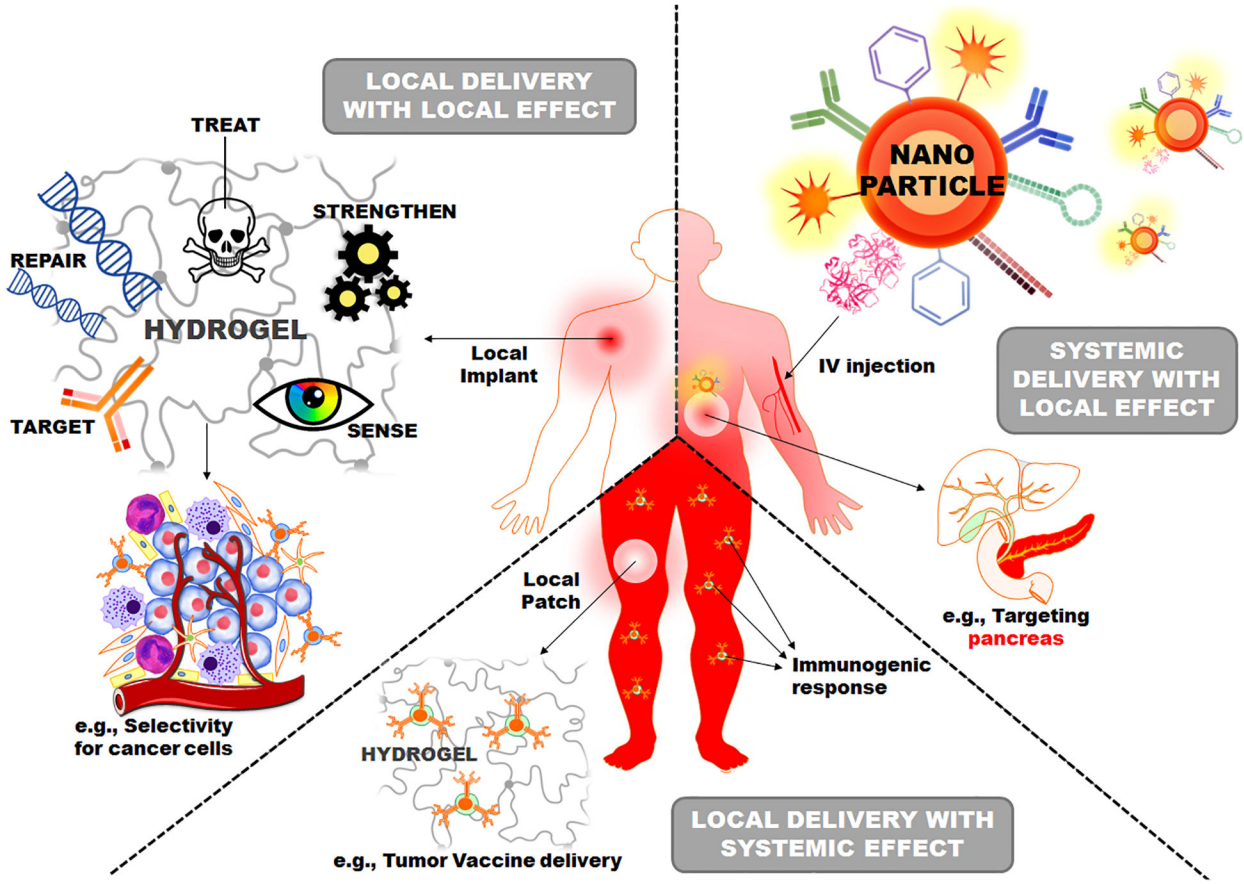


Figure 1.

Potential treatment approaches. The current gold standard, systemic therapy to elicit local effects, is suboptimal in treating primary solid tumors. The use of local platforms to elicit local effects or to induce systemic effects may circumvent the drawbacks of systemic therapies.

