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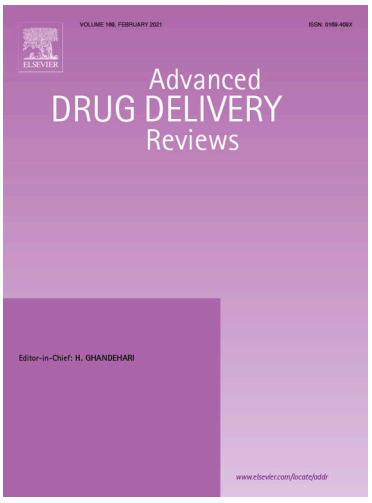

Immunotherapies for locally aggressive cancers

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Immunotherapies for Locally Aggressive Cancers

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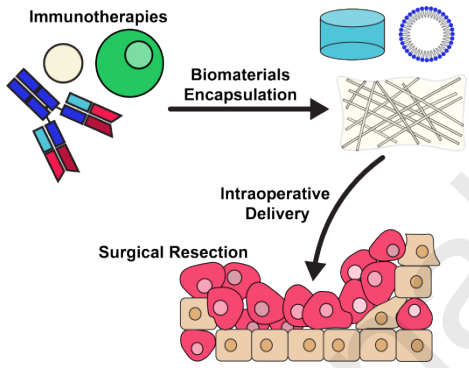
Improving surgical resection outcomes for locally aggressive tumors is key to inducing durable locoregional disease control and preventing progression to metastatic disease. Macroscopically complete resection of the tumor is the standard of care for many cancers, including breast, ovarian, lung, sarcoma, and mesothelioma. Advancements in cancer diagnostics are increasing the number of surgically eligible cases through early detection. Thus, a unique opportunity arises to improve patient outcomes with decreased recurrence rates via intraoperative delivery treatments using local drug delivery strategies after the tumor has been resected. Of the current systemic treatments (e.g., chemotherapy, targeted therapies, and immunotherapies), immunotherapies are the latest approach to offer significant benefits. Intraoperative strategies benefit from direct access to the tumor microenvironment which improves drug uptake to the tumor and simultaneously minimizes the risk of drug entering healthy tissues thereby resulting in fewer or less toxic adverse events. We review the current state of immunotherapy development and discuss the opportunities that intraoperative treatment provides. We conclude by summarizing progress in current research, identifying areas for exploration, and discussing future prospects in sustained remission.

Keywords: Drug delivery; Intraoperative; Cancer; Hydrogel; Nanoparticles; Biomaterials; CAR T; Antibody; Small Molecules; Mesothelioma; Sarcoma; Non-small cell lung cancer



TOC Graphical Abstract

1. Current state of locally aggressive cancers

Locoregional recurrence (LRR) after surgery or other local cancer therapy represents a major source of morbidity and mortality for patients with locally aggressive malignancies[1]. Despite advances in treatments and care, cancer remains the second leading cause of death in the United States, with an estimated 610,000 deaths and 2 million newly diagnosed cases in 2024[2]. Although 67-90% of cancer deaths are attributed to metastasis, there is a subset of lethal cancers that are initially non-metastatic. Mesothelioma, retroperitoneal sarcoma, non-small cell lung cancer, esophageal cancer, and pancreatic cancer have 5-year survival rates ranging from 5 to 31% and are hampered by high local recurrence rates (Figure 1A)[3–8]. For these cancers and the approximately 580,00 patients diagnosed each year, the standard treatment is a macroscopically complete (R0/R1) resection of the primary tumor, preferably with negative microscopic margins (R0 resection)[2,5,9–13]. While pre- or post-surgical intervention (neoadjuvant and adjuvant therapy, respectively) improves outcomes, LRR remains a major barrier to survival in locally aggressive cancers[14,15]. Historically, LRR therapeutic

development has preceded most advances in treatments for intractable metastatic disease. Therefore, continued development of LR therapeutics is necessary[6,16].

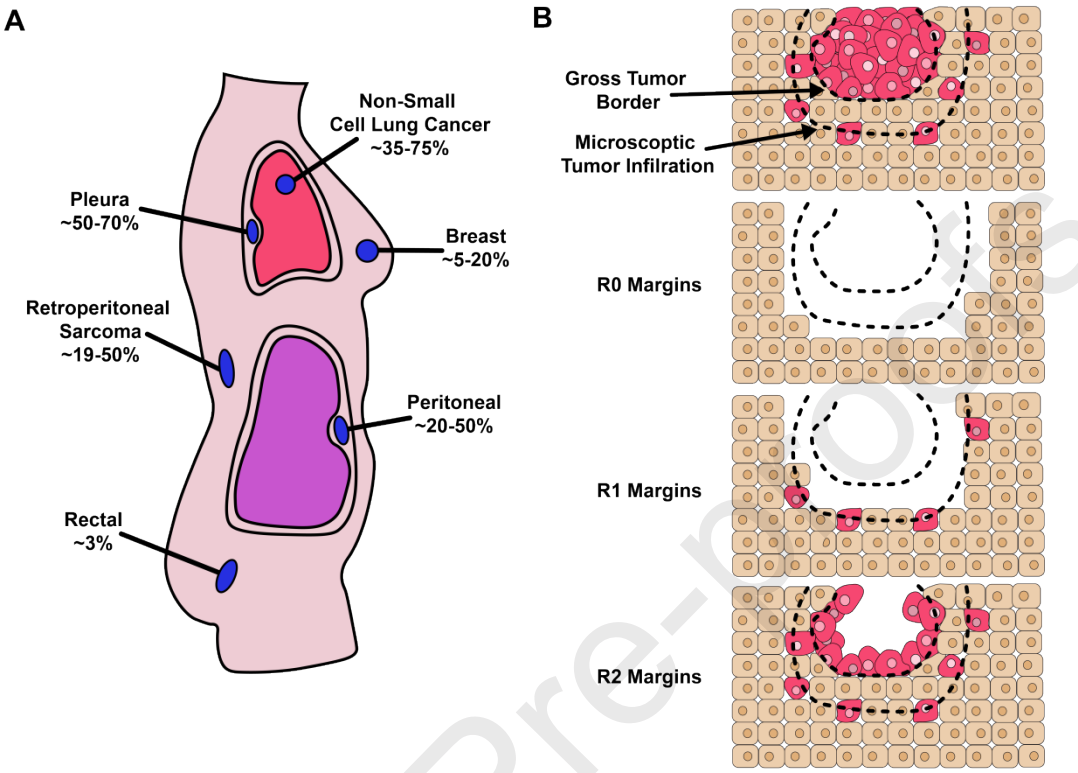


Figure 1. A) Summary of recurrence rates across post-surgical resection for several cancer types. **B)** Graphical representation of R0, R1, and R2 resection margins in a local tumor environment.

One of the major challenges in treating locally aggressive tumors via surgery is the proximity to critical structures (preventing complete resection), inability to see microscopic residual disease, and the inability to safely deploy radiation given excessive harm to healthy tissues in a specific area[1]. Curative-intent surgery is the preferred treatment modality when feasible. However, certain tumors (e.g., mesothelioma, retroperitoneal sarcoma) may invade or expand contiguously into critical structures, thereby limiting the ability to achieve an R0 resection without significant morbidity or mortality. In such cases, an incomplete (R2) resection may be performed to improve quality of life or palliate symptoms, but this rarely improves survival outcomes and disease progression is inevitable. As noted above, resections are categorized as R0, R1, and R2, based on pathological classification of resection margins after surgery (Figure 1B)– with the caveat that only a small section of the resected tissue is histologically analyzed. An R0 margin demonstrates no histopathological evidence of cancerous cells at the inked margin, an R1 margin shows microscopic tumor cells, and an R2 resection signifies an incomplete resection with grossly visible disease remaining in the patient. Margin classification is prognostic for recurrence, with 10-year LR rates of 8%, 21%, and 44% for R0, R1, and R2 resections respectively in extremity/truncal soft tissue sarcoma[17]. Margins also impact survival, with cancer-specific five-year survival rates of 44%, 26%, and 10% for R0, R1, and R2 resections of recurrent rectal cancer[18]. Effective approaches for eliminating existing cancer cells after a resection are widely sought after due to the potential to improve durable remission.

