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Biomaterial-Based Implantable Devices for Cancer Therapy

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Please submit a plain text version of your cover letter here. **If you are submitting a revision of your manuscript, please do not overwrite your original cover letter. There is an opportunity for you to provide your responses to the reviewers later; please do not add them here**.	Dear Editor, It is my great pleasure to submit to Advanced Healthcare Materials on behalf of my co-author Dr. Sue Anne Chew, our review manuscript entitled “Biomaterial-based implantable devices for cancer therapy” by S.A. Chew and S. Danti In this review, the application of biomaterials for the local delivery of cancer therapy and promising upcoming research in this field were highlighted and discussed. There are several authoritative review articles that focus on the delivery of therapies locally using biomaterial-based micro- and nanoparticles that have been published over the year. Our review differs from these reviews as it focuses instead on biomaterial-based implantable devices (namely, macroscale materials often provided with micro-and nano-scale features) that have been emerging as functional modes for the local delivery or actuation of cancer therapies. In this manuscript, we highlight the use of implantable devices not only for the delivery of different chemotherapy agents, but other innovative applications including combinational therapies (i.e. anti-angiogenic agents with radiotherapy or systemic chemotherapy) and promising future applications such as immunotherapy, poly-chemotherapy, gene therapy and capturing of metastatic cells. I confirm that neither the manuscript nor any parts of its content are currently under consideration or published in another journal. My co-author and I declare that no conflict of interest exists for this study. Hoping that you may find our contribution innovative, interesting, and suitable for publication in Advanced Healthcare Materials. Yours sincerely, Serena Danti
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Abstract:	This review article focuses on the current local therapies mediated by implanted macroscaled biomaterials available or proposed for fighting cancer and also highlights the upcoming research in this field. Several authoritative review articles have collected and discussed the state-of-the-art as well as the advancements in using biomaterial-based micro- and nano-particle systems for drug delivery in cancer therapy. On the other hand, implantable biomaterial devices are emerging as highly versatile therapeutic platforms, which deserve an increased attention by the healthcare scientific community, as they are able to offer innovative, more effective and creative strategies against tumors. This review summarizes the current approaches which exploit biomaterial-based devices as implantable tools for locally administrating drugs and describes their specific medical applications, which mainly target resected brain tumors or their metastases for the inaccessibility of conventional chemotherapies. Moreover, a special focus in this review is given to innovative approaches, such as combined delivery therapies, as well as to alternative approaches, such as scaffolds for gene therapy, cancer immunotherapy and metastatic cell capture, the latters as promising future trends in implantable biomaterials for cancer applications.

Optional Cover Letter

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Pisa, 30th September 2016

Dear Dr. Jos Lenders,

We thank you and the reviewers of our review article entitled "***"Biomaterial-based implantable devices for cancer therapy"***" (adhm.201600766) for their comprehensive and critical evaluation. We have revised our manuscript based on their constructive technical comments and recommendations.

Attached, please find the reply to the specific comments of the reviewers. The revised manuscript with the changes highlighted has been uploaded. Please let us know if the revised manuscript is acceptable for publication in Advanced Healthcare Material.

If you require any additional information or have any questions, please feel free to contact me immediately.

Yours sincerely,

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Biomaterial-Based Implantable Devices for Cancer Therapy

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Dedicated to Sabrina Danti and all the people who are fighting against cancer.

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Keywords: cancer; scaffolds; glioma; chemotherapy; immunotherapy.

Abstract

This review article focuses on the current local therapies mediated by implanted macroscaled biomaterials available or proposed for fighting cancer and also highlights the upcoming research in this field. Several authoritative review articles have collected and discussed the state-of-the-art as well as the advancements in using biomaterial-based micro- and nano-particle systems for drug delivery in cancer therapy. On the other hand, implantable biomaterial devices are emerging as highly versatile therapeutic platforms, which deserve an increased attention by the healthcare scientific community, as they are able to offer innovative, more effective and creative strategies against tumors. This review summarizes the current approaches which exploit biomaterial-based devices as implantable tools for locally administrating drugs and describes their specific medical applications, which mainly target resected brain tumors or their metastases for the inaccessibility of conventional chemotherapies. Moreover, a special focus in this review is given to innovative approaches,

such as combined delivery therapies, as well as to alternative approaches, such as scaffolds for gene therapy, cancer immunotherapy and metastatic cell capture, the later as promising future trends in implantable biomaterials for cancer applications.

1. Introduction

Cancer, also known as malignant tumor or neoplasm, accounts for a large number of diseases in which the cells have undergone mutations in their genetic material leading to uncontrolled growth. Cancer affects people of all ages, sex, social status and ethnicity and second to cardiovascular diseases, is the leading primary cause of illness-related death in the world, resulting in 8.2 million death in 2012.[1] There were 14 million new cancer cases in 2012 and this number is expected to rise to 22 million within the next two decades. The growing impact of cancer on global health and the dismal prognosis for patients, including large mortality rates, poor quality of life and high costs for therapy, have resulted in this pathology being labelled as a societal challenge for this century. There is a continuously ongoing search for improved or novel treatments to fight this deadly disease. Systemic delivery of anti-neoplastic agents, which can inhibit or halt the progression of tumors, such as chemotherapy or anti-angiogenic drugs, has long been one of the traditional methods of treating cancer. A number of technologies have been used and investigated to fight cancer systemically such as chemotherapy administered via oral capsules, injections of nano/microparticles; immunotherapy, administrated via engineered cell infusion. However even with these technologies, there still remain many shortcomings associated with systemic delivery, including low local drug concentration at the targeted tumor site, non-target cell and organ toxicity as well as low efficacy of the delivered drug due to its short half-life. The modest success and toxicity associated with current systemic delivery of drugs has motivated researchers to find a more direct approach to deliver agents for cancer therapy.

Local therapy systems, delivering the drugs directly to the targeted site of interest via an implantable system, are a promising alternative to systemic delivery. Local delivery systems are usually designed to be implanted immediately after a tumor debunking surgery, which omit the need of performing an additional surgery to place the therapeutic material in the patient. By delivering drugs topically, the pharmaceutical concentration at the tumor environment can be maximized, non-target systemic exposure and organ toxicity can be minimized and the need of finding a method to cross the blood brain barrier (BBB) for brain cancer treatments can be avoided. Furthermore, on-site delivery can increase the efficacy of the drug by bypassing the harsh environment and longer journey that the drug has to take to reach the site of interest when delivered systemically. Usually, the development of new drugs is associated with high cost and time consuming research efforts. Thus, it would be beneficial if new treatment methods are designed to successfully deliver currently available therapeutic agents. In fact, many of them have been shown to be promising *in vitro* however failed or resulted in modest outcomes when delivered *in vivo* systemically due to the barriers associated with this delivery method. Optimally designed implantable devices that can locally deliver already available and clinically-tested drugs may be an intelligent solution to repurpose promising drugs for cancer treatment.

Common implantable devices used for cancer therapy refer to subcutaneous ports for systemic drug infusion. A port, also known as a port-a-cath, is a totally implantable drug dispensing system composed of a small reservoir, refillable through periodic injections, made by a metal holder and a silicon membrane, which is placed subcutaneously and connected to a catheter that delivers the drug directly into the blood stream through an implanted needle. These devices need to be refilled periodically during therapy, washed to prevent occlusion, and finally removed by surgery, thus carrying the risks for infections and thrombosis. On the other hand, biomaterial-based implantable devices are non-hydraulic drug delivery systems where the biomaterial is the key enabler for a local therapy. Owing to the tailorability of

biomaterials, these devices can release multiple drugs and catalyze cellular reactions over different time-scales, and be designed to be resorbed instead of surgically explanted after a certain time. Some biomaterial devices are able to self-assemble upon injection, thus also avoiding the need for a surgical procedure to implant the device. Moreover, the risk for thrombosis and infections associated with these devices are low as they are not intravenous systems with no percutaneous access.

Over the years, the field of biomaterials has emerged to become a useful tool to better study cancer *in vitro* (e.g. 3D culture as an intermediate stage between 2D culture and animal models),[2, 3] for diagnostic applications (e.g. biomaterials-based immunoassay to detect biomarkers),[4, 5] for imaging (e.g. biomaterials to facilitate the delivery of contrast agents),[6] as well as for the advancement of therapies for this disease (e.g. biomaterials to assist in drug targeting and delivery).[7, 8] Biomaterial properties such as their size, shape, charge, surface chemistry, morphology and physiochemical properties can easily be tailored,[9] and thus, can be used to tackle the specific challenges in malignancies and thus, can serve as a useful innovative tool to improve the current technologies available for cancer diagnostic, imaging and therapeutics.

In this review, we focused on highlighting the biomaterials-based implantable devices that have been developed for cancer therapy. Biomaterials in the form of nanoparticles,[10] microparticles,[11] liposomes,[12] dendrimers,[13] and nanotubes,[14] have often been used to improve the systemic delivery of therapeutics such as drugs or genes for the treatment of cancer which have been address by many distinguished review papers,[15-18] and thus, are beyond the scope of this review article. Such particle-based systems have also been used to deliver drug locally to the site of interest. Although the administration of drug systemically mediated by these types of biomaterials is able to overcome some of the barriers of delivery, these particulate systems are still unable to overcome many of the challenges associated with systemic delivery including low local drug concentration at the targeted tumor site, non-target

cell and organ toxicity as well as low efficacy of the delivered drug due to its short half-life. The delivery of therapeutics locally with these types of biomaterials will not be as easily retained at the site of interest due to their small size. Implantable drug devices may be a promising alternative to overcome the drawbacks of other delivery systems whose action is not or cannot stay confined within a specific target area. Moreover, the use of implantable biomaterial devices has recently been demonstrated as an intriguing and versatile component for innovative cancer therapies different from mere drug delivery, thus appearing as next generation tools for multifunctional cancer treatments.