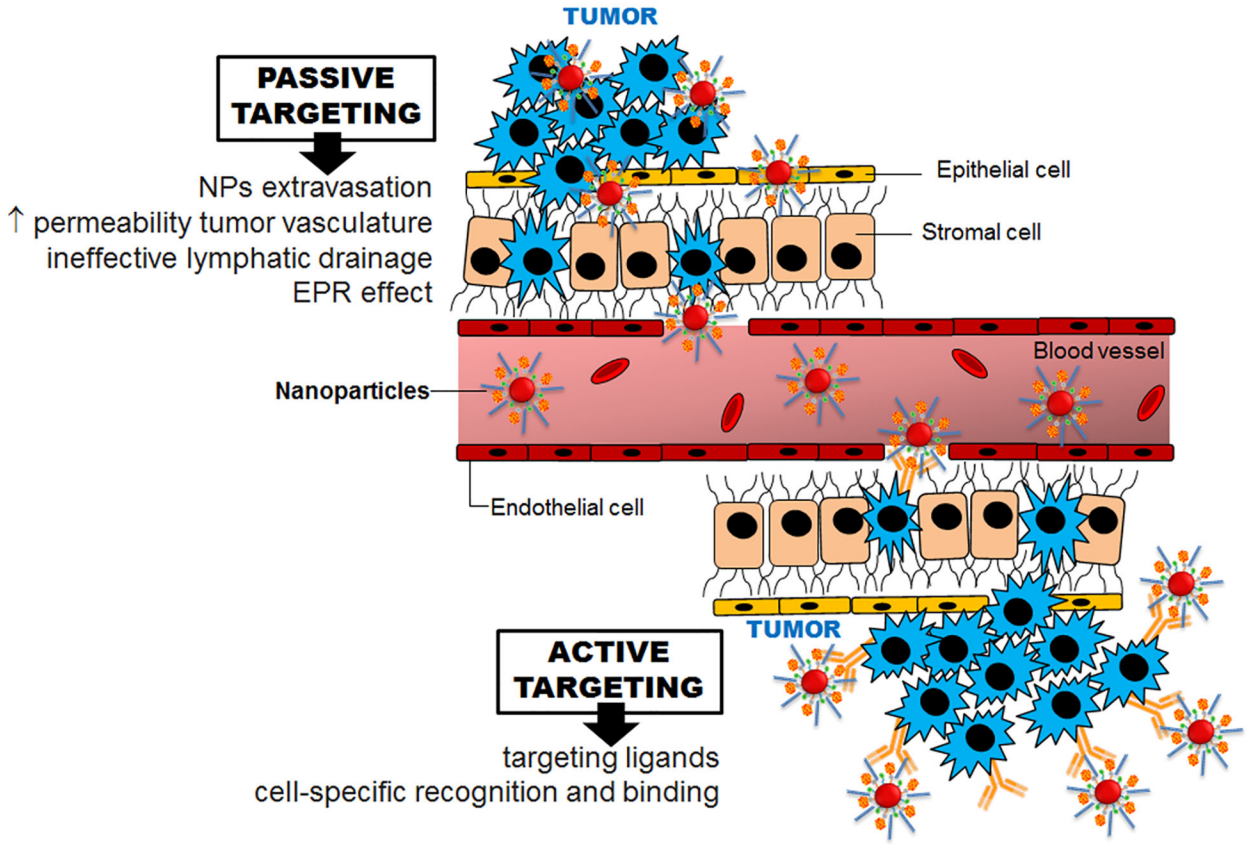


Figure 2.

Passive versus active tumor targeting using nanoparticles. Passive tumor targeting is accomplished by extravasation of nanoparticles via the EPR effect. Active targeting takes advantage of the characteristics of the tumor microenvironment, such as overexpressing cell-surface receptors, to enhance accumulation of nanoparticles at the tumor site. Adapted with permission from ref 9. Copyright 2015 Elsevier.

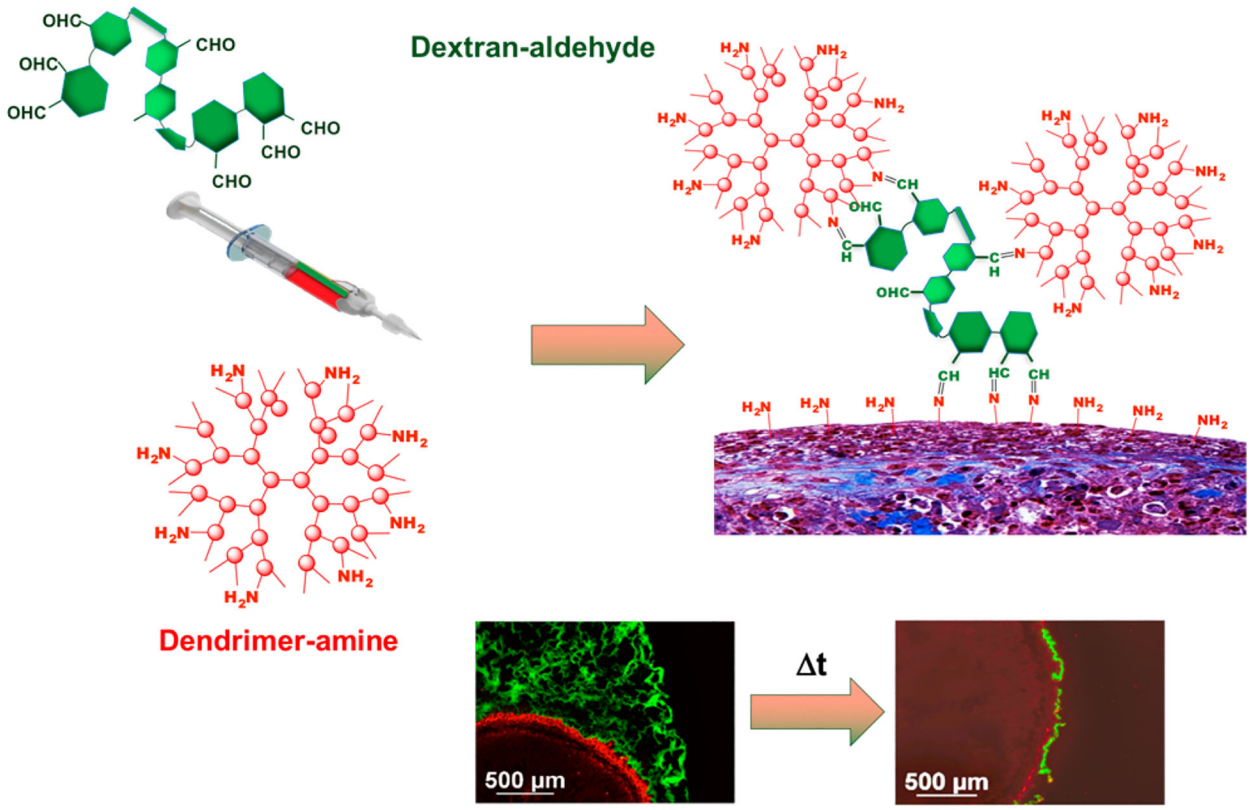


Figure 3.