While traditional neoadjuvant and adjuvant treatments improve patient outcomes, these methods are often not curative due to poor drug trafficking to the tumor, short residence times within the tumor, and off target toxicities. One method to circumvent trafficking to the tumor is intratumoral injections of chemotherapy or immunotherapies. This delivery route is currently being explored in numerous clinical trails, however, intratumoral injections have several limitations [19]. For deep abdominal tumors, such as sarcomas, intratumoral injections are immensely challenging to accurately deliver to the tumor. Additionally, patients must return to the clinic to receive their intratumoral injection, and for treatments utilizing proteins with short half-lives, such as cytokines, this requires frequent patient visits to the clinic further complicating the treatment regime. An alternative route is intraoperative delivery of treatments during the operation after the tumor has been resected. Intraoperative strategies benefit from direct access to the tumor microenvironment (TME) which improves drug uptake to the tumor and simultaneously minimizes the risk of drug entering healthy tissues thereby resulting in fewer or less toxic adverse events. We begin with a brief review of the biomaterial delivery devices followed by a discussion of the immunotherapies utilized in cancer treatments and finally summarize the state of intraoperative delivery of immunotherapies.

2. Biomaterial delivery of immunotherapies as a treatment modality against locally aggressive cancers

Broadly, immunotherapy refers to a class of drugs that either suppress or activate the immune system to fight disease. A prototypical example of activation is vaccination: a vaccine against a pathogen (such as the flu) stimulates the immune system to be primed against that disease. Since the immune system identifies foreign or diseased cells and proteins, interest in targeting cancer via the immune system is a long-standing goal. Instead of systemic treatments that traditionally attack cells and tissues non-discriminately, the goal of immunotherapies for cancer treatments is to specifically target cancer cells, reducing the toxicities associated with chemotherapy and radiation. Within immunotherapies, there are three broad classifications used to describe them further: small molecule agents, large macromolecules (primarily antibodies), and cellular therapies. As of this writing, several immunotherapies are regulatory approved, and their uses have revolutionized treatment for patients[20–25]. For instance, Immune Checkpoint Inhibitors (ICIs) improve the one-year survival of patients with advanced Non-Small Cell Lung Carcinoma (NSCLC) by more than 10% over traditional systemic chemotherapies, while reducing adverse events caused by treatments[26]. However, the current clinically available immunotherapies are limited in the indications by cancer type. For ICIs, their efficacy is predominantly driven by high expression of the ICI target, for instance Programmed Cell Death Ligand 1 (PD-L1). Thus, tumors with low PD-L1 expression observe lower objective response rates when treated with the corresponding ICIs[27]. Thus, challenges remain to fully utilize immunotherapies for all cancer patients. The primary challenge is the heterogeneity associated within the TME. The TME of solid tumors are generally classified into four groups: immune responsive, immune exclusion, immunosuppressive, and immune deserts[28]. Additionally, adverse events due to over activation of immunotherapies in cancer patients are lethal[29,30]. Thus, for immunotherapies to be applicable across all TMEs, new strategies must be employed to improve their safety and efficacy.

A proven method for improving biocompatibility, targeting, localization, and pharmacokinetic control with chemotherapy is delivery with biomaterial devices[31–37]. Biomaterial delivery of chemotherapies demonstrates enhanced efficacy, however, the

indications are still limited to brain, prostate, and breast tumors[38–40]. Immunotherapies utilizing biomaterials achieve prolonged release and improve targeting in both clinical trials and preclinical *in vivo* models[41], and the most common vehicles for immunotherapy delivery are hydrogels, nanoparticles (NPs), and meshes and films. Biomaterials for immunotherapy delivery are designed based on the application for each cancer type. For instance, meshes provide significant mechanical strength and flexibility, and, thus, are candidates as drug-eluting buttresses for treatment of early-stage lung cancer following resection. The differences between these biomaterial delivery platforms are summarized in Table 1. The following section describes the current state of immunotherapies in cancer treatments within small molecule agents, proteins, and cell therapies and the strategies for improving intraoperative delivery of these immunotherapies using biomaterials.

Table 1. Drug Delivery Platform Characteristics

		Nanoparticles (NPs)	**Hydrogels**	**Meshes and Films**
Therapeutic Loading Mechanism	**Small Molecules**	Covalent bonds, physical entrapment of hydrophobic compounds with single emulsion	Covalent bonds, Physical entrapment	Physical entrapment, Conjugated to the backbone of the polymer
	Proteins and Nucleic Acids	Covalent bonds to exterior of the NP, Physical entrapment of nucleic acids with lipid NPs	Covalent bonds, Physical interactions (electrostatic, stimuli response release, high affinity binding domains)	Adsorption or chemical conjugation to the exterior of the mesh
	Cell Therapies	N/A	Physical entrapment	Surface conjugation or adsorption
Degradation Rate		Days to Weeks	Weeks to Months	Weeks to Years
Injectable		Yes	Some	No
Surgical Fixation		No	No	Yes
Advantages		Avoids surgery related complications, Less technical expertise for use, Repeated dosing possible	Amenable to various administration routes, High biocompatibility, High loading of proteins	Long sustained release, High local therapeutic delivery, Strong mechanical integrity

Disadvantages	Limited loading of proteins, Low residence of circulating NPs to target tissue, High trafficking of NPs to the liver	Burst release during swelling, Low mechanical integrity in the swollen state	Requires surgery, Activates foreign body response, Limited locations for implant

2.1 Small Molecule Agents

Small molecules, defined as those with molecular weights typically less than 900 Da, regulate or disrupt a biological pathway. In cancer immunotherapies, small molecule agents are often agonists (initiating a physiological response when combined with its receptor) or inhibitors (preventing the propagation of a molecular pathway) to specific immune system pathways. Several reviews discuss the development of small molecules for cancer immunotherapies[42–44]. Here, we focus on those agents when combined with a biomaterial delivery system.

Toll-Like Receptors (TLR) agonists

TLRs are a class of immune system receptors found on the cell membranes of dendritic cells, macrophages, Natural Killer (NK) cells, T cells, and B cells. Canonically, activation of TLR receptors upregulates the production of pro-inflammatory cytokines and type I Interferons that stimulates both the innate immune system and the adaptive immune system (Figure 2A). TLR ligands are diverse, but the two primary families of ligands relevant to cancer immunotherapies are Pathogen-Associated Molecular Patterns (PAMPs) and Damage-Associated Molecular Patterns (DAMPs). PAMPs derive from the exogenous domains of molecules from pathogens while DAMPs derive from the endogenous domains of dying or damaged cells. The importance of TLR expression to oncogenesis and tumor progression is well documented[45,46]. In fact, TLRs are overexpressed and possess a unique pattern signature in colorectal cancer, melanoma, and ovarian cancers[47]. The high expression of TLRs in the TME results in TLR activation and chronic inflammation of the TME. This chronic inflammation induces aberrant release of cytokines and chemokines which suppress antigen presentation cell function and tumor associated antigen - specific immunity. Consequently, the TME becomes immunotolerant, maintains support cells (such as cancer associated fibroblasts) and promotes tumor angiogenesis. Alternatively, acute TLR activation within immune cells of the TME, particularly dendritic and T cells, improves the anti-tumor effect[48]. Thus, TLRs known in dendritic and T cells are exciting candidates for TLR agonists with examples of TLR4, TLR7, TLR8, and TLR9 agonists regulatory approved or in clinical trials. Imiquimod, a TLR7/TLR8 agonist, is FDA-approved for the treatment of superficial Basal Cell Carcinomas. When Imiquimod binds to TLR8

it activates MyD88 with subsequent dimerization of the NF-κB subunits to induce the production of pro-inflammatory cytokines, specifically Tumor Necrosis Factor-α. Imiquimod binding to TLR7 follows a similar pathway, however it causes upregulation of ISRE pathways and subsequent production of interferons, specifically, Interferon-α. Imiquimod exhibits toxicity with frequency use. In a clinical trial, daily application of a 5% Imiquimod cream affords skin rashes (including ulcers and scabbing), pruritis, and pain in all patients[49]. While TLR agonists show promise in stimulating the immune system against cancer, toxicities limit their broader use for a greater variety of cancers.