Various non-biodegradable [ethylene-vinyl acetate copolymer (EVAc)][19-22] as well as biodegradable materials [e.g. polyanhydride poly[bis(p-carboxy-phenoxy)propane-sebacic acid] copolymer (p(CPP:SA))],[7, 23-32] fatty acid dimer–sebacic acid copolymer (FAD-SA),[33] poly(lactic-*co*-glycolic acid) copolymer (PLGA)[34-38] and poly-ϵ-caprolactone (PCL)[39-41] have been investigated for the local delivery of different cancer therapeutic agents including chemotherapy drugs [e.g. paclitaxel, doxorubicin, bis-chloroethylnitrosourea (BCNU)] and anti-angiogenic factors such as minocycline,[8, 22, 23] and endostatin fragment.[29] The implantable materials can be in different forms including wafers, discs, films, rods or meshes and can be fabricated by different methods such as electrospinning, solvent casting, extrusion or compression molding. An overview of these biomaterials-based local delivery devices for cancer treatments is given in Table 1.

Besides the delivery of a chemotherapy drug alone, local delivery systems can also be used for other applications such as for the delivery of a combination of chemotherapy drugs (known as poly-chemotherapy) or concurrent delivery of a chemotherapy and an anti-angiogenic factor. These implantable scaffolds can also be used to delivery genes instead of only drugs. Some groups have also started developing scaffold systems for immunotherapy applications in which engineered immune cells, monoclonal antibodies, and/or immune

checkpoint inhibitors are loaded into the devices to act as cell delivery systems or vaccine sites. All these alternative applications to single chemotherapy delivery within implantable devices represent future biomaterial-based trends for novel and more effective cancer therapies (Table 1).

This review article aims at summarizing and discussing the state-of-the-art of implantable biomaterial devices as innovative tools for cancer treatment in order to provide a comprehensive and influential scientific base supporting future strategic directions in cancer therapies. This review begins by discussing the targets of localized cancer therapy in Section 2 which includes an emphasis of targeting resected primary gliomas and intracranial metastases. The biomaterial-based implantable devices for the delivery of chemotherapy is then discussed in Section 3, followed by a review of other applications of implantable biomaterial devices for cancer therapy. Specifically, Section 4 focuses on combinational therapies where local delivery of a chemotherapy or anti-angiogenic agent is combined with radiotherapy, or local delivery of an anti-angiogenic agent is combined with systemic chemotherapy. The review ends with a discussion of future applications of implantable biomaterial devices for cancer therapy in Section 5, which includes the local delivery of both an anti-angiogenic and chemotherapy drug, poly-chemotherapy, gene therapy, immunotherapy and biomaterial polymer composites.

2. Targets of Localized Cancer Therapy

2.1. Resected Primary Gliomas

Brain cancer is mostly common during childhood and later in old age.[42] Around 14,000 people are annually diagnosed with brain cancer,[42] and most of them do not survive past 2 to 5 years after being diagnosed with this malignancy.[36] Among primary brain tumors, gliomas are the most widespread, with glioblastoma multiforme (GBM) being their most

malignant and common high-grade form.[43] GBM is associated with a median survival of about 14 months.[43-46] Gliomas are usually treated by resection surgery and external beam radiation and sometimes by systemic chemotherapy or a combination of these methods.[31] Following resection surgery, tumor recurrence can occur due to the infiltrative nature of the malignant gliomas,[47] which are usually within 2 cm of the original lesion.[48] Thus, following tumor resection surgery, systemic chemotherapy treatment is often given to patients as an adjuvant therapy. However, for brain cancer, systemic delivery is not efficient as many of the drugs are usually excluded from the central nervous system (CNS) due to the BBB.[49] Although some chemotherapy agents, such as the classes of anti-proliferation alkylating agents temozolomide and nitrosoureas bis-chloroethylnitrosourea (BCNU) and lomustine, are able to cross the BBB at some extent and have been used clinically,[50] the efficacy of these drugs even as a concurrent treatment with radiotherapy has revealed to be modest.[51, 52] The insufficient improvement in patients' prognosis with current drugs is partly due to an inadequate delivery: their low local concentrations may prevent them to be really effective at the targeted sites.[53, 54] Furthermore, the short half-life (e.g., about 15-20 min for BCNU) and systemic toxicities are also problems associated with systemic delivery of these drugs.[31]

Different methods have been investigated and employed to improve the delivery of drugs across the BBB such as hydrophobic side group modification, conjugation to ligands with known BBB carriers like transferrin, or delivery with biomaterials such as liposomes or nano-particles.[55] Unfortunately, none of these approaches have been clinically successful in the treatment of glioma. This has led researchers to discover methods to deliver drugs directly at the targeted site to avoid the challenges of systemic delivery. Specifically, the devices are designed to be implanted during a resection surgery of primary gliomas as an adjuvant therapy. The outcome of implantable drug delivery devices may be different when used for a primary versus recurrent surgery in terms of the clinical benefit and safety profile. Tumor cells after recurrence tumor resection may not be as assessable due to gliosis and may prevent

diffusion of the drug into the brain parenchyma.[31] Thus, these devices are usually developed for primary and not for recurrence tumor resections.

Frazier *et al*. showed that in their rat intracranial tumor model, resection was not necessary to achieve significant increase in median survival time when the anti-angiogenesis drug minocycline was delivered locally with or without systemic BCNU (100% and 200% increase compared to no treatment, respectively).[8] However, owing to the limit in drug penetration experienced with unresected primary tumors, more focus is placed on applying local delivery of agents for resected sites.

2.2. Resected Intracranial Metastases

Brain metastases represent a frequent complication of cancers and are actually more common than primary brain tumors.[56] Around 20%-40% of patients affected by malignant neoplasms suffer from brain metastases. About 170,000 patients are diagnosed with brain metastases each year in the US which is more than 10-fold higher than those diagnosed with primary brain malignancy.[57-59] Lung cancer (minimum 50%), breast cancer (15%-25%) and melanoma (5%-20%) are the most common cancer associated with brain metastases. These metastatic brain lesions usually develop late, after extracranial metastatic sites. Despite advances in treating brain metastases, the median survival is only 7-16 months.[60-63] Novel types of therapy are thus vital to cure and prolong survival of patients with brain metastases. Furthermore, adjuvant treatment is needed by patients whose overall survival cannot be prolonged, however, can benefit from palliative care to relief neurological symptoms.[64, 65]

For multiple brain lesions (four or more), brain metastases are mostly treated with whole-brain radiotherapy (WBRT). Alternatively, for up to three lesions, a surgical approach is still used to remove the lesions prior to radiotherapy. Nonetheless, recurrence tends to occur due to microscopic-infiltrative tumor left behind after the surgery as the surgeon tries to avoid the risk of causing neurologic dysfunction.[66] Chemotherapy is not usually applied to treat

brain metastases and only considered after the other methods, (i.e. surgery, WBRT and stereotactic radiosurgery) have been exhausted.[43] This is because chemotherapy is usually ineffective as the BBB prevents the drugs to be administered to the lesions. Local control of recurrence with an implantable device may be a promising strategy as an adjuvant therapy to compliment surgical resection for brain metastases. Ewend *et al*. have developed p(CPP:SA) copolymer wafers loaded with chemotherapy agents (i.e. BCNU, carboplatin or camptothecin) for the treatment of brain metastases from breast cancer[7] and colon, renal and lung cancer and melanoma.[26] These local delivery systems were implanted and tested with or without external beam radiotherapy.

2.3. Other Types of Cancer

Due to the challenge of having to cross the BBB, a lot of the research being performed on biomaterials-based local delivery systems for cancer treatment have been focused on combating brain cancer either as an adjuvant therapy for primary malignant gliomas or metastatic intracranial tumors. However, besides the treatment of primary malignant gliomas and brain metastases, local delivery systems have also been developed and investigated for the treatment of other malignancies. Keskar *et al*. studied the delivery of cisplatin for the treatment of cervical cancer.[19] Cervical cancer is the second most common cancer among women worldwide. It is the leading cause of death from cancer among women in developing countries with an estimated death of 274,000.[67] Local delivery is a promising treatment method for cervical cancer because of the easy accessibility of the tumor due to the location of the cervix. Keskar *et al*. modeled the cisplatin local delivery device on currently available ring-based-intra-vaginal devices that are available for contraception. The great advantage of this device compared to other local delivery systems developed for other malignancies is that this device can be easily inserted and replaced by the patients themselves.

Liu *et al.* investigated local delivery as an adjuvant therapy for sarcoma.[68] Locoregional recurrence of sarcoma often occurs in the abdomen, pelvic and retroperitoneum after macroscopically complete resections. The currently available conventional adjuvant therapies such as systemic chemotherapy, single-dose hyperthermic intraperitoneal chemotherapy (HIPEC) and radiation have not revealed to be very beneficial. Local delivery of chemotherapy may be a potential option to replace these current adjuvant therapies. Liu *et al*. showed that the delivery of paclitaxel from a poly(glycerol monostearate-*co*-ε-caprolactone) polymer film can reduce locoregional recurrence rate and improve overall survival.