Dendrimer−dextran reaction scheme. Dextran molecules can react with amines on the surface of the tissue and the dendrimer simultaneously to provide adhesion and cohesion, respectively. The labile nature of imine bonds makes this hydrogel biodegradable.

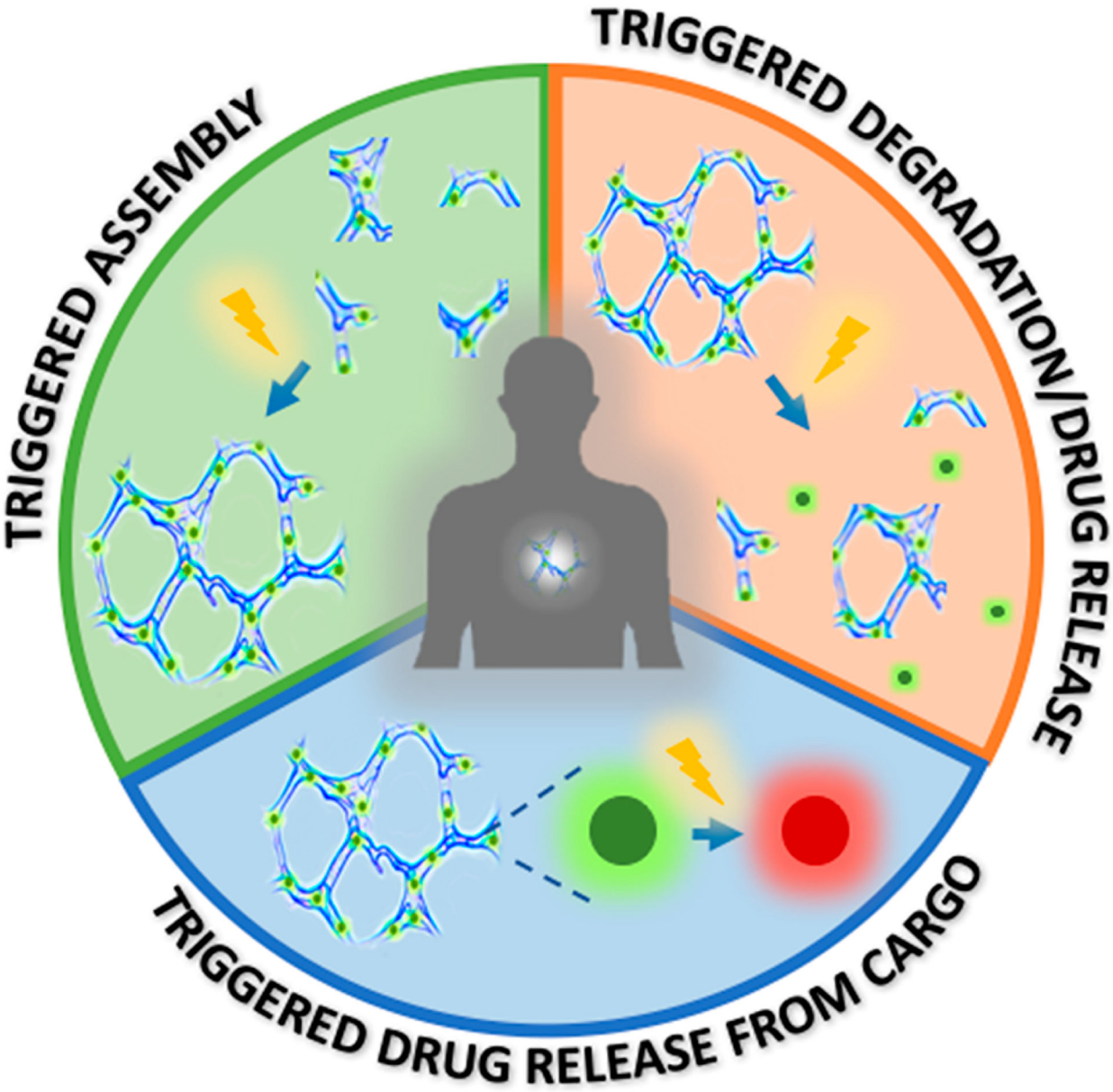


Figure 4.

Stimuli-responsive hydrogels for eliciting local therapeutic effects. Rational material design allows for disease-triggered in situ material assembly, degradation that drives drug release, and hydrogel-embedded responsive cargo.