To mitigate the non-specific effects of TLR agonists and reduce rapid renal clearance, biomaterials are being actively investigated. Encapsulation of the TLR7 agonist 3M-052 in silica-lipid NPs improves tumor residence times by >40X compared to IV infusion of the free drug (Figure 2B)[50]. The NPs reduce tumor growth in a pancreatic cancer (KPC) murine model over free IV injected drug. To improve the targeted delivery, Park et al. describe a cross-linked hyaluronic acid hydrogel, loaded with the TLR7/8 agonist R848, placed into the resection site using an orthotopic breast cancer murine model[51]. The hydrogel delivers a fluorescent molecule signal for 21 weeks with minimal fluorescence detected in other tissues. Rwandamuriye et al. report the potential of intraoperative delivery of a TLR3 agonist polyinosinic:polyctidylic acid, using a hyaluronic acid based hydrogel *in vivo* in a soft tissue tumor

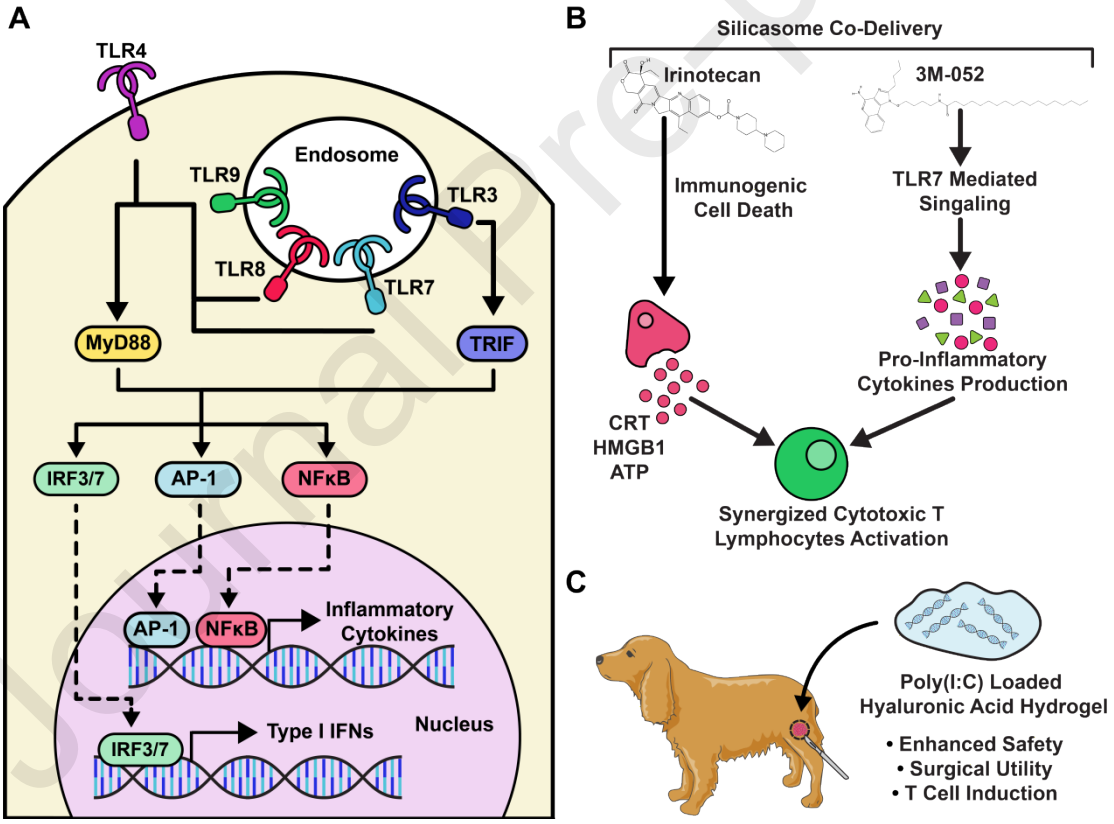


Figure 2. Toll like receptor (TLR) agonists as immunotherapies. **A)** A schematic of relevant TLR mediated pathways for immune cell activation. **B)** The TLR7 agonist 3M-052 demonstrates lymphocyte activation when co-delivered with the immunogenic chemotherapeutic irinotecan, using a lipid bilayer coated silicasome (adapted from Luo et al.[50]). **C)** Local delivery of the TLR3 agonist poly(I:C) incorporated into a hyaluronic acid hydrogel prevents tumor recurrence when applied at the site of resection as showcased in a canine model (adapted from Rwandamuriye et al.[52]).

canine model. Two weeks post-surgery, all canine subjects with the hydrogel show no apparent side effects to the implant and demonstrate priming of T cells against the antigen local to the TME (Figure 2C)[52].

Stimulator of Interferon Genes (STING) Agonists

Similar to the TLR pathway, the cyclic GMP-AMP synthase (cGAS)- STING pathway is a key mechanism for the innate immune response against cytosolic double-stranded DNA (dsDNA). Canonically, dsDNA (for instance from a pathogen or damaged mitochondria) binds to cGAS and triggers the formation of cyclic GMP-AMP (cGAMP) from ATP and GTP. cGAMP then binds to STING in the endoplasmic reticulum (ER), where STING traffics to the Golgi. Subsequent activation of transcription factors IRF3 and NF-κB transport to the nucleus, and upregulate inflammatory genes including interferon-β (Figure 3A)[53]. Mutations in cGAS and dysregulation of the STING pathway occur in several cancers, including lung cancer[54–56].

Most STING agonists mimic cGAMP binding to the STING receptor on the ER. Currently, there are several STING agonists being evaluated in clinical trials either on their own or in combination with another immunotherapy. The majority of cGAMP STING agonists exhibit short *in vivo* half-lives of ~two hours due to the electronegative charge and hydrophilicity and, therefore, several ongoing clinical trials prefer intra-tumoral delivery routes in an attempt to achieve efficacy[57]. Synthetic agonists are under development to increase the half-life with success in preclinical models; however, these agonists have yet to demonstrate an increased half-life in clinical trials[58]. Additionally, as these agonists are non-specific, adverse events are commonly reported with systemic delivery.

Biomaterials and drug delivery strategies offer the potential to extend the half-life and enhance the localization of STING agonists. For example, the STING agonist SR717 loaded within a self-assembled ferritin RGE fusion protein NP activates the innate immune system and prolongs survival in a murine glioblastoma model[59]. Pulsatile release of cGAMP using cubic polylactic-co-glycolic acid (PLGA) microparticles (MPs) delivers cGAMP to the TME in three bursts over 10 days *in vivo* in orthotopic murine models for triple negative breast cancer and melanoma. In a post-resection melanoma murine model, these PLGA MPs improve the survival of mice treated with these MPs over a one-time intratumoral injection of cGAMP[60]. In a dual therapy approach, ICIs combined with cyclic dinucleotides (CDNs) loaded into poly(beta-amino ester) NPs prevent tumor growth in a melanoma murine model in comparison to the free CDN or empty NP groups[61]. Using the previously mentioned cross-linked hyaluronic acid hydrogel described by Park et al., a loaded STING agonist STING-RR prolongs survival in a murine lung carcinoma model post-resection over free drug controls (Figure 3B). Abrogation of STING-RR loaded hydrogel efficacy occurs with depletion of NK cells or CD8+ T cells as well as with an innate immune signaling inhibitor[51]. Wang et al. report an *in situ* nanotube (NT) hydrogel loaded with STING agonist c-di-AMP (CDA) which prolongs release of CDA over three weeks. In an immunosuppressive murine breast cancer model, the NT hydrogel improves survival over free CDA (Figure 3C)[62].