Local delivery devices have also been developed recently to combat lung cancer. Wolinsky *et al.* designed a drug eluting polymeric device for the delivery of a potent anticancer agent, 10-hydroxycamptothecin (HCPT), for the treatment of lung cancer.[69] Due to the limited pulmonary reserve, lung cancer patients often are susceptible to local tumor recurrence following primary treatment. The device developed by Wolinsky *et al.* successfully prevented local growth of malignant cells *in vivo*. Liu *et al*. used the same polymeric material to deliver paclitaxel for the treatment of non-small cell lung cancer (NSCLC) to prevent local tumor recurrence.[70] Other cancer types in which biomaterial-based devices show promising applications include leukemia and melanoma, under immunotherapy applications, which are discussed in section 5.4. A detailed discussion of the different types of biomaterials that have been used to develop implantable devices for local delivery of chemotherapy is presented in the next section.

3. Materials Used as Implantable Devices for Local Delivery of Chemotherapy

Both non-biodegradable and biodegradable materials have been used to develop implantable devices as local delivery systems for cancer therapy. For non-biodegradable materials, the release of the drug is usually administered by diffusion through the polymer

matrix which is driven by the concentration gradient of the drug in the solid. The diffusion rate of the drug will also depend on its solubility in the polymer matrix and surrounding medium, diffusion coefficient, molecular weight, concentration throughout the polymer matrix and the distance necessary for the drug to diffuse. As for biodegradable materials, the release of the drug is not only governed by diffusion but also on the erosion of the polymer matrix and thus, there are more options to control the release kinetics of the drug from these types of materials. Erosion occurs through physical dissolution of the polymer matrix by degradation. Biodegradable polymers are usually designed to degrade by hydrolysis or enzymatically. Degradation can occur through surface erosion, in which any contact between material and water is confined at the surface of the material causing polymer chain scission only at its surface, or through bulk erosion, in which water penetrates the bulk polymer causing erosion of the entire material. For both biostable and biodegradable materials, the early stage of release is often diffusion-controlled as there is a burst release of drugs adsorbed on the surface or entrapped near the surface of the matrix. This burst release is then often followed by the sustained release of the drug through erosion or further diffusion of the drug entrapped in the matrix. Although capable of successfully delivering intact drug in a controlled manner, the application of non-biodegradable materials is limited as it is more suitable for applications where the device will be removed in the future and thus, the long-term response of the body to the implant left at the site will not be a concern.

3.1. Ethylene-Vinyl Acetate Copolymer (EVAc)

Ethylene-vinyl acetate copolymer (EVAc) is a non-biodegradable material that has been used clinically for birth control applications,[71] as well as for the treatment of glaucoma.[72] This material has been shown previously to be non-inflammatory in a rabbit cornea assay.[73] Since EVAc is non-degradable, the release kinetics are based on diffusion

alone and not on the erosion of the material and thus, can easily be studied. However, because it does not degrade, the device will remain as a permanent implant.

EVAc disc or cylinders are usually fabricated by solvent casting. Yang *et al*. designed local delivery devices loaded with of Bis-chloroethylnitrosourea, (BCNU**,** also known as carmustine) from EVAc discs to avoid toxicity associated with systemic delivery and to increase local concentration of the drug for the treatment of localized brain tumors.[74] BCNU is an alkylating agent used for chemotherapy that has a very short half-life of about 15-20 min *in vivo*.[75] Compared to other drugs, BCNU is actually capable of penetrating the BBB to a certain extent due to its good liposolubility and low molecular weight.[76] However, the high systemic toxicity and short half-life of this drug makes it a good candidate that will benefit significantly from being incorporated inside an implantable system. The implantable device was fabricated by dissolving the drug and polymer in methylene chloride and the solution was then pipetted into cooled glass cylindrical molds. After evaporating the solvent, the cylinders were cut to desired weight. Yang *et al.* determined that the implantable discs were able to control the release of intact BCNU both *in vitro* and *in vivo*.[74] Furthermore, discs implanted in a rat intracranial model resulted in significantly higher concentration of the drug to the implanted hemisphere and lower levels in the peripheral circulation compared to the systemic delivery of the drug. Two other groups have also studied applications of this material to deliver the chemotherapy drugs amsacrine (Brand name: Amsidine®)[21] and mitoxantrone (Brand name: Novantrone)[20] to rat intracranial glioma models and found that their delivery from EVAc discs had potential anti-tumor effects *in vivo*.

Keskar *et al*. investigated the delivery of cisplatin from an EVAc device for the treatment of cervical cancer.[19] This biomaterial implantable device was fabricated using a similar method as Yang *et al.*;[74] however, with Teflon molds instead of glass molds. As shown in Figure 1, the cisplatin crystals were uniformly dispersed in the EVAc scaffold, resulting in two distinct phases of the polymer matrix and cisplatin crystal. *In vitro* studies

showed that the device was effective against both HPV positive and negative cervical cancer cell lines.

3.2. Polyanhydride Poly[bis(p-Carboxy-Phenoxy)Propane-Sebacic Acid] Copolymer (p(CPP:SA))

Polyanhydride poly[bis(p-carboxy-phenoxy)propane-sebacic acid] copolymer (p(CPP:SA)) is a material that has been used widely for the delivery of cancer drugs in a form of an implantable device. The biocompatibility of this material has been widely tested and found to be non-toxic.[30] The degradation rate of this polymer can be controlled by the ratio of the PCCP and SA monomers in the polymer, which provides versatility in controlling the release of the drug encapsulated. The delivery systems are usually prepared by dissolving the drug and copolymer in methylene chloride followed by evaporation of the solvent, which is usually performed in vacuum desiccators or under a nitrogen stream.[30] A dried powder is obtained through this process and then processed via compression-molding into wafers/discs. Among the implantable devices made from this material that have been investigated thus far, Gliadel®, a commercial implant which is made out of p(CPP:SA), so far is the most advanced biomaterial studied for the treatment of brain gliomas (Figure 2). Gliadel® is a p(CPP:SA) 20:80 wafer (14 mm diameter × 1 mm thickness, and loaded with 7.7 mg of drug)[31, 77, 78] that is designed to release BCNU over a 2-3 week period.[79] It has been approved by the U.S. Federal Food and Drug Administration (FDA) for the treatment of new diagnosis of high grade malignant glioma in addition to surgery and radiation, as well as for the treatment of recurrent GBM in addition to surgery. There are many studies that have investigated the benefit of Gliadel® wafers for malignant glioma.[24, 31, 80-84] Although a promising device, O^6-Alklyguanine-DNA alkyltransferase (AGT), a DNA-repair protein found in the majority of brain tumors results in resistance to BCNU. As a consequence, Gliadel® is only useful in a very limited number of patients.[85]

Other drugs and biomolecules have also been loaded into p(CPP:SA) wafers for the treatment of malignant gliomas: taxol (Paclitaxel),[30] mitoxantrone,[25] doxorubicin (DOX),[86] carboplatin,[28] and interleukin-2 (IL-2) in combination with Adriamycin (ADR).[27] Lesniak *et al.* investigated the delivery of DOX from p(CPP:SA) wafers.[86] Animals treated with DOX resulted in decreased tumor burden and tissue necrosis within the tumor and in the surrounding brain (Figure 3). More recently, Wicks *et al.* investigated the delivery of cancer-cell glycolytic inhibitors 3-bromopyruvate (3-BrPA) and dichloroacetate (DCA) with pCPP:SA wafers both by themselves or in combination with the chemotherapy drug temozolomide (TMZ) and radiation therapy (XRT).[32] They found that the delivery of 5% 3-BrPA wafer and temozolomide produced a synergistic effect compared to either therapy alone. The treatment with 5% 3-BrPA wafer in combination with both TMZ and XRT (triple combination) did not result in a statistical advantage in survival compared with the combination therapy of TMZ and XRT. However, the triple combination therapy (5% 3-BrPA wafer given on day 0 in combination with TMZ and XRT) did result in long-term survivorship of 30%.

In addition to being tested as an implantable device for adjuvant therapy at the primary glioma tumor site following resection surgery, p(CPP:SA) wafers have also been designed by Ewend *et al.* for the treatment of intracranial metastases existing from various types of cancer.[7, 26] Three different chemotherapy agents were loaded into the p(CPP:SA) wafers (1.5 mm diameter × 0.5 mm height, 5 mg in weight, 0.5%, 1%, 10%, 20% drug): BCNU, carboplatin and camptothecin. They found that the delivery of local chemotherapy alone or in combination with radiation was effective in prolonging the lives of mice with intracranial metastases for some of the combination of drugs and models (intracranial melanoma, lung carcinoma, renal cell carcinoma and colon carcinoma metastases) tested[26]. Overall, they highlighted that BCNU was the most effective chemotherapy agent. The same group also studied these three chemotherapy drugs in an intracranial EMT-6 breast cancer metastases

mouse model and demonstrated that BCNU wafers were able to significantly prolong the survival time.[7]

Hsu *et al*. investigated the local delivery of Adriamycin (ADR) from p(CPP:SA) scaffolds combined with the injection of interleukin-2 (IL-2) gelatin-chondoroitin 6-sulfate microspheres.[27] ADR works by inhibiting topoisomerase II, resulting in blocking of DNA and RNA synthesis. *In vitro*, ADR has been shown to have potent anti-glioma activity;[87] however, the effect of systemic ADR has been limited in intracranial tumors. IL-2 is a cytokine that function paracrinely to result in an anti-tumor response. In this study, Hsu *et al*. showed that the delivery of IL-2 microspheres locally by injection coupled with ADR loaded in the scaffolds were able to prolong survival in an gliosarcoma animal model compared to either therapy alone. Besides this study, they have also investigated the delivery of genetically engineered tumor cells that produce IL-2 with scaffolds loaded with BCNU or carboplatin,[88] and also the combinational delivery of IL-2 microspheres with BCNU loaded p(sCPP:SA) scaffolds.[89]

3.3. Fatty Acid Dimer-Sebacic Acid Copolymer (FAD-SA)

When choosing a biomaterial to be used for controlled delivery of a certain drug, the compatibility of the drug and biomaterial is a key parameter that should be considered. The p(CCP:SA) wafer revealed to be unsuccessful for the delivery of an innovative drug, 4-hydroperoxycyclophosphamide (4HC) due to 4HC hydrolytic instability in this copolymer. Thus, Judy *et al.* investigated the use of a copolyanhydride of a fatty acid dimer, erucic acid, and sebacic acid (1:1) to deliver 4HC.[33] This alternative polymer, FAD-SA, is able to maintain the hydrolytically unstable 4HC in a stable state for local delivery. The delivery of 4HC drug with the FAD-SA implantable device resulted in higher anti-tumor efficacy compared to the delivery of BCNU.