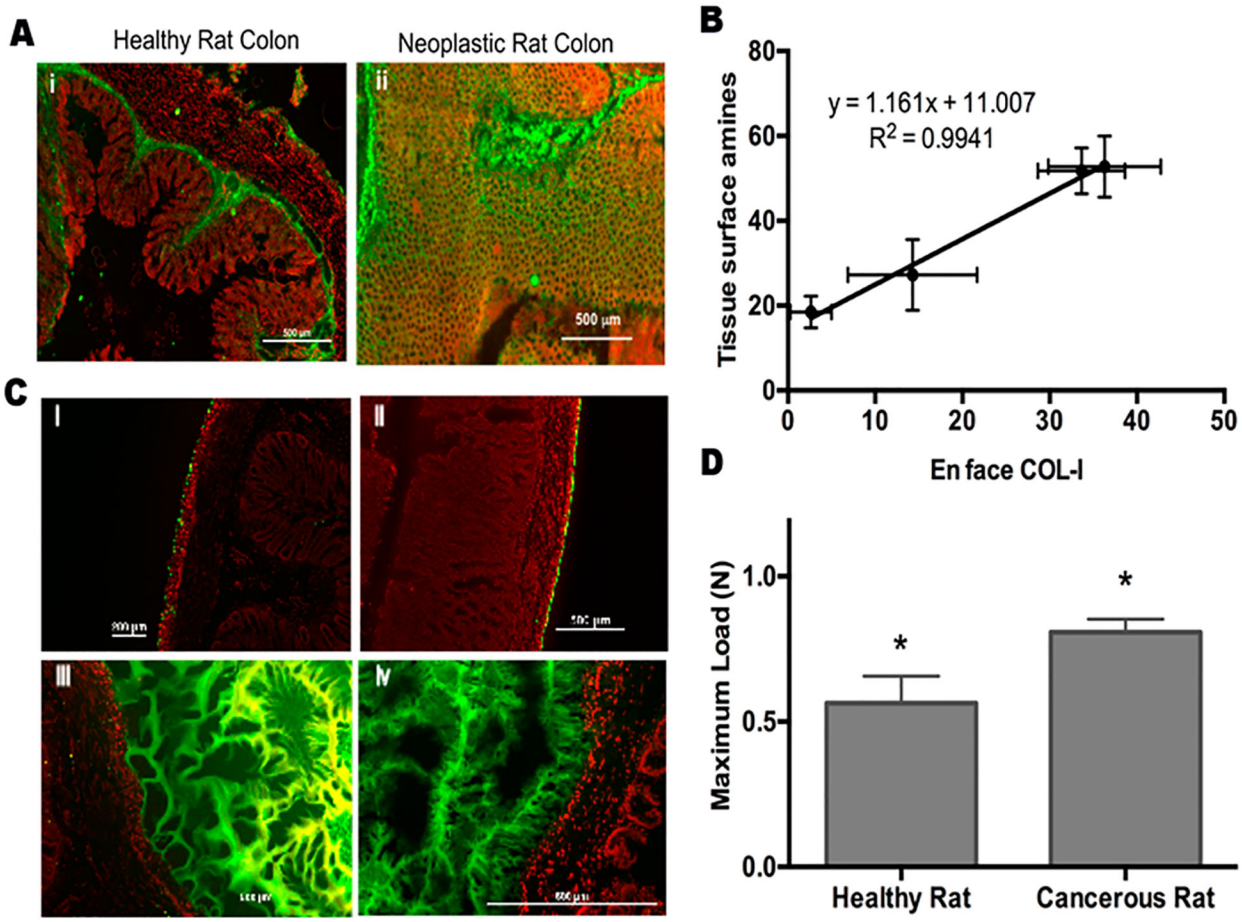


Figure 5.

Dendrimer−dextran presents disease-responsive adhesion. (A) Collagen I immunostaining (green) in (i) healthy and (ii) neoplastic tissues (red). (B) High correlation is achieved between collagen and amine density en face ($R^2 = 0.99$, $P < 0.05$). (C) Amine density on the colon serosal layer was assessed by aldehyde-coated fluorescent microspheres (green) in (i) healthy and (ii) cancerous rat tissues (red), and dendrimer−dextran adhesive (green) morphology on the colon serosal layer was assessed when applied to (iii) healthy and (iv) neoplastic rat tissues (red). (D) Maximum load at failure measured for healthy and cancerous tissues. Adapted with permission from ref 27. Copyright 2015 AAAS.