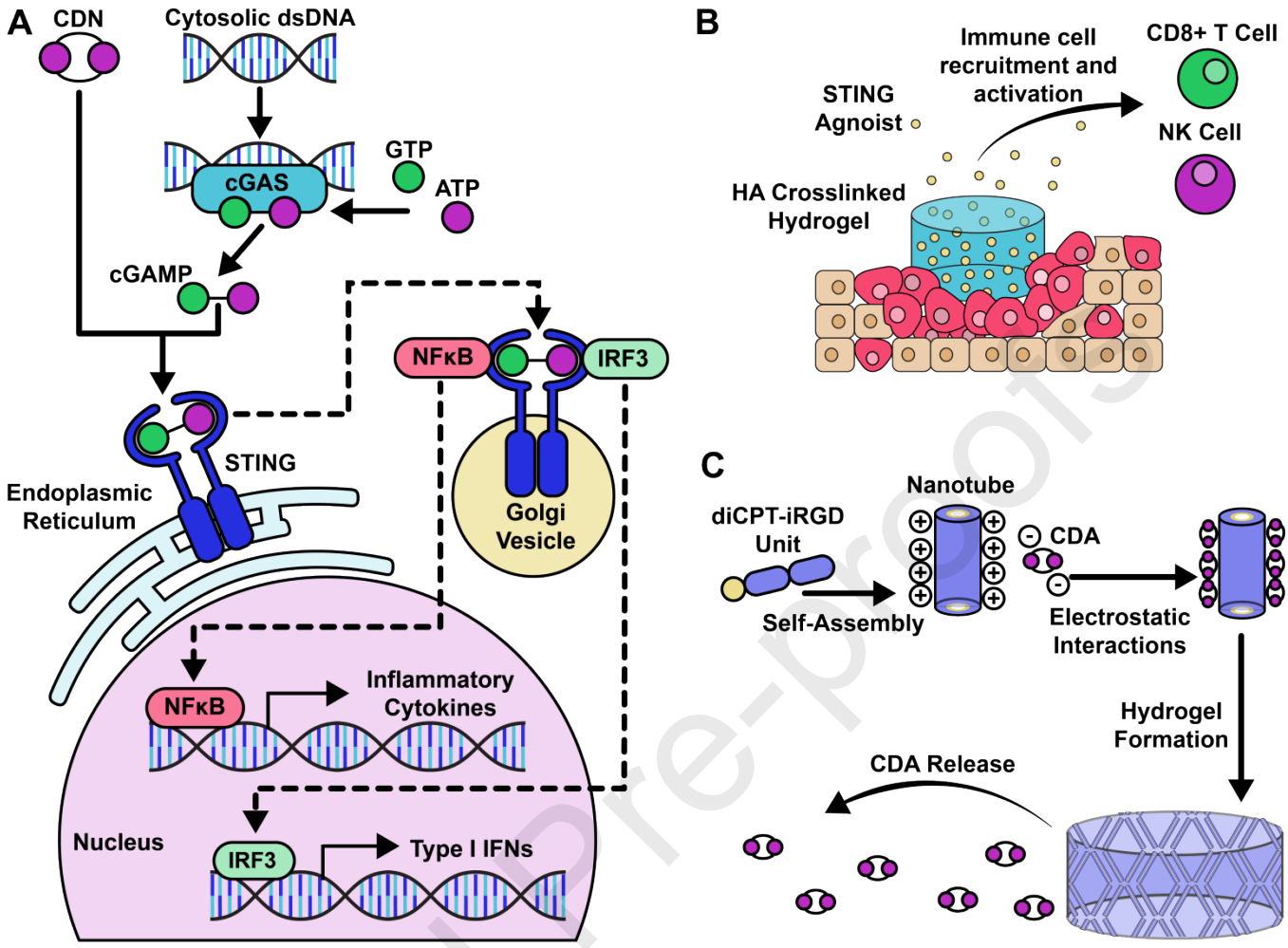


Figure 3. **A)** A schematic of the STING mediated immunity. **B)** The incorporation of STING RR in a hyaluronic acid crosslinked hydrogel, localizes the delivery of STING-RR, reduces tumor recurrence rates post- resection, and activates and recruits immune cells (adapted from Park et al.[51]). **C)** Graphical representation of *in situ* nanotube (NT) hydrogel loaded with STING agonist c-di-AMP (CDA). The gel forms using a drug amphiphile diCPT-iRGD (hydrophilic iRGD peptide with the hydrophobic anticancer drug CPT) which self-assemble into nanotubes in aqueous phase. The positive charge of the nanotube exterior allows for complexation of negatively charged CDA via electrostatic interaction. These nanotubes spontaneously form hydrogels upon injection at the tumor site, sustains delivery of CDA in the tumor (adapted from Wang et al.[62]).

2.2 Protein Therapeutics

Monoclonal antibody (mAb) treatments are particularly effective against cancers which express high levels of their respective antigen. Infusion of mAbs results in binding to its cognate antigen with subsequent activation of the immune system via multiple pathways. Blocking of the antigen receptor inhibits signal transduction of key pathways inducing apoptosis of the cancer cell. Antibodies targeting the antigen expressed on the cancer cell may recruit Natural Killer (NK) cells or macrophages to induce Antibody-Dependent Cellular Cytotoxicity (ADCC) or Antibody-Dependent Cellular Phagocytosis (ADCP), respectively. Finally, the antibodies may mediate the cancer antigen presentation to prime T and B cells (Figure 4A) [63–65]. The monoclonal antibody are conjugated with chemotherapies to induce additional cytotoxic effects – known as Antibody

Drug Conjugates (ADC). Methods for conjugating drugs to ADCs vary and have been well discussed in other reviews[66–68]. Over a dozen ADCs are regulatory approved for treatment of various hematopoietic malignancies as well as cervical, ovarian, breast, and lung cancers; however, their use in intraoperative treatment has yet to be explored.

Outside of conventional mAbs, researchers design proteins to function as adaptor molecules between a cancer cell and an immune cell, most commonly a T cell. The designs combine the VL and VH domains from an antibody to form a single-chain variable Fragment (scFv), one for the cancer cell and the other for the T cell. This adaptor protein acts as a bridge between the two cells, inducing T cell activation against the cancer cell (Figure 4B). With T cells, the adaptor proteins are called Bispecific T cell Engagers (BiTE)[69,70]. The use of BiTEs in solid tumors has been explored in over 40 clinical trials, and there are now 5 FDA approved BiTEs for hematologic cancers as of 2023[71]. However in several phase II trials, several BiTEs cause adverse events due to the high dose required to ensure efficacy[72]. This result provides motivation to investigate drug delivery systems to alter pharmacokinetics and to reduce on-target off target toxicities.