3.4. Poly(Lactic-co-Glycolic Acid) (PLGA)

Poly(lactic-*co*-glycolic) acid (PLGA), also referred as poly(lactide-*co*-glycolide) (PLG) is an FDA approved copolymer,[90] which is often employed for medical products. This material has been used to fabricate drug release vehicles in the form of scaffolds[91-93] and microparticles,[94-96] for many different applications, including tissue engineering and vaccinations. The degradation rate of PLGA can be tailored by tuning the lactic to glycolic acid ratio, molecular weight and the end cap groups of the copolymer. When PLGA is exposed to water, hydrolytic degradation of the ester bonds occurs, causing the polymer chain to degrade into smaller fragments and eventually yielding lactic and glycolic acid which can be metabolized by natural pathways.[97] One of the disadvantages of PLGA is that degradation byproducts of the polymer (i.e. lactic and glycolic acid) can cause a decrease in local pH, which can result in an inflammatory response and cell death at the implant site. Furthermore, the acidic degradation byproducts are associated with the accelerating of autocatalytic degradation of the polymer and thus, may result in premature release of encapsulated drug and loss of mechanical properties of the scaffold.

Xie *et al.* developed electrospun paclitaxel-loaded PLGA ultrafine- and nano-fiber implants for the treatment of brain gliomas.[38] The drug and PLGA were dissolved in methylene chloride with or without different amount of the organic salt tetrabutylammonium tetraphenylborate (TATPB) and electrospun to produce different meshes with fiber diameter of around 30 nm to 10 µm. Figure 4 are SEM images of the micro and nanofibers formed. Figure S1b and S2b in Figure 4 are images of scaffolds after 61-day of release where most of the fibers were broken and melted together due to degradation. The meshes were able to sustain the release of the drug for over 60 days. Ranganath *et al*. have also investigated the use of PLGA for the delivery of paclitaxel in malignant gliomas.[37] The paclitaxel-loaded PLGA fibrous meshes manufactured via electrospinning were able to sustain the release of drug for 80 days. The PLGA implants resulted in much smaller tumors in a mouse

subcutaneous C6 glioma *in vivo* model compared to placebo and Taxol® injected control groups.

As discussed earlier, BCNU-loaded p(CPP:SA) wafers have been widely studied and is currently clinically available as Gliadel® wafers. However, the improvement of survival with this implantable device is still modest and thus, further research is needed to find a better delivery system for this promising drug. Although the release period of drug from the p(CPP:SA) wafers can be increased by increasing the ratio of CPP to SA in the copolymer, the maximum duration of release could only reach 18 days (50:50 ratio).[98-101] Seong *et al.* proposed PLGA wafers to deliver BCNU, as this copolymer has a slower degradation rate than polyanhydride.[102] BCNU-loaded PLGA microparticles were first prepared by spray-drying and later used to fabricate wafers by compression molding. Due to the short half-life of the drug, the cytotoxic activity of free BCNU powder disappeared within 12 h. When loaded into the PLGA wafers, the release of BCNU was prolonged to 8 weeks with cytotoxic activity continuing over 1 month. The release of BCNU from these wafers was dependent on molecular weight of PLGA, concentration of PLGA in the spray drying polymer solution and initial amount of BCNU loaded into the wafers. Lee *et al*. also prepared BCNU-loaded wafers however using a different technique.[34] The drug and PLGA were mixed by vortexing and fabricated into wafers by compression molding. These BCNU-loaded PLGA wafers significantly inhibited the proliferation of 9L gliosarcoma cells *in vitro* and delayed the growth of the tumor in a subcutaneous rat model compared to the delivery of the powder itself. As seen by Seong *et al.*, due to the short half-life of BCNU, its delivery from the wafers resulted in higher efficacy and for a longer period than free BCNU powder.[102]

PLGA has also been applied in the delivery of doxorubicin for malignant gliomas.[36] Doxorubicin is a chemotherapy drug which is well recognized for its safety and has been commonly used for patients with disseminated lymphoma or leukemia in the cerebrospinal fluid. PLGA and doxorubicin were mixed and dissolved in chloroform and then

copolymerized by the solvent-evaporation method. Manome *et al*. discovered that 3×3 mm tetragon sheets implanted into a subcutaneous mice model were completely absorbed after 80 days. PLGA sheets containing doxorubicin placed next to subcutaneous tumor nodule as covering layers significantly inhibited tumor growth compared to the empty sheet controls.

PLGA thin films were used to deliver 5-[^{125}I]iodo-2'-deoxyuridine ([^{125}I]IUdR]) to an intracranial tumor mice model by Mairs *et al.*[35] [^{125}I]IUdR] is a thymidine analogue that facilitates the delivery of lethal radiation to proliferating cells, and not to quiescent cells. The delivery of this radiopharmaceutical locally after resection surgery can be a promising method of treatment for residual glioma. [^{125}I]IUdR] was added and incorporated into PLGA by sonication and then cast into a small silicon petri-dish. From this study, Mairs and coworkers concluded that the release of [^{125}I]IUdR] from an osmotic pump was superior than from the biodegradable implant and thus, further studies are needed to achieve a more promising delivery of the drug from these films.

3.5. Poly(ε-Caprolactone) (PCL)

PCL is a biodegradable, biocompatible material that has been widely utilized in many biomedical applications. One advantage of PCL is its moldability. This material is often electrospun into scaffolds, [103, 104] but it can also be used as a surgical paste. The paste is produced by heating PCL at its melting point (50-55°C) followed by injection or topical application directly to the tumor resection site, where it will harden up to a solid state at physiological temperature.[105] The addition of biological substances such as gelatin, albumin and methylcellulose can be applied to tune the release rate of the drug that is encapsulated in this polymer.[41] Due to the comparably low meting point of PCL (10-15°C above physiological temperature), thermal damage at the site of implantation is not a concern. Methoxypolyethylene glycol (MePEG) can be added to PCL to decrease the melting temperature by 5°C.[105] A relevant advantage of PCL being used as an injectable material is

the versatility in the shape and size that the material can form. As the exact contour of the resection cavity is unpredictable, the PCL-drug injectable implant can easily conform to the topography of the site.

Winternitz *et al*. studied the delivery of paclitaxel incorporated into surgical paste consisting of blends of PCL with MePEG.[105] The *in vitro* release profile for the drug was biphasic, with a burst release lasting 1 or 2 days which was followed by a slow sustained release of the drug. The PCL paste discs had anti-angiogenic activity as evaluated with the chick chorioallantoic membrane (CAM) assay of angiogenesis. The same system was used to deliver an anti-neoplastic drug, bis(maltolato)oxovanadium (BMOV) for the treatment of cancer.[39] Jackson *et al*. successfully showed that the pharmacologic effect was dependent on the prolonged exposure of the cells to the drug. The placement of the 5% BMOV-loaded PCL at the resected murine radiation-induced fibrosarcoma (RIF-1) tumor site (90% tumor resection) prevented tumor regrowth.

Dordunoo *et al*. showed that the incorporation of microparticles having co-precipitates of paclitaxel/hydrophilic additive (gelatin, albumin and methylcellulose) into the PCL paste can increase the *in vitro* release of the drug.[41] The release of the drug was dependent on the type of water-soluble agent, the microparticle size and the proportion of the additives. They also showed that the implantation of paclitaxel/gelatin/PCL surgical paste in a subcutaneous mouse tumor model resulted in 63% mean tumor regression compared to controls. By controlling the release rate of the drug with the addition of water-soluble polymers, the efficacy of drug inhibition could be improved. As for PLGA, the disadvantage of PCL is that its degradation byproducts are acidic (i.e. caproic acid) and thus, may result in an adverse cytotoxic effect at the implant site if the byproducts are release at a high concentration.