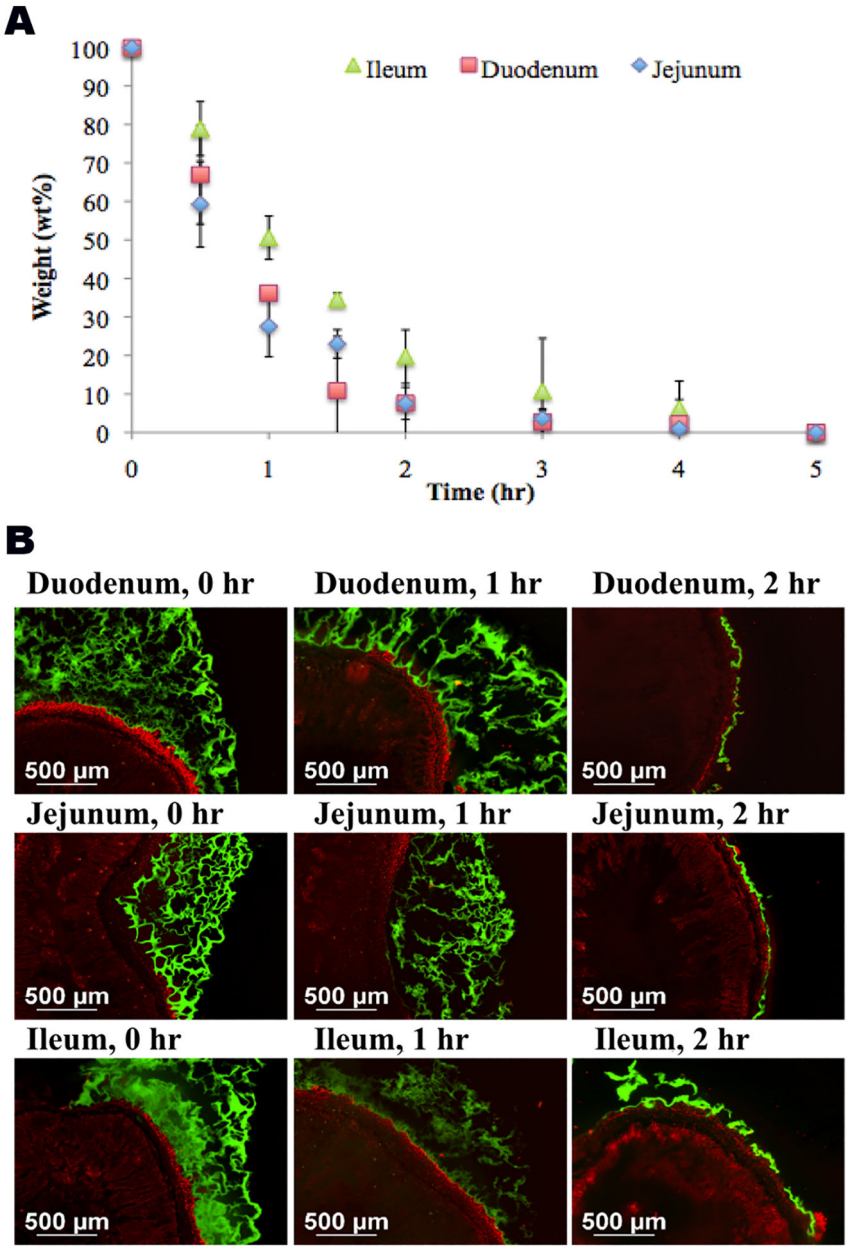


Figure 6.

Tissue-type chemistry triggers different degradation profiles. (A) Tissue surface chemistry affects material degradation. (B) Snapshots of material (green) degradation as a function of the tissue (red) to which it was applied. Adapted from ref 26. Copyright 2012 American Chemical Society.