Table 3. FDA Approved BiTE Therapies

Therapy	Target	Indication	Year
Blincyto	CD19	B cell acute lymphoblastic leukemia, Philadelphia chromosome-negative relapsed B cell leukemia	2014
Tecvayli	BCMA	Multiple Myeloma	2022
Lunsumio	CD20	Follicular Lymphoma	2022
Epkinly	CD20	Diffuse large B cell Lymphoma	2023
Columvi	CD20	Diffuse large B cell Lymphoma	2023

Immune Checkpoint Inhibitors are antibodies that block cancer cells from turning “off” the T cells in the TME thereby allowing the T cells to attack the cancer cells. There are two primary ICI pathways: Cytotoxic T-Lymphocyte Associated Protein (CTLA)-4 and Programmed Cell Death (PD)-1. Canonically, a healthy immune system uses these inhibitory pathways to prevent overactivation of the immune system by expressing ligands that bind to a T cell, thereby suppressing its activity (Figure 4C). For instance, fibroblast expression of PD-1’s ligand (PD-L1) binds to PD-1 on the T cell, inhibiting proliferation, cytokine production, and signaling activation. In the TME, cancer hijacks this mechanism to prevent T cell activation and create a peritumoral immunosuppressive environment. ICIs block either the ligand expressed on the cancer cell or

the receptor on the T cell, allowing for T cell activation and killing of the cancer cells. ICIs are currently one of the most successfully therapies clinically available in oncology for multiple malignancies. However, due to poor bioavailability of proteins and trafficking to the TMEs, ICIs exhibit minimal success in some cancer types, thus motivating the development of biomaterial platforms for local delivery of ICIs to the TME.

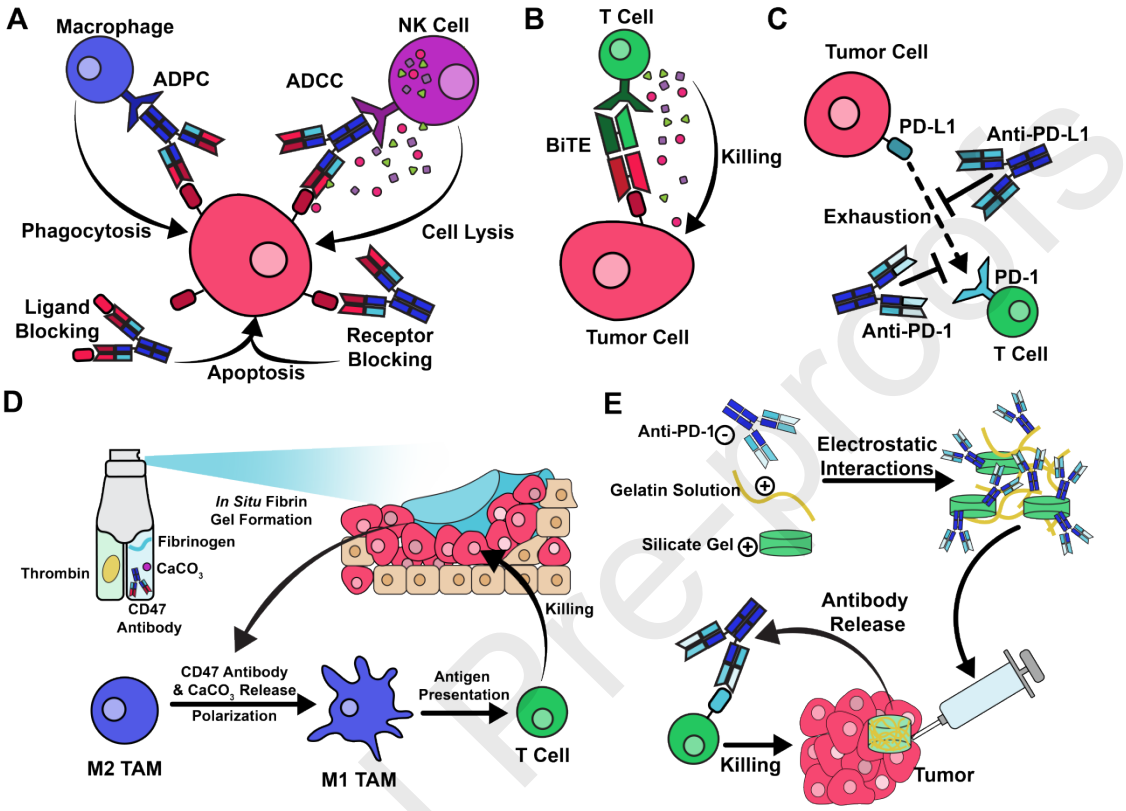


Figure 4. Mechanisms of action for **A)** Antibody therapy, **B)** BiTE, and **C)** Immune Checkpoint Inhibitors (ICIs). **D)** An *in situ* bio-responsive fibrin glue generates by combining αCD47 antibodies loaded $CaCO_3$ nanoparticles with fibrinogen and thrombin (fibrin gel components). When applied to the post-resection tumor bed, the encapsulated nanoparticles release CD47 thereby polarizing tumor associated macrophages (TAM) towards an M1 (pro-inflammatory) phenotype, and recruiting T cells to the tumor site (adapted from Chen et al.[89]). **E)** Anti-PD-1 antibodies incorporated into a gelatin silicate hydrogel localize delivery of the anti-PD-1 ICI to prevent the exhaustion of T cells, thus promoting tumor killing (adapted from Wu et al.[91]).

Protein delivery poses unique challenges for drug delivery[73–77]. Most therapeutic proteins, particularly recombinant proteins or non-human proteins are subject to rapid protease degradation and exhibit poor bioavailability[78]. Further, traditional encapsulation processes used for small molecule agents such as nanoprecipitation or polymer emulsion protocols involve potential contact or solubilization in organic solvents, which are known to denature proteins, leading to a complete or partial loss of bioactivity[79]. Thus, delivery of proteins through NPs is challenging, often conjugating the antibodies to the exterior surface of the NP using click chemistry[80–82]. An alternative method for protein delivery is the assembly of proteins to form 3D nanostructures, commonly known as protein vaults. These barrel shaped hollow structures of less than 70 nm in all dimensions assemble in eukaryotes[83]. A chemoattractant CCL21 protein vault, as reported by Kar et al., increases migration of Tumor Infiltrating Lymphocytes

(TIL) and production of pro-inflammatory cytokines. The CCL21 vaults reduces tumor growth and the presence of immunosuppressive cells in murine lung cancer models[84].

Protein delivery using hydrogels encompasses several strategies, including physical entrapment in a polymer network[85], polymer degradation[86], electrostatic interactions[87], or stimuli-responsive release[88]. In the intraoperative delivery space, an *in situ* fibrin gel loaded with anti-CD47 antibodies, reported by Chen et al., induces phagocytosis of macrophages in the resection bed[89]. In their recurrence model of melanoma, the antibody loaded fibrin gel prevents recurrence in half the mice and prolongs survival (Figure 4D). Importantly, isolated macrophages from the TME exhibit higher anti-tumoral phenotypes than untreated mice. In a poly(carboxybetaine) hydrogel decorated with neutravidin binding sites, biotinylated BiTEs bind to the neutravidin sites within the hydrogel, and without the trigger molecule, biotin, slowly release the BiTEs with about 25% release after two weeks[90]. However, in the presence of increasing biotin concentrations, the hydrogel releases the BiTEs faster over the same time span. Hydrogels loaded with BiTEs against CD133, a marker for glioblastoma, show improved cytotoxicity against glioblastoma spheroids for over two weeks in comparison to free BiTEs or hydrogel loaded BiTEs in the absence of biotin. This system offers a unique advantage that until the trigger molecule is added, the release of the protein is slow, which may be advantageous in cases where immune cell trafficking requires a longer time. Implantation of a physically entrapped ICI anti-PD-1 loaded gelatin silicate hydrogel in mice, bearing melanoma tumors, increases survival and lowers tumor weights compared to mice given local tumor injection of the ICI (Figure 4E)[91]. Combination therapy approaches are being explored with chemotherapies and ICIs co-delivered within the same biomaterial. In a dual anti-PD-1 and doxorubicin loaded PEG-oxidized dextran hydrogel, Si et al. describe increased survival in colorectal cancer bearing mice that received both therapies over single drug loaded hydrogels[92]. An equivalent IP dose of both doxorubicin and ICI affords significant toxicity with all animals dying after 4 days.