Aimed to investigate alternative surgical paste formulations, Zhang *et al*. studied the release of paclitaxel from PCL combined with other biomedical polymers, namely: *(i)* poly(D,L-lactide)-*block*-poly(ethylene glycol)-*block*-poly(D,L-lactide) (PDLLA-PEG-

PDLLA) copolymers, and *(ii)* blends of low molecular weight poly(D,L-lactic acid) and poly-ϵ-caprolactone (PDLLA:PCL).[40] Implantation of molten paste in a subcutaneous lymphosarcoma cell (MDAY-D2 tumor cells) mouse model showed that both the paclitaxel loaded (PDLLA-PEG-PDLLA) copolymer and 90:10 PDLLA:PCL blend formulations could inhibit tumor growth. In this work, Zhang *et al*. concluded that the surgical paste with a faster *in vitro* release rate resulted in greater efficacy *in vivo*, as exhibited by tumor inhibition.

3.6 Poly(Glycerol Monostearate -Caprolactone) Copolymer

Films made out of poly(carbonate-*co*-ester) copolymers based on glycerol and ε-caprolactone is another biomaterial device that has been investigated for localized cancer therapy. This polymer is very versatile as functional groups can be attached to it and thus, enabling it to be responsive to stimuli from the local environment (such as pH) and tailor its ability for different biomedical applications including drug delivery, targeting and imaging.[106] Another advantage of this copolymer is that it can be processed into different structures including fibers, particles and 3D constructs.

Liu *et al*. investigated the delivery of paclitaxel from poly(glycerol monostearate-co-caprolactone) films for non-small-cell-lung cancer (NSCLC).[70] The polymeric films were prepared by first dissolving the polymer and drug in dichloromethane. The solution were then cast onto glass cover slips or collagen-based strips, depending on the assay or experiment that it will be used for. Liu *et al.* found that the implantation of the films following surgical resection was able to prevent the recurrence of local tumor without impairing wound healing. Poly(glycerol monostearate-*co*-caprolactone) films loaded with paclitaxel have also been tested in a recurrent sarcoma model.[68] The implanted device was found to reduce locoregional recurrence and improve overall survival compared to paclitaxel delivered by intravenous injection. In addition, Wolinsky *et al*. looked at using the same material to deliver a potent anticancer agent 10-hydroxycamptothecin (HCPT) to treat lung cancer.[69] They

concluded that the device was able to prevent local tumor growth compared to intravenous treatment or unloaded composites which developed rapid local tumors.

4. Other Biomaterial-Based Implantable Therapies

Besides the application of biomaterial-based implantable devices for the local delivery of chemotherapy as discussed in Section 3, these devices can also be used to deliver other cancer therapies. Concurrent therapies are a promising alternative approach to monotherapies. When optimally designed, they can result in a synergistic effect in combating cancer with reduced side effects and toxicity to surrounding cells. When combining two therapies, it is important to take overlapping toxicities into consideration.

4.1. Chemotherapy or Anti-Angiogenic Agent Combined with Radiation

Systemic chemotherapy in combination with radiotherapy is often used to treat different types of malignancies. As an alternative method of treatment, Ewend *et al.* investigated the local delivery of chemotherapy agents (i.e. BCNU, carboplatin or camptothecin) concurrently with external beam radiation (XRT) with p(CPP:SA) copolymer wafers.[7, 26] Unlike the treatment with local chemotherapy alone which allows higher doses of the drug to be tolerated by the patients, the combination of chemotherapy and radiation therapies needs to be done with lower concentrations of the drug to take into account the possible additive toxicity effect between the two treatments.[7] For their breast carcinoma metastases model, Ewend *et al.* found that the delivery of BCNU alone with p(CPP:SA) copolymer wafers was more effective than in combination with XRT which could be due to the higher dose (20% vs 10% loaded) that could be used for BCNU alone.[7] Ewend *et al.* also tested the combination in renal, colon, lung cancer and melanoma.[26] In the renal cancer and melanoma metastases models, BCNU and XRT together were more effective than XRT or BCNU alone. If chemotherapy is used without XRT, a higher dose of drug can be tolerated.

Thus, depending on the type of metastasis, some may benefit from the higher dose of chemotherapy alone or a combination of XRT and a lower dose of chemotherapy. Among chemotherapy drugs, alkylating agents such as temozolomide and nitrosourea (BCNU) are often combined with radiation,[107, 108] as they can synchronize cells in the G2M phase, resulting as radiosensitizers when applied with irradiation.[36] The local delivery of carmustine with whole-brain radiotherapy (WBRT) was investigated for adult patients who underwent craniotomy for a single brain metastasis.[66] It was concluded that the combinational treatment was safe and there was no local recurrence, but further study is required to assess the real effectiveness of the treatment.

Besides chemotherapy agents, the potential of anti-angiogenic factors can also be enhanced by radiation therapy by increasing the sensitivity of tumor blood vessels to the anti-angiogenic inhibition. Specifically, the sensitivity of blood vessels to vascular endothelial growth factor (VEGF) inhibition was augmented and led to growth delay of human tumor xenografts.[109] Vice versa, anti-angiogenic treatment can increase the effects of ionizing radiation by preventing the repair of endothelial cells that are damaged by radiation, and thus combining anti-angiogenic drugs with radiation is also a promising method of therapy.[110] Recently, Bow *et al*. showed that the combination of local delivery of an anti-angiogenic factor, minocycline using an implantable p(CPP:SA) wafer with radiotherapy resulted in 139% and 289% increase in median survival compared to radiotherapy or minocycline polymer alone, respectively.[23] The delivery of an anti-angiogenic factor locally can potentiate the effect of radiotherapy.

4.2. Anti-Angiogenic Agent Combined with Systemic Chemotherapy

As for radiation therapy, chemotherapy can also augment the sensitivity of blood vessels to anti-angiogenic factors by increasing the sensitivity of tumor blood vessels to the anti-angiogenic inhibition.[109] Specifically, blood vessels sensitivity to VEGF inhibition can

be augmented which lead to growth delay of human tumor xenografts.[109, 111] Vice versa, anti-angiogenic factors can improve the clinical response to chemotherapy. Although the activity of anti-angiogenic factors have been promising in patients suffering from different types of cancers, the benefits of current anti-angiogenic treatments by themselves on patient survival has been very modest as its often cytostatic rather than cytoreductive. Thus, there is a need for the combination of anti-angiogenic therapy with other available therapeutic advances. The anti-VEGF inhibitor bevacizumab (the first FDA approved anti-angiogenic drug), when combined with conventional chemotherapies has been shown to significantly increase overall survival or progression-free survival of patients with metastatic colorectal cancer, NSCLC and breast cancer.[112-114] A concern with concurrent delivery of other therapeutics with anti-angiogenic factors is that the inhibition of blood vessel formation may result in impediment of the delivery of the other factors into the tumor. In contrast, as suggested by Mineli *et al*., the therapeutic factor may be entrapped in the tumor, increasing its bioavailability but the sequence and kinetics of delivery of the two different agents is vital for this to occur. [9] This window of opportunity is critical when combining with a cytotoxic agent such as a chemotherapy drug and the optimal dosing and scheduling of the anti-angiogenic agent is very vital. As stated elegantly by Ma *et al*., the net outcome of the combination therapy of an anti-angiogenic and cytotoxic drug is the balance between *(i)* tumor cell starvation by the anti-angiogenic drug, and *(ii)* decrease in cytotoxicity due to the availability of the cytotoxic drug in the tumor.[115] When the cytotoxic drug is the predominant factor as is usually the case because anti-angiogenic factors are not very beneficial alone,[8, 22] the efficacy of the cytotoxic drug may be compromised by the anti-angiogenic factor, instead of resulting in a synergistic effect. When net effect of the balance of new vessel formation and inhibition by drugs favors neovascularization, the tumor may still grow, but at a slower rate.[22] Interestingly, it has been shown that there is an improved clinical response when low dose of bevacizumab is combined with conventional chemotherapy compared to high dose of the drug.[116] This was also the

case with another anti-angiogenic factor, sunitinib where the interstitial fluid concentration of the chemotherapy agent temozolomide was increase when tumors were pretreated with a lower sunitinib concentration compared to the higher dose.[117] For monotherapy, chronic treatment of the anti-angiogenic factor with uninterrupted treatment may be beneficial. However, when combined with chemotherapy or other cytotoxic agents, a pre-treatment or concurrent delivery with a chemotherapy agent but in the earlier part of the treatment process would be more beneficial.

Malignant gliomas has very extensive microvascular proliferation and are among the most vascular of solid tumors,[118, 119] and thus, anti-angiogenesis treatment may be an important therapy for this type of cancer. Weingart *et al.* used EVAc discs to administer an anti-angiogenic drug, minocycline (Brand name: Minocin), with or without systemic delivery of BCNU.[22] Minocycline as well as other tetracyclines have been long used as an antibiotic and have also been applied for the treatment of cancer. Weingart *et al*. found inhibition of growth and prolonged survival time when local minocycline was delivered at the time of rat intracranial 9L glioma tumor implantation or after resecting the tumor. However, local delivery of minocylcline with the EVAc discs did not increase survival time when treatment was performed 5 days after tumor implantation, which mimics the time when extensive vascular proliferation has occurred. Combining the local delivery of minocycline with systemic delivery of the chemotherapy drug, BCNU significantly extended survival time but not better than the systemic delivery of BCNU alone. Thus, this suggests that for malignant gliomas with substantially developed vascular supply, minocycline delivered locally by EVAc discs is not able to significantly inhibit tumor progression by itself.