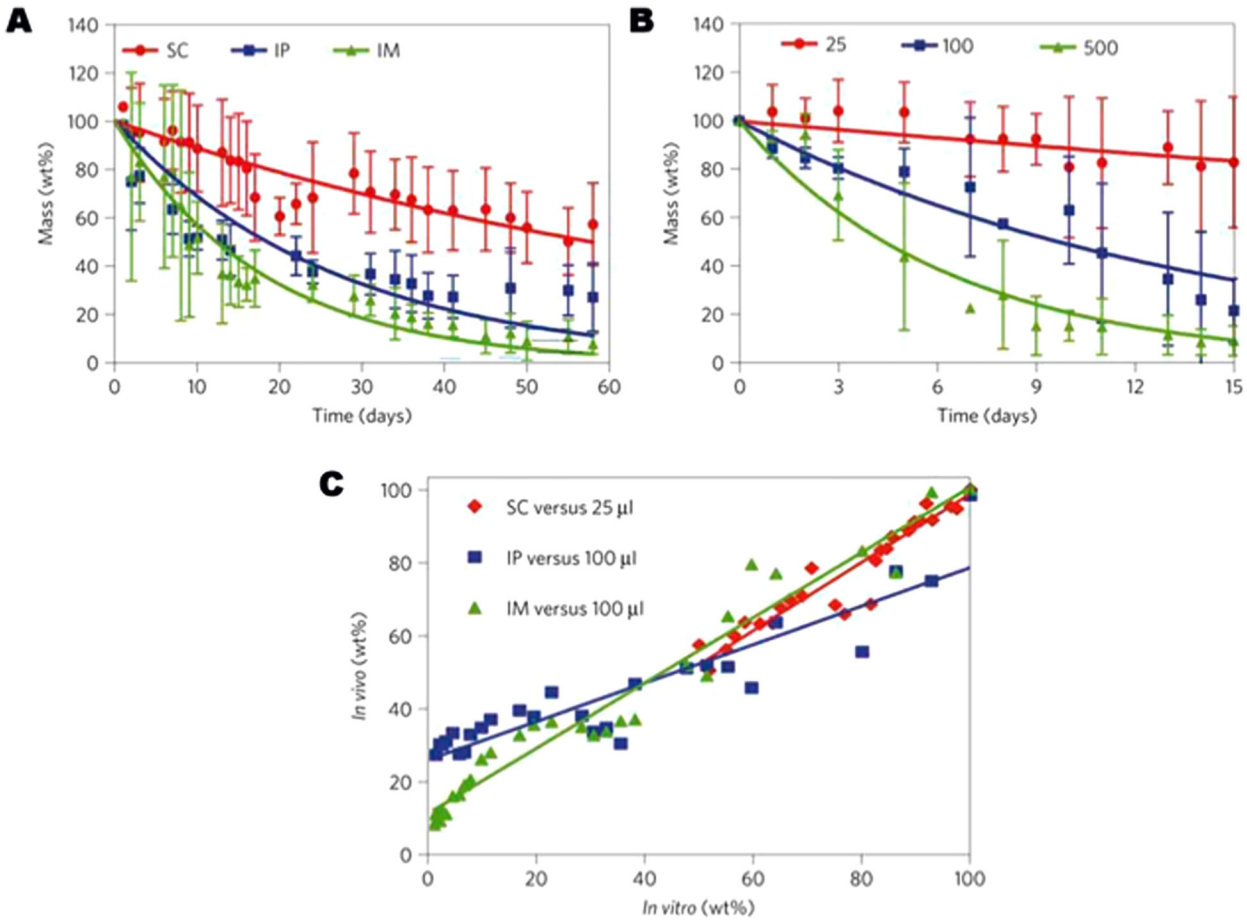


Figure 7.

In vivo degradation profile is site-dependent. (A) In vivo erosion at target sites (subcutaneous (SC), intraperitoneal (IP), and intramuscular (IM)) is site-dependent. (B) In vivo erosion profiles were used to infer physiologically relevant conditions that linearly are correlated with the in vivo erosion. (C) A correlation between the erosion profiles in vitro and in vivo was achieved with varying volumes of solution with the physiological collagenase concentration. Adapted with permission from ref 39. Copyright 2011 Nature Publishing Group.