2.3 Cellular Therapies

T Cell Therapy

Tumor Infiltrating Lymphocytes perform a key function of the immune response within the TME[93]. The presence of TILs in breast cancer, melanoma, rectal cancer, and ovarian cancer correlates with improved patient outcomes [94–96]. In clinical trials for cervical cancer, renal cancer, melanoma, and NSCLC, treatment with TILs shows efficacy and as of February 2024 TILs are FDA-approved for treatment of metastatic or unresectable melanoma[97,98]. However, the process for generating these therapeutic TILs is timely and costly. First, patients must undergo a surgical tumor resection, and from the tumor, TILs are isolated. Depending on the patient, the number of TILs isolated can be quite low[99]. Isolated TILs are then screened and clonally expanded to generate sufficient cell numbers to inject back into the patient. While this Adoptive Cell Therapy (ACT) is effective for some patients, overall response rates are limited due to the lack of control over which antigens the TILs target. Improvements for ACT with biomaterials are an active area of research. Stephan et al. report an alginate hydrogel for delivering T cells to a tumor resection site and enhancing *in situ* proliferation through extended release of an IL-15 super agonist from silica microparticles embedded within the hydrogel. The hydrogel increases T cell activity in the TME and improves survival over IV and IP bolus doses of T cells in both murine models of breast (4T1) and ovarian (ID8) cancers[100].

In comparison, Chimeric Antigen Receptor (CAR) T cells are a subset of ACT therapies engineered to recognize and attack specific cancer antigens. The typical structure of the receptor includes a scFv, a transmembrane domain, and signaling domains including CD28 and CD3 (Figure 5A). The FDA has approved six CAR T cell therapies targeting CD19 and B-Cell maturation antigen (BCMA) as of 2024 for relapsed and refractory leukemia, lymphoma, and multiple myeloma, establishing CAR T cell therapy as a proven cancer treatment modality (Table 2)[101]. However, efficacy using CAR T cells in solid tumors is limited by a lack of specific antigens, poor T cell persistence in the immunosuppressive TME, and on-target, off-tumor toxicity, wherein CAR T cells recognize healthy cells expressing low levels of antigen[102–104].

Current approaches to overcoming barriers in the treatment of solid tumors with CAR T cells include receptor engineering for enhanced sensitivity or specificity, combination immunotherapy with ICIs or co-expression of cytokines to improve persistence, or expression of homing ligands to improve trafficking[105]. Logic-gated CARs represent a major advance in the sensitivity and specificity of CAR T cell therapy. Such CARs utilize engineered receptors that sense multiple inputs (e.g., multiple cancer antigens) to produce predefined responses, much like a logic gate performing Boolean logic in an integrated circuit[106]. Common examples include OR gates[107], which respond to multiple antigens, AND gates[108], which require recognition of two antigens for activation, and NIMPLY (or NOT) gates[109], which enable CAR activation only when one antigen and NOT another are present.

Table 2. FDA Approved CAR T cell Therapies

Therapy	Target	Indication	Approval
Kymriah	CD19	B cell acute lymphoblastic leukemia, Diffuse large B cell lymphoma	2017
Yescarta	CD19	Diffuse large B cell lymphoma, Follicular lymphoma	2017
Tecartus	CD19	Mantle cell lymphoma, B cell acute lymphoblastic leukemia	2020
Breyanzi	CD19	Diffuse large B cell lymphoma	2021
Abecma	BCMA	Multiple myeloma	2021
Carvykti	BCMA	Multiple myeloma	2022

Logic gates are often incorporated into complex CAR systems such as universal and inducible CAR T cells to allow tunable signaling and control. Inducible CAR T cells use split proteins or proteases to trigger signaling upon cellular uptake of a small molecule agent. Wu et al. report an inducible CAR that clears $CD19^{+}$ leukemia cells after systemic administration of

rapalogs[110]. Labanieh et al. and Li et al. utilize grazoprevir, a small molecule NS3 protease inhibitor, to activate or deactivate CAR T cells, allowing fine-tuned, on-demand modulation of CAR T cell activity *in vivo* (Figure 5B), SNIPCAR and VIPER CAR respectively[111,112]. Universal CAR T cells utilize the same receptor for all CAR T cells and bind to an adaptor targeting a particular antigen. Such systems enable a CAR T cell to target multiple antigens, switch antigens, or modulate activation responses based on the adaptor molecule targeting and concentration[113]. Cho et al. describe tunable signaling and antigen switching in universal CAR T cells called SUPRA (split, universal, programmable) CAR T cells (Figure 5C), enabling cell-type specific programming and control of cytokine release while achieving high efficacy against NALM6 and SKBR3 tumors preclinical murine models[114]. Further, this technology enables complex biocomputations such as 3-input logic circuits and intercellular communication pathways[115]. However, translation of logic, universal, and inducible CAR technologies into solid tumors requires greater spatiotemporal control of inducer or adaptor molecules. While these approaches show efficacy in murine models, recapitulating aspects of human disease such as antigen heterogeneity, immunosuppression in the tumor, and on-target, off-tumor toxicity prove challenging. Moreover, very few preclinical models allow assessment of CAR T cell therapy in the context of neoadjuvant or adjuvants, a clinical setting in which immunotherapies are crucial for the treatment for cancer, such as lung cancer.