Besides BCNU, p(CPP:SA) wafers have also been used to deliver anti-angiogenic factors locally. Specifically, Pradilla *et al*. investigated the delivery of synthetic endostatin fragment (EF) from p(CPP:SA) wafers (10 mg in weight, 10%, 20%, 40% drug).[29] Endostatin is known to block matrix-metalloproteinase-2 (MMP-2) and inhibit endothelial

cell proliferation.[29] Recombinant endostatin protein is often employed as an anti-angiogenic agent; however, its use is limited due to the high production costs associated to it. Pradilla *et al*. found that EF can inhibit angiogenesis *in vitro* and *in vivo*. In a rat cornea micropocket angiogenesis assay, they saw that corneas treated with scaffolds loaded with EF had significantly lower angiogenesis index (AI) compared with corneas treated with empty scaffolds at Days 12, 15 and 20. As a single agent, EF was not able to extent the survival time, however, when combined with the chemotherapy drug BCNU, a synergistic effect in prolonging survival was observed. Moreover, p(CPP:SA) wafers have also been used to deliver the anti-angiogenic drug minocycline. As discussed above, Weingart *et al*. investigated the delivery of minocycline with the non-biodegradeble copolymer EVAc.[22] Based on the finding from their previous study, the same group moved forward and tested the delivery of this drug with the biodegradable polymer, p(CPP:SA) in an intracranial rat model with and without concurrent systemic delivery of BCNU.[8] The implantation of the minocycline wafer (3 mm diameter × 1 mm height, 10 mg in weight, 50% drug by weight) at the time of tumor implantation resulted in an 100% increase in long-term survival compared to untreated control. When implanted 5 days after tumor implantation, there was only a modest increase in median survival time, which suggests that minocycline delivery alone is only effective before the development of substantial vascular supply. When combined with systemic BCNU, the median survival time when implanted 5 days after tumor implantation increased by 82%, 121% and 200%, compared to systemic BCNU alone, minocycline wafer alone and no treatment, respectively.

Frazier *et al.* also showed similar results, however using a biodegradable p(CPP:SA) wafer.[8] The treatment of intracranial tumors in rats with the local delivery of minocycline alone from these wafers only had a modest minimal effect compared to no treatment. However, when combined with the alkylating chemotherapy drug, BCNU, the median survival time was extended by 200%. This suggests that for minocycline to be therapeutically

effective, a prior critical reduction in the tumor mass by BCNU is needed. The results obtained by Weingart *et al.*[22] and Frazier *et al.*[8] suggests that local delivery of anti-angiogenic alone may only be beneficial for resected tumor sites. When patients are diagnosed with malignant gliomas, extensive vascular proliferation has already occurred and thus for the treatment of these highly vascularize unresected tumors, concurrent delivery of a chemotherapy agent may be needed.

Recently, Bow *et al.* investigated the combination of local delivery of anti-angiogenic factor, minocycline with oral chemotherapy (i.e. temozolomide) for glioma.[23] The delivery of the anti-angiogenic factor locally with a p(CPP:SA) wafer potentiated the effects of oral temozolomide. The combination resulted in a 38% and 53% increase in median survival compared with temozolomide or minocycline alone, respectively. Bow *et al.* concluded that the combination of local delivery of an anti-angiogenic factor (instead of systemically) with oral chemotherapy may be able to increase median survival of glioblastoma patients.

Sengupta *et al.* developed an innovative nanoscale delivery system that allows the delivery of a cytotoxic chemotherapy agent, doxorubicin and an anti-angiogenic agent, combretastatin that they term as "nanocell".[120] This material delivered systemically, was able to improve the therapeutic index and reduce untargeted toxicity. Doxorubicin was first conjugated to PLGA nanoparticle and the combretastatin was trapped within the PEGylated-phospholipid block-copolymer envelope of the nanocell. The combretastatin is first released from the outer shell of the nanocell, causing a vascular shutdown and intra-tumoral trapping of the nanoparticles and this is followed by the release of the cytotoxic agent from the core of the nanocell.

Anti-angiogenic chemotherapy drugs are chemotherapy agents that also have anti-angiogenic properties such as paclitaxel, DC101 and cyclophosphamide. These type of agents have also been shown to act synergistically with direct anti-angiogenic drugs such as the

combination of the anti-angiogenic drug, DC101 with vinblastine,[121] and anti-angiogenic drug, CD105 with cyclophosphamide.[122]

5. Future Directions

Besides the application of biomaterial-based implantable devices for mono-chemotherapy and combinational therapy (i.e. local delivery of a chemotherapy or anti-angiogenic agent combined with radiotherapy or local delivery of an anti-angiogenic agent combined with systemic chemotherapy), there are other promising innovative applications of these devices to combat cancer which are discussed below.

5.1. Local Concurrent Delivery of Chemotherapy and Anti-Angiogenic Agent

Anti-angiogenic therapy is generally less toxic and less lightly to result in resistance compared to chemotherapies making it beneficial to be used as an anti-neoplastic agent. However, the benefits of anti-angiogenic treatment alone on patient survival has been very modest, and thus, there is a need for the combination of anti-angiogenic therapy with other available therapeutic advances. So far, anti-angiogenic drugs have been delivered locally with the systemic delivery of a chemotherapy agent.[8, 22, 23, 29] Another option to this is to deliver both drugs locally, in the same implantable device where the release kinetics of the different drugs can be tailored by the material properties of the biomaterials. This will allow an increase in local bioavailability of both drugs and also avoid systemic toxicity of the drugs.

5.2. Local Delivery of Poly-Chemotherapy

Combination chemotherapy has been used widely as lower doses of each drug can be delivered to reduce cytotoxicity as well as decrease the occurrence of resistance. When designing a combinational chemotherapy regimen that will be effective synergistically with

low cytotoxicity and decreased chance of resistance, it is important to: *(i)* choose drugs that do not have overlapping toxicities, *(ii)* use agents that have different mechanism of action, and *(iii)* use drugs with proven activity as a monotherapy.[123] Current strategies for combinational therapy have been focused on systemic delivery. Local delivery of the different drug is an alternative method that should be considered to lower systemic toxicity and increase local concentration of the drugs.

5.3. Gene Therapy as an Alternative to Drug Delivery

The original objective of gene therapy is to deliver a gene which replaces a defective gene.[97] However, the field of gene therapy has evolved to encompass introducing a new gene that encodes a specific therapeutic protein to a defect site in order to alter or control the path of cellular action.[124] Researchers have successfully identified proteins for different therapeutic purposes such as cancer; however, shortcomings associated with delivering recombinant protein have led to the use of gene therapy as an alternative approach to deliver the gene that encodes the protein of interest. Compared to the delivery of proteins, gene therapy allows for a longer bioavailability of the growth factors as DNAs have longer half-lives compared to proteins.[125] Furthermore, manufacturing these recombinant proteins are expensive and more difficult compared to manufacturing the genes that encode the growth factors. By using gene therapy, the proteins are synthesized *in vivo*, and as a result, the proteins can be delivered in a more biologically active form,[126] with more precise post-translational modification and tertiary structure formation.[127, 128] Hicks *et al.* investigated the delivery of the genetic sequence of bevacizumab (Avastin), an anti-human VEGF monoclonal antibody using adeno-associated virus (AAV) for the treatment of GBM.[129] The delivery of the vector with nAAV inhibited angiogenesis, reduced tumor growth and increased median survival in mice.

There are many promising implantable biomaterial based devices that have been developed for non-cancer applications, such as tissue engineering. These devices are usually composite systems which are made out of a scaffold component and a gene delivery vector that can assist in efficiently delivering the gene of interest. These vectors can be viral vector such as adenovirus and lentivirus or non-viral gene delivery vectors such as polymeric or lipid-based gene delivery vectors. Unlike the delivery of protein or drugs, the incorporation of a delivery vector component is crucial in aiding in the successful delivery of DNA because of the highly negative charge of DNA. An example of such composites is a composite developed by Curtin *et al.* which is made out of a collagen scaffold and nano-hyoxyapatite (nHA) as a non-viral gene delivery vector to deliver plasmid DNA.[130] Another example is Saraf *et al.'s* electrospun PCL fiber mesh scaffolds which incorporates poly(ethylenimine)-hyaluronic acid (PEI-HA) as a non-viral gene delivery vector.[104] These and many more other gene delivery implantable biomaterial-based devices developed under aa tissue engineering approach, may be promising candidates to be repurposed for cancer therapy applications.

5.4. Scaffolds for Cancer Immunotherapy

Immunotherapy is another strategy that aims to fight cancer, and has recently been considered as the fourth anti-cancer treatment method alongside surgery, chemo- and radio-therapy. The purpose of immunotherapy is to generate an effective and durable immune response against cancer cells. Immunotherapy strategies may act via either stimulating the intrinsic immune system and/or providing extrinsic immune system components, such as specific proteins to be targeted by the immune cells.[131] The main types of conventional immunotherapy for cancer include: *(i)* monoclonal antibodies, *(ii)* immune checkpoint inhibitors, and *(iii)* cancer vaccines. Despite the rapid advancements in this field, the success rate of current immuno-oncology is still marginal. To date, these therapies need cumbersome and expensive laboratory manipulations, which, however, have so far resulted in low homing

of *ex vivo* engineered cells in lymph nodes, thus suggesting that the present approaches should be synergized with other scientific areas to succeed in a broader population of cancer patients, with long-lasting disease eradication.[132] Consistent with this view, additional types of immunotherapies have been studied, which exploit biomaterial-based implantable scaffolds. Using a locally implanted delivery system can be a strategy to maximize the immune response at the targeted site. Some recent highlights combined immunotherapy with biomaterial devices in very different and intriguing ways.[133] So far, implantable biomaterials have been used as scaffolds for three main immunotherapy applications: *(i)* to transplant lymphocytes pre-engineered against the tumor, *(ii)* to generate vaccine sites, and *(iii)* to capture metastases.