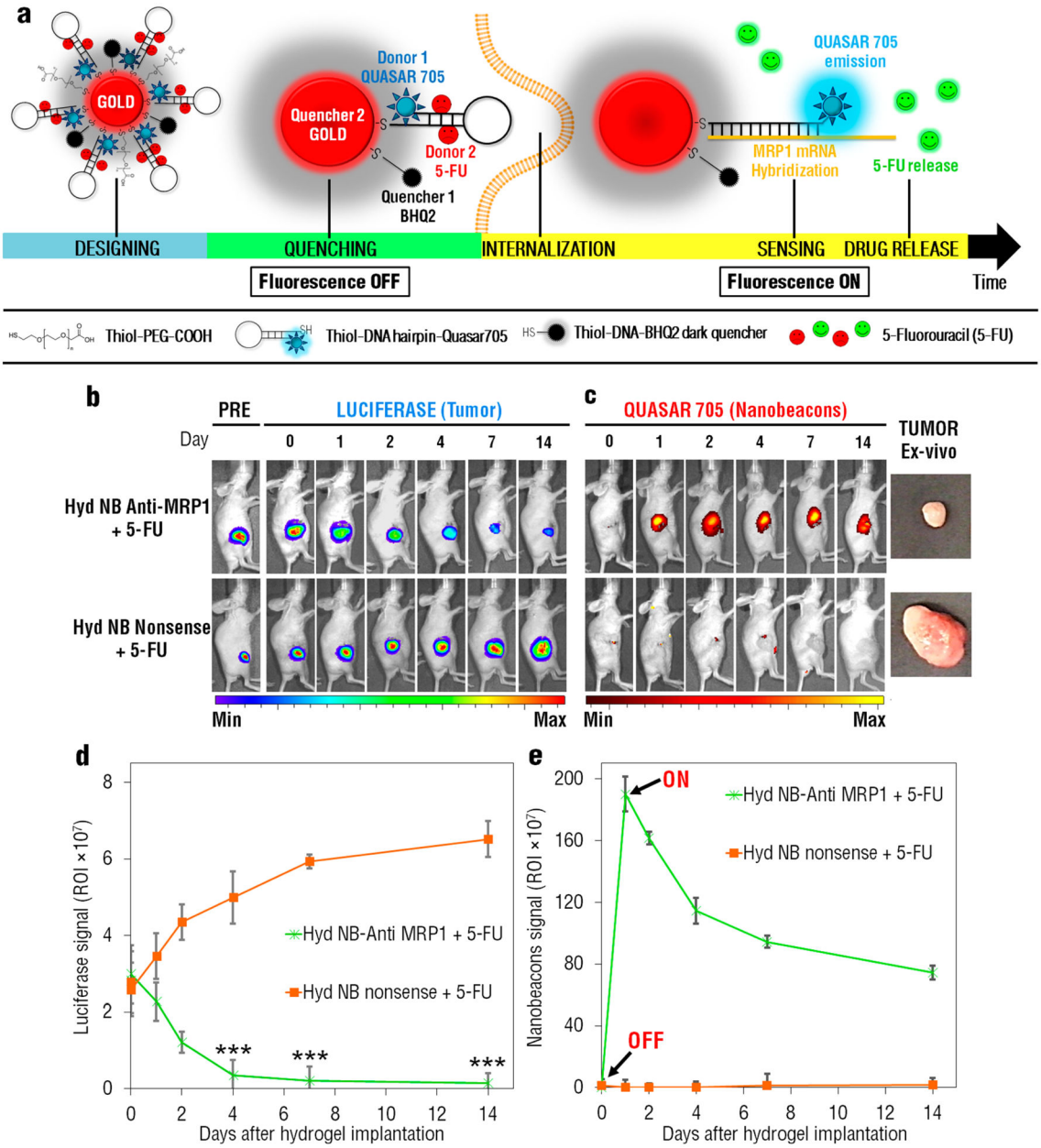


Figure 8.

(a) Scheme of dark-gold nanobeacons designed to sense and overcome cancer multidrug resistance. (b, c) IVIS tomography imaging of mice xenografted with breast tumors implanted with hydrogels embedded with nanobeacon anti-MRP1 with 5-FU and nanobeacon nonsense with 5-FU. (d) Evaluation of change in tumor size as a function of time after treatment with nanobeacons (n = 5; ***, $P < 0.005$). (e) Nanobeacon probe signals as functions of time after treatment with hydrogel nanobeacons (n = 5; ***, $P < 0.005$). Adapted with permission from ref 24. Copyright 2015 National Academy of Sciences.

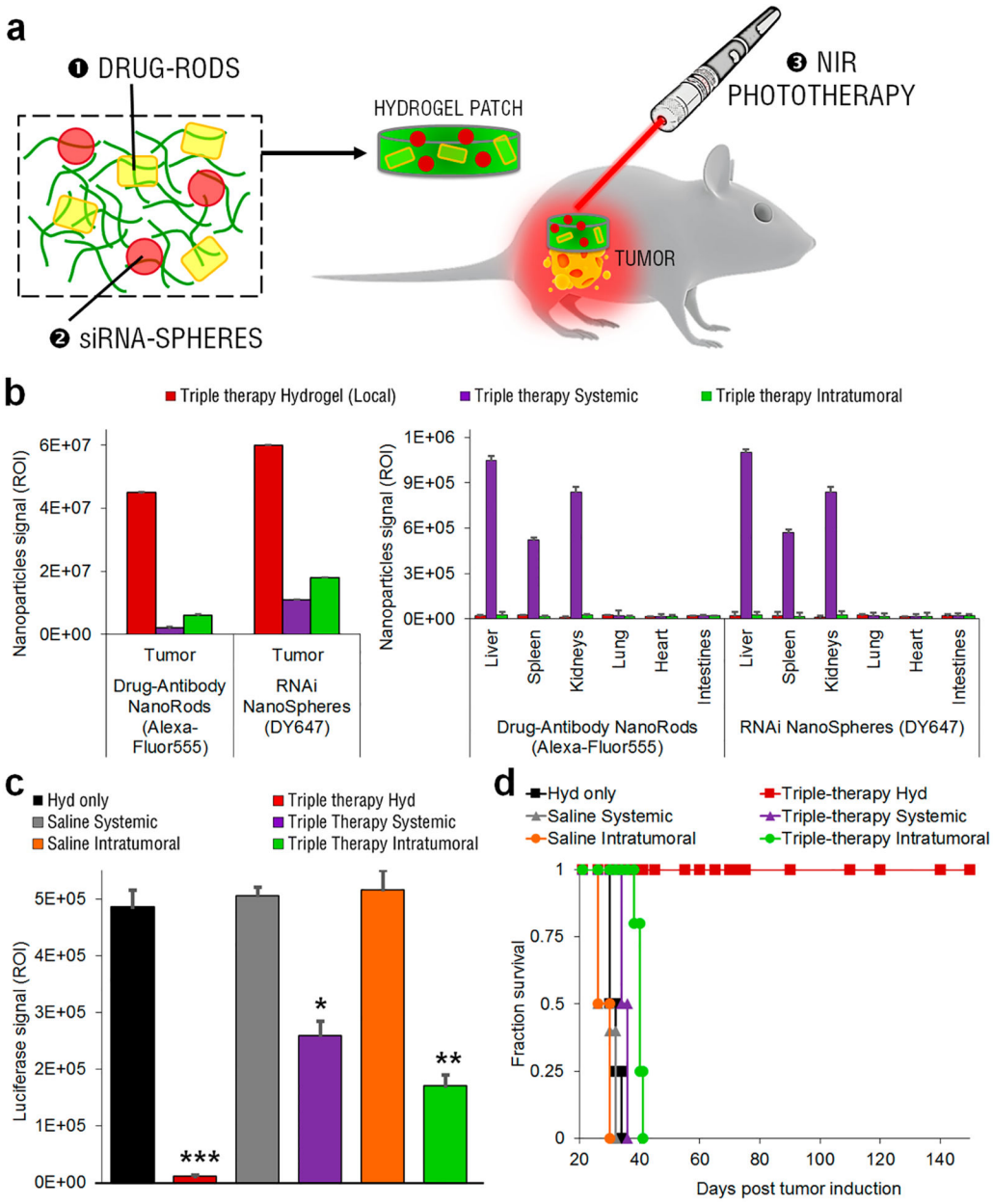


Figure 9.