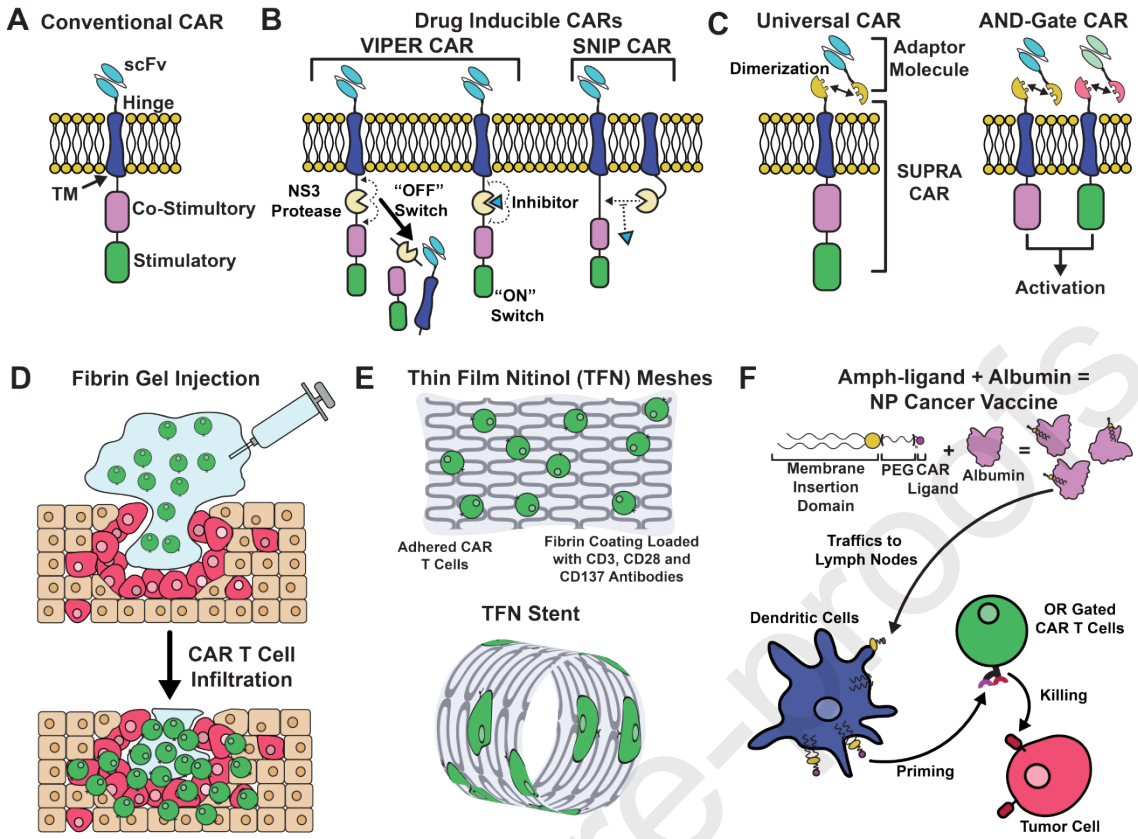


Figure 5. Chimeric Antigen Receptor designs for the antigen targeting domain (scFv), Hinge, Transmembrane (TM) and stimulatory domain across **A)** conventional, **B)** drug inducible (adapted from Li et al. and Labanieh et al.[111,112]), and **C)** universal and logic gated (adapted from Cho et al.[114]). **D)** Fibrin gels encapsulating CAR T cells prevents tumor recurrence when applied at the site of tumor resection to enhance anti-tumor activity (adapted from Ogunnaike et al.[118]). **E)** Nitinol meshes coated with fibrin and T cell binding antibodies promote CAR T cell adhesion, enabling the formation of various biomaterial geometries from standard meshes to cylindrical meshes (adapted from Coon et al.[122]). **F)** A cancer vaccine using synthetic amphiphilic ligand to traffic to lymph nodes and inserting into the membrane of dendritic cells. This primes OR Gated CAR T cells, enabling potent anti-tumor toxicity of heterogenous tumors (adapted from Ma et al.[123])

Biomaterial delivery of CAR T cells is a rapidly developing space with researchers investigating methods for delivery of the CAR T cells or, in the case of logic CAR T cells, the agents that modulate the CAR T cell response. Hyaluronic acid hydrogels containing a cocktail of CAR T cells, polymeric NPs delivering IL-15, and ICIs for anti-PD-L1 conjugated to platelets, demonstrate efficacy in a murine model of melanoma[116]. A transient injectable dodecyl-modified hydroxypropyl methylcellulose hydrogel delivers anti-B7H3 CAR T cells and IL-15 thereby cultivating a pro-inflammatory niche in the TME. In a murine model of human medulloblastoma, delivery of both CAR T cells and IL-15 outperforms the individual components[117]. In murine glioblastoma and adenocarcinoma models, the local application of CAR T cells within a fibrin gel to the surgical bed improves CAR T cell efficacy while reducing on-target, off-tumor toxicity, as reported by Ogunnaike et al. and Uslu et al., respectively (Figure 5D) [118,119].

Huang et al. describe DNA particles for spatiotemporal controlled delivery of *in vivo* priming signals to enhance synNotch CAR T cell activity. The particles allow modular loading of immunomodulatory proteins such as ICIs, cytokines, and stimulatory ligands. Delivery of these particles and AND-gate CAR T cells induces robust expression of CAR and improves survival in a murine model. A benefit of this system is the presentation of the bio-orthogonal ligands for stimulation at a specific site thereby localizing CAR T cell activity[120]. Similar formulations, such as alginate scaffolds with incorporated stimulator of STING agonists and nitinol films carrying CAR T cells demonstrate efficacy *in vivo* (Figure 5E) [121,122].

Biomaterials used to deliver cancer vaccines also improve CAR T cell activity. Ma et al. describe synthetic amphiphile ligands, conjugated to an antigen, that complex with albumin to travel to the nearby draining lymph nodes. The amphiphile self-inserts into the surface of antigen presenting cells, specifically dendritic cells, where the CAR T cells are primed against the antigen on the amphiphile (Figure 5F). This cancer vaccine enhances expansion and antitumor efficacy of CAR T cells in immunocompetent murine models of glioma and melanoma. The antigen on the synthetic amphiphile may be swapped to a bio-orthogonal antigen such as FITC, thus allowing for an OR-gated CAR T cell with one antigen targeting domain being FITC and the other being tumor specific increasing the tumor clearance[123].

CAR Natural Killer (NK) Cells

Due to cost, safety, and efficacy challenges, researchers are implementing CAR in the innate immune system, primarily with NK cells and macrophages. NK Cells are effector lymphocytes that assist in immunosurveillance and kill cancerous cells without any prior sensitization[124]. This trait stems from the regulation of NK cells by activating and inhibitory receptors. NK cell mediated killing occurs through various mechanisms, including cytotoxic granule production, upregulation of death-ligand expression such as Fas and TRAIL, cytokine production, and antibody-dependent cell-mediated cytotoxicity[125]. NK cells offer several advantages, including allogenic treatments, as there is no host issue and tunable activation since NK killing is tuned by several activating and inhibitory receptors.

Similar to the CAR T design, CAR NK receptors contain an extracellular scFv and hinge domain, a transmembrane domain, and intracellular signaling domains. These activating domains originate from a large variety of receptors, including cytokine receptors critical for NK cell activity. First generation designs for CAR NK include the activation domain of CD3ζ, with proceeding generations including costimulatory domains such as CD28, tumor necrosis factor or single lymphocytic activation molecule family of genes[126].

There are currently 40 actively recruiting clinical trials for CAR NK cells, spanning hematological malignancies, such as acute myeloid leukemia and B cell lymphoma, as well as solid malignancies such as ovarian and small cell lung cancer[127–132]. Three clinical trials for CAR NK treatment ALL, CLL and Non-Hodgkin Lymphoma have been completed and report promising results in the safety and efficacy of these therapies[133–135]. Additional preclinical work supports CAR NK therapies for other tumors. For example, NK cells electroporated with RNA encoding an NKG2D CAR increases NK cell activity when assessed *in vitro*, leading to pilot studies for treating chemotherapy refractory metastatic colorectal cancer patients [124,136]. CAR NK are of particular interest for the treatment of solid tumors such as glioblastoma, breast cancer, and ovarian cancer[137], as designer CAR NK therapies may overcome the challenges of poor infiltration and low persistence in the TME seen with CAR T cell therapies[124].

CAR Macrophages

In addition to NK cells, monocytes and macrophages are also explored as a potential alternate cell type for using CAR constructs. Macrophages are an integral part of the innate immune defense and perform a crucial role in the immune system's fight against cancers. Broadly speaking, macrophages are classified into one of two polarized phenotypes, being the pro-inflammatory phenotype M1, or the pro-healing phenotype M2. Additionally, macrophages switch their polarization states and may exist in a spectrum between the two states. Macrophages that infiltrate solid tumors, or tumor associated macrophages, often skew towards an M2 state and function in a pro-tumoral manner. While efforts focus on polarizing TAMs from an M2 to M1 state add a CAR (CAR M) to provides greater potential for clearing solid tumors.

CAR M receptors are designed similarly to their CAR NK and CAR T counterparts; an antigen binding domain (usually an scFv), a hinge and transmembrane domain, and intracellular signaling domains. Pre-clinically, CAR M shows substantial promise for mediating tumor killing both *in vitro* and *in vivo*, across various antigens, including HER2, mesothelin, GD2, MUC1, EGFR III, and CD19[138]. The intracellular signaling domains for CAR M receptors include one or more stimulatory domains to generate signaling. While CD3ζ is a common signaling domain across the CAR cell types listed, additional domains investigated to increase phagocytosis of CAR M include CD147, FcRγ and Megf10[139–141].

There are currently four active CAR macrophage clinical trials with one phase-1 showing promising preliminary results for solid tumors. The first-in-human trial of CT-0508, an anti-HER2 CAR M generated using autologous monocyte derived macrophages, involved 18 patients with unresectable or metastatic solid tumors overexpressing HER2 (cholangiocarcinoma or breast, esophageal, ovarian, or salivary carcinoma), that received CAR M over the course of a single or multiple days (NCT04660929)[142]. For the 9 patients for whom pharmacokinetic data is available, CAR M cells are present in the TME of 8 patients. Best overall responses correlate with elevated pro-inflammatory cytokine levels, TME remodeling, T-cell expansion and tumor infiltration. Regarding safety, most adverse effects were grade 1 to 2 with cytokine-release syndrome (CRS) and infusion related reactions being the most common. These results for CAR M therapies are promising and serve as an initial benchmark as more clinical data is generated from other studies.