Transfusion of lymphocytes, also known as adoptive T cell therapy, belongs to personalized medicinal therapies. It can potentially increase antitumor immunity and vaccine efficacy, thus holding the promise for the treatment of many cancer types. However, a limited efficacy has been pointed out during the clinical trials, which has ultimately restricted these therapies due to cost justification. Most importantly, in 40% - 60% of cases, the lymphocytes were able neither to be efficiently delivered to the tumor sites nor to further expand within immunosuppressive tumor microenvironments.[134] To increase lymphocyte concentration and delivery in proximity of cancer lesions, biomaterial-based devices can be extremely effective as they can be implanted next to inoperable tumors, or in resectioned tumor areas to attack the cancer cells possibly remaining in the surroundings.

Under this approach, Stephan *et al.* developed bioactive polymeric scaffolds for delivering and expanding tumor-reactive T cells.[135] These authors tested their strategy in a mouse breast resection model and in a multifocal ovarian cancer model, also checking its efficacy in tumor-reactive lymph nodes. Tumor-targeting engineered T cells were prepared and seeded on porous alginate hydrogels. Alginate is an anionic polysaccharide that is derived from brown seaweeds, which represents an interesting biopolymer as it is obtained from a

renewable source. A water-insoluble form of alginate is obtained by crosslinking with calcium chloride. Alginate hydrogels are very versatile biomaterials for medical purposes: they are used for tissue engineering, drug delivery and can be chemically or physically modified to adjust their properties.[136] Stephan *et al.* functionalized alginate scaffolds with lipid-coated microparticles conjugated to antibodies, which provided adhesion molecules and stimulatory factors enabling fast migration, sufficient expansion, and efficient release of T cells, as shown by *in vitro* assays, such as migration, release, cytotoxic activity, and cytokine expression by lymphocytes (Figure 5). In animal models, these implants effectively sustained tumor-targeting T cells and efficiently triggered tumor regression compared to conventional adoptive T cell therapies. The platform developed by Stephan and colleagues may be versatile to provide reservoirs of other cells useful in immunotherapy, such as natural killer T cells, thus appearing as a useful method for localized cell delivery in the treatment of cancer.

In addition to T cell release, scaffold systems have shown to have a great ability in tuning vaccination kinetics by recruiting/delivering cells from/to a target area. Dendritic cells (DCs) are key actors in triggering and regulating T cell mediated immunity, thus are promising targets for immunotherapy. Usually, sequences in pathogenic DNA, such as lipopolysaccharides and cytosine-guanosine (CpG) are able to activate DCs via binding to Toll-like receptors (TLRs). Thereafter, activated DCs diffuse to lymph nodes targeting specific activation and replication of T cells. When this mechanism is dysregulated, tumors develop and grow without an appropriate response by cytotoxic T-lymphocytes (CTLs). Cancer vaccines exploit patient-derived blood monocytes, as they can be easily turned into DCs *ex vivo*, activated, and infused back to the patients with the purpose to activate T cells to kill cancer cells. However, these systemic approaches for cancer vaccines have generally failed to generate a sufficient number of functional CTLs, needed to achieve a durable anti-tumor immunity.

A remarkable approach focused on the design of implantable biomaterials that regulated cell biology at a distance via targeting or mimicking specific cellular microenvironments in which certain cell populations were able to grow and differentiate. One remarkable example consisted of generating DC vaccines on implanted scaffolds (Figure 6).[137] This kind of device are designed to recruit and activate a sufficient number of DCs in order to further prime specific T cell response in lymphoid tissues. It is known that DNA plasmids encoding tissue-inductive proteins can be released from polymeric scaffolds leading to the transfection of large numbers of cells.[138] Polymeric scaffolds show the ability to attract and house host DCs via cytokine release, and to induce their activation upon exposure to danger signals and cancer antigens pre-loaded in the material. As a result, these systems can enhance DC homing to lymph nodes in remarkable numbers, which is ultimately expected to lead to specific and powerful anti-tumor immunity. To prove this concept, Ali *et al.* used a macroporous PLG scaffold loaded with both granulocyte macrophage colony-stimulating factor (GM-CSF) as an inflammatory signal, and cancer antigens (in the form of tumor lysates) to be released in a defined spatiotemporal manner within an *in vivo* melanoma model.[139] In particular, the authors exposed the mice to B16-F10 cells, which are highly aggressive and poorly immunogenic. The encapsulation efficiency of GM-CSF into PLG scaffolds via a high pressure CO_2 foaming process was 54%. The release profile of these matrices was tuned to accomplish an effective diffusion of GM-CSF in the surrounding tissue area, which was ultimately able to recruit host DCs. The scaffold released 60% of the bioactive factor within the first 5 days, followed by slow and sustained release of bioactive GM-CSF over the next 10 days. PLG matrices loaded with 3 μg of GM-CSF were implanted subcutaneously in C57BL/6J mice. This system allowed about 10^6 DCs to be first recruited and differentiated, which is the number usually administered by *ex vivo* protocols. These materials were able to sustain even larger numbers of DCs over time. In this way, a specific and protective anti-tumor immunity was achieved, which gave rise to 90% survival of treated

animals compared to 100% death in control groups (Figure 7). Using the same copolymer and various combinations of GM-CSF as an inflammatory cytokine, poly(ethylenimine) cytosine-phosphodiesterguanine oligodeoxynucleotide (PEI-CpG-ODN) solution as danger signal, and tumor lysates as antigen, Ali *et al.* also proved that the PLG scaffold was able to control the activation and *in situ* localization of diverse host DC subtypes, which ultimately primed powerful and sustained activation of CD8(+) CTL, while inhibiting immunoregulatory mechanisms.[140] The findings of this study highlighted that a minimum number of DCs ($4.2 \cdot 10^6$), allocating defined fractions of plasmacytoid DCs (pDCs) and CD8(+) DCs subtypes ($1.2 \cdot 10^6$ and $0.6 \cdot 10^6$, respectively) is necessary to induce high immunoprotection, which ultimately resulted in 90% survival in a subsequent tumor event.

In a subsequent study, Ali *et al.* tested different classes of adjuvants in PLG scaffolds to select the best combination that induced tumor protection, thus identifying DC subsets and cytokines critical for vaccine efficacy.[141] In particular, the authors showed that CD8(+) DCs, pDCs, interleukine-12 (IL-12), and G-CSF were of utmost importance to activate antitumor responses. Lately, this PLG scaffold system was also combined with immune checkpoint antibodies, antiCTLA-4 or antiPD-1, demonstrating to enhance CTL activity and induce the regression of melanoma (solid B16) cancer in mice.[142]

To avoid surgery for biomaterial device implantation, Bencherif *et al.* developed an injectable shape-memory cryogel based on alginate, incorporating both GM-CSF and CpG-ODN, that is able to attract and activate DCs, respectively.[143] This alginate scaffold was modified with covalently coupled RGD peptides to improve cancer cell adhesion via integrin binding, and was pre-loaded with irradiated B16-F10 melanoma cells (Figure 8). The underlying hypothesis of this study was that an injectable biomaterial-based vaccination is able to retain the pre-loaded cancer cells within the scaffold microenvironment, whereas allowing the resident DC to traffic and interact with the antigen-carrying tumor cells. The use

of homologous tumor cell/scaffold vaccination also aims at overcoming the high costs for extensive *ex vivo* genetic manipulation of patients' tumor cells and the regulatory issues of conventional whole-tumor cell vaccination, which, in the end, turned out not to be counterbalanced by the scarce efficacy shown in phase 3 trials. The scaffold system of Bencherif *et al.* displayed good encapsulation efficiency of GM-CSF and CpG ODN, and a sustained release of these molecules in a month time period, thus ensuring a durable microenvironment conditioning. The tumor cell/scaffold construct induced DC maturation by creating a powerful immunogenic microenvironment that ultimately evoked a strong T-effector cell response.

A key feature of biomaterial scaffolds for immunotherapy relies on the combination of specific chemokine concentration gradients to attract DCs and suitable pore features - wide enough and fully interconnected - to accommodate their trafficking into and out of the scaffold. These two characteristics were demonstrated to strongly interplay by testing DCs with a 3D scaffold model, microfabricated to have defined pore sizes and 100% interconnectivity and also incorporating the chemokine CCL19.[144] Specifically, the 3D architecture of the scaffolds remarkably affected cell chemotaxis depending on pore size, and the activation state of the cells also concurred to influence their migration inside the scaffold. This study led to the identification in microfabricated scaffolds of a 75 μm pore size that, in presence of a chemokine concentration gradient, was not hindering cell motility, thus appearing suitable for biomaterial-aided vaccination.

One approach pursued by Kim *et al.* used injectable mesoporous silica to generate a vaccine site in a mouse model injected with lymphoma cells.[145] Silica crystals exhibit inflammatory properties that are sensed by the cytoplasmic receptor NALP3, thus inducing innate immune response. The silica rods were 88×4.5 μm^2 in size and had 10.9 nm pores, supported a tumor antigen and, upon subcutaneous injection, randomly self-assembled in a 3D

macroporous structure, which spontaneously developed an active microenvironment for recruiting and activating host immune cells, while discouraging fibroblast infiltration (Figure 9). Coexistence of pore classes belonging to such different sizes was hypothesized to concur to efficient enrolment and organization of immune cells. The high surface area of this scaffold permitted specific signaling molecules to be released, which ultimately modulated the activity of the recruited host immune cells, such as DCs and prime CD8(+) and CD4(+) T cells. This system generated strong humoral and cellular immune responses, which gave rise to prolonged survival time of treated animals, thus disclosing intriguing opportunities for implanted biomaterials to act as vaccine sites via inducing antigen-specific adaptive immune responses.