(a) Development of a smart hydrogel−nanoparticle patch for in vivo local gene/drug delivery combined with phototherapy. (b) Quantification of the drug-antibody nanorod and RNAi nanosphere signals from ex vivo tumors and organs from mice treated with triple therapy administered via local implantation of the hydrogel or injected via systemic and intratumoral administrations. (c) Luciferase activity as a measure of the tumor burden (n = 5; ***, P < 0.001). (d) Kaplan−Meier survival curves. Adapted with permission from ref 23. Copyright 2016 Nature Publishing Group.

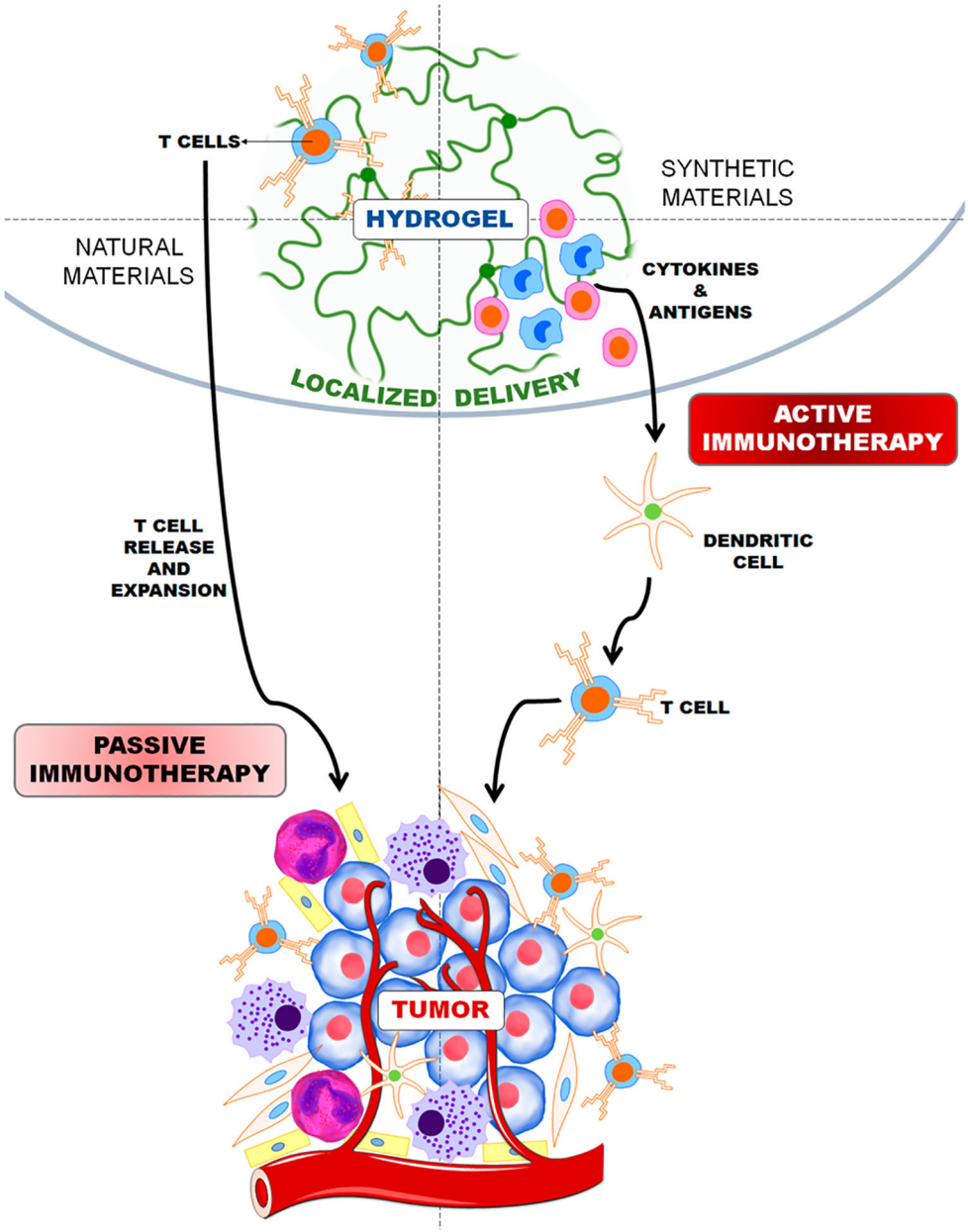


Figure 10.

Hydrogel-mediated immunotherapy as local therapy with systemic effects. Natural materials can act as T-cell depots to allow expansion and release prior to implantation to attain passive tumor immunotherapy. Alternatively, synthetic materials can be used to differentiate host's innate dendritic cells into T cells capable of recognizing tumor cells in an active immunotherapy process.