Both CAR NK and CAR M therapies pose several advantages compared to conventional CAR T therapies (Table 3). The greatest of these advantages are the fact that they present the potential for truly allogenic cell therapies, as both NK and macrophages pose minimal risk of CRS. Additionally, given the variety of options for sourcing NK cells and macrophages such as PBMC's, induced pluripotent stem cells (iPSCs), and immortalized cell lines (NK92 and THP1), these therapies are a better candidate for potential off-the-shelf therapies.

Table 3. Comparison of T Cells, NK Cells, and Macrophages for CAR Therapy

	CAR T	CAR NK	CAR M
Transmembrane Domain	CD8, CD28	CD8, NKG2D, CD28	CD8, CD147, CD28

Intracellular Signaling Domain(s)	CD3ζ, CD28, 4 1BB, CD137	CD3ζ, DAP10, DAP12, CD28, 4-1BB, 2B4	CD3ζ, Megf10, OX40, CD28, 4-1BB, CD86, CD147, TIR, TLR, Bai1, PIE3K, MerTK, MYD88, FcRγ
Efficacy in Solid Tumors	Low	Moderate	High
Cell Sources	Primarily Autologous Allogeneic - MHC-I Matched T Cells	Autologous or Allogeneic NK-92 PBMC Cord Blood hESC iPSC	Autologous or Allogeneic THP-1 PBMC hPSC/ iPSC
Off the shelf potential	Low	High	High
Clinical Status/ Approval	6 FDA approved therapies	40 actively recruiting trials	4 active or completed clinical trials
Mechanism of Action	CAR Mediated	CAR Mediated Fas/TRAIL Ligand Production Cytokine Secretion	CAR Mediated Trogocytosis/ Whole cell eating Reactive Oxygen Species Secretion Antigen Presentation Cytokine Secretion

While both therapies hold significant promise, substantial challenges must be overcome for their broader application. Both cell therapies face manufacturing hurdles, especially with regards to transduction of cell types with the CAR constructs using common lentiviral and retroviral methods. For example, hydrogel scaffolds are being investigated to improve manufacturability, streamline the process, reduce cost, and shorten the time between isolation of the T cells and treatment. The Brudno group generates CAR T cells using a facile cryo-alginate scaffold process and observes comparable CAR transduction to traditional centrifuge-based techniques[143]. These gels have not been explored for transduction of NK cells or macrophages, however this is a logical extension and worthy of exploration. Additionally, use of nanoparticulate nucleic acid complexes may enable alternative manufacturing options such as *in situ* programming of both NK cells and macrophages, thus improving the safety and manufacturability of these cell therapies by utilizing non-genomic tools for CAR expression and removing the need for *ex vivo* culture of these cells[126,138]. Besides the challenge of CAR expression for NK cells and macrophages, both cell types will require co-delivery of immunomodulatory factors to improve their efficacy in the TME. For NK cells the absence of cytokine support lowers persistence and for macrophages, polarization to a pro-tumor phenotype

will reduce the efficacy of the cell therapy[124]. Biomaterial delivery of pro-inflammatory cytokines locally to the TME will enhance the persistence of these cell therapies without over activation of the immune system. As of writing this review, intraoperative utilization of these therapies has yet to be explored; however, the combination of these therapies with biomaterials and treatment via an intraoperative route offers solutions to address the challenges mentioned above.

3. Future outlooks on immunotherapies delivered by biomaterials intraoperatively

Immunotherapies are the fourth mainstay of antineoplastic therapy, alongside surgery, chemotherapy/targeted therapy, and radiation therapy. This breakthrough treatment offers immense potential for improving patient outcomes for cancer therapies; however, safety and efficacy concerns limit their use. Biomaterials and drug delivery strategies provide a means of focusing the cytotoxic effects of immunotherapies to achieve efficacy without concomitant toxicity. Biomaterial depots for small molecule agents, STING and TLR agonists, improve the immune system response in the TME while reducing the non-specific effects of these agonists. Additionally, the use of biomaterial depots for controlling the spatial location and activity of CAR T cells is an area of active and continuing research. As the delivery of these depots intraoperatively maybe challenging given the location, imaging offers a unique partnering opportunity to precisely deliver these immunotherapy-loaded biomaterials to the TME. Currently, imaging modalities such as x-ray and ultrasound are being utilized intraoperatively to determine the precise location of structures, and, thus, x-ray and ultrasound responsive biomaterials are of interest to accurately and on-demand deliver an immunotherapy payload [144–146]. In models of on-target, off-tumor toxicity, Ogunnaike et al. and Uslu et al. report the enhanced safety of conventional CAR T cells, simply by spatially concentrating their delivery to the tumor space instead of systemic circulation via IV injection[118,119]. Further, by focusing the biodistribution and pharmacokinetics of active agents delivered to a tumor, one can maximize anti-cancer activity in a localized manner, increasing efficacy. This is especially the case of agents where the circulation half-life is short, such as small molecules and recombinant proteins.

While single agent delivery improves the immune response in the TME, combinations of multiple immunotherapies or immunotherapy plus chemotherapy induce sustained anti-tumor responses within the TME. The primary focus of this review is on immunotherapies on their own, however; a future direction for this field is the co-delivery of cytotoxic drugs, such as chemotherapy. Several advantages are forefront as local delivery of chemotherapy will likely improve the basal tumor clearance. Furthermore, chemotherapies may synergize with immunotherapies as some chemotherapies induce immunogenic cell death. Co-delivery of ICIs and doxorubicin from a hydrogel depot enhances tumor clearance and illustrates the potential for further co-delivery treatments[117]. Multiplexing the delivery of multiple agents will only continue to expand as the factors required to induce full remission in each TME becomes known. In the case of conventional CAR T cells, co-delivery with cytokines improves the robust response, but does not ensure clearance of heterogeneous tumors with diverse target antigens. Thus, delivery of an additional immunomodulatory factor may improve the presentation of other antigens or induce logic-gated killing on multiple antigens.

While the preclinical studies mentioned above demonstrate the substantial potential for biomaterials to enhance immunotherapies intraoperatively, several challenges exist in translating these technologies to clinical trials. Depending on the biomaterial, the manufacturing scale-up for several of these systems is likely challenging. For instance, protein-based biomaterials maybe expensive to produce at scale due to the cost and purification required.

Additionally, novel biomaterials may require multi-year clinical trials for their safety. However, several of the biomaterials mentioned in this review are already FDA approved and used in the clinic. For example, fibrin gels are widely used in the clinic, produced on a scale for commercial use, and their safety profile is already established. The combination of CAR T cells and fibrin glues is a smart, translationally favorable delivery approach. Finally, the nature of the immunotherapy being delivered significantly affects the likelihood of entering a clinical trial. For example, small molecules such as STING agonists are much cheaper, easier, and faster to manufacture than CAR T cells. Thus, translation also depends on the therapeutic of interest.

The challenges to immunotherapies in solid tumors are incredibly complex and require a multi-pronged strategy to include optimization of the administration method, biomaterial form factor, and agent pharmacokinetics, as well as the use of combination therapy. As such, immunotherapy is a prime example where only through collaborating teams of scientists, engineers, and clinicians/surgeons will we continue to advance the field with the goal of improved patient care. We advocate for intraoperatively delivered immunotherapies, particularly at the time of resection, as this is a viable therapeutic solution which capitalizes on advances in biomaterials and drug delivery with direct access to the tumor.

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