The studies conducted by Ali, Bencherif, Kim and their coworkers all differ from Stephen's, since the scaffolds were used with different approaches, the formers as vaccine sites for resident lymphocytes, whereby Stephen's system was used for the delivery of *ex vivo* engineered tumor-reactive lymphocytes. In both approaches, the biomaterials played a primary role to trigger cellular reactions that ultimately promoted tumor immunotherapy.

A former investigation of Hori *et al*. may collocate at a mid-way in between the above mentioned approaches, as their device was intended both for cell/molecule delivery and for inducing an immunoresponse. These authors delivered therapeutic DCs, proteins/cytokines or other immunoregulatory factors using alginate 'self-gelling" hydrogels.[146] These hydrogels were implanted at peritumoral level through injection to ovalbumin (ova)-expressing B16F0 murine melanoma tumor, therefore the tumor growth and recruitment of leukocytes were investigated. B16-ova tumor cells were inoculated in mice and 7 or 14 days later they had received a peritumoral injection of empty or loaded self-gelling alginate matrices, as depicted in Figure 10. Hori *et al*. found that compared to systemic injection, interleukin-15 superagonist (IL-15SA), IL-15SA-carrying alginate gels were able to concentrate the cytokine in the tumor site approximately 40-folds and suppress tumor growth for a week or more. They

also found that there was not a need to delivery DCs with the immune stimulatory factors, as the delivery of IL-15SA and TLR ligand CpG or two injections of IL-15SA alone were able to elicit comparable anti-tumor activity without the delivery of DCs. The local delivery of immunotherapy with the injectable alginate hydrogels was able to promote local immune response and limit the systemic side effects.

There are different studies that investigated the delivery of a chemotherapy agent (ADR, BCNU or carboplatin) from an implantable scaffold with the local delivery of immunotherapy agents loaded in microspheres by injection.[27, 89] Development of implantable devices loaded with both the chemotherapy and immunotherapy agents in single implantable device may be a promising alternative if the release of the drugs, molecules and cells are properly controlled. Beside melanoma immunotherapy, which has been widely investigated in this decade, many other cancer types may benefit from localized immunotherapy combined with conventional chemotherapies or radiotherapies. In immunocompromised patients, such as for leukemia, in which the induced immunoresponse can be largely insufficient to fight cancer, a biomaterial-based approach could pre-stimulate the immune system by helping to reconstitute the hematopoietic cell niche before vaccination, and this is the subject of ongoing ambitious studies.

In addition to their intriguing capabilities for tumor-localized drug and immune cell delivery/recruitment, biomaterial-scaffolds have shown other unexpected properties to fight cancer. One of them is the scaffold ability to attract metastatic cells *in vivo* as reported by Azarin *et al.*[147] By exploiting the local inflammatory response generated following the scaffold implantation, immune cells were attracted to the scaffold that further recruited circulating breast metastatic cells at the early onset of the metastatic process. A porous PLGA scaffold obtained via particle-leaching was used for this purpose (Figure 11). It was engineered with lentivirus for the chemokine CCL22 to enable the infiltration of immune cells that finally attracted metastatic cell infiltration through modulation of the local immune

microenvironment. The detection of cancer cells was revealed by changes in tissue nanoarchitecture via inverse spectroscopic optical coherence tomography. The ability of this scaffold to reduce tumor burden in metastatic sites of breast cancer may disclose new therapeutic tools to improve patient prognosis and survival.

5.5 Polymer-Based Composites

Therapies that involve multiple drugs may require different release kinetics for each drug to be beneficial and result in a synergistic outcome. Especially for a therapy involving a chemotherapy and an anti-angiogenic drug, the outcome of the therapy will be different when one factor is given before the other. Past studies that have looked at delivering both a chemotherapy and an anti-angiogenic factor together, delivered the anti angiogenic factor locally with an implantable material, however, the chemotherapy drug was delivered systemically.[8, 22, 29] The delivery of both agents locally by embedding them in a single scaffold would not allow much control of the two different drugs. Thus, an implantable delivery system which will allow the tailoring of two different release kinetics is much needed. The incorporation of another component to the implantable delivery device, such as micro- and nano-particles, to result in a composite system can enable a better control of the different drugs. Micro- and nano-particles have already been widely used for cancer treatment systemically, as well as locally. Implantation or injection of particles at the site of interest will result in dispersion of the particles in a short amount of time. However, when incorporated inside the scaffold, the particles will only be release as the polymer of the scaffold erodes. Embedding the particles in a scaffold is a useful way to help control and prolong the release of the drug and further protect the drug from degradation, which will ultimately lead to its inactivation. Examples of such devices are reported by Patel *et al.*[148] and Young *et al.* [149] and are biomaterial-based implantable composites which incorporates protein-loaded (i.e. BMP-2 and VEGF) gelatin microparticles in poly(propylene fumarate) (PPF) scaffolds for

bone tissue engineering applications. As discussed in Section 5.3, delivery system for genes also require composite systems that incorporates a scaffold component with a gene delivery vector that can efficiently aid in the delivery of the plasmid DNA, siRNA or microRNA to the cells of interest. Jeon *et al.* have shown that the incorporation of plasmid DNA into composites of PLGA microspheres and an injectable PLGA scaffold resulted in prolonged released compared to the delivery of the plasmid DNA in the PLGA scaffold alone.[150] Many biomaterial-based implantable composites have been developed for the delivery of drugs,[151] proteins,[148, 149] and genes[152, 153] for other applications, such as tissue engineering. Implantable composite systems such as these may serve as potential candidates to be used for cancer therapy applications.

One example of implantable polymer composite system that has already been investigated for cancer is a halloysite (Hal)-nanocomposite hydrogel that was developed by Rao *et al.* for colon cancer drug delivery.[154] Hal nanotubes are made out of natural occurring aluminosilicates. This material can be obtained at a low cost and has good biocompatibility, thus appearing a promising material compared to carbon nanotubes.[155] Rao *et al.* loaded their drug of interested, 5-Fluorouracil (5-FU), an anticancer drug, inside the Hal nanotubes, as well as in the hydrogel network. The release of the drug could be sustained for a longer period of time compared to using the hydrogel on its own and thus, displaying the benefits of using a composite system.

6. Conclusion

Through biomaterial-based implantable devices, the local delivery of cancer therapeutic agents, which can overcome obstacles faced by systemic delivery, may result in a more successful outcome. As a consequence, advancements in treatment by the application of local delivery devices may allow the repurposing of drugs that may have previously failed with systemic treatment. Future development of biomaterial-based implantable devices should

focus on the local delivery of a combinational therapy instead of the delivery of one traditional method alone. When designing combinational therapies, several important parameters should be taken into account, such as the timing of combining these different strategies. A number of factors, including the drug concentration, exposure time and drug administration schedule, and sequence of delivery have to be carefully considered when designing a successful drug delivery systems. It is important to note that local delivery may be suitable for localized lesions, which will be benefited from a regional therapy; however, for tumors that are poorly localized and that have spread, an approach which combines local delivery and systemic delivery may be more appropriate. All in all, biomaterial-based implantable devices offer amazing versatile and tailorable approaches to fight cancer: they can deliver different drugs or proteins of interest locally with controlled modes, and/or serve as tissue engineering scaffolds for immune cell recruitment/activation/proliferation, thus representing a key weapon for next generation therapies.

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Table 1. Biomaterials that have been investigated for local delivery

Device	Bioactive Factor	Type of Bioactive Factor	Type of Cancer	Year	Reference
NON-BIODEGRADABLE					
Ethylene-vinyl acetate copolymer (EVAc)					
Cylinders	BCNU	chemotherapy	glioma	1989	Yang *et al.*[74]
Discs	Minocycline (with or without systemic BCNU)	anti-angiogenic factor with systemic chemotherapy	glioma	1995	Weingart *et al.* [22]
Rods	Amsacrine	chemotherapy	glioma	1996	Wahlberg *et al.*[21]
Triangle shaped fragments	Mitoxantrone	chemotherapy	glioma	2004	Saini *et al.*[20]
Pellets	Cisplatin	chemotherapy	cervical cancer	2006	Keskar *et al.*[19]
BIODEGRADABLE					
Polyanhydride poly[bis(p-carboxy-phenoxy)propane-sebacic acid] copolymer (p(CPP:SA))					
Wafers	Paclitaxel	chemotherapy	glioma	1994	Walter *et al.* [30]
Wafers	BCNU Gliadel	chemotherapy	glioma	1995	Brem *et al.*[81]
Wafers	Carboplatin	chemotherapy	glioma	1996	Olivi *et al.* [28]
Wafers	BCNU, arboplatin and camptothecin (with or without external beam radiotherapy)	chemotherapy	Intracranial metastases from lung, renal, colon cancer and melanoma	1996	Ewend *et al.* [26]
Wafers	BCNU, carboplatin and camptothecin	chemotherapy	Intracranial metastases from breast cancer	1998	Ewend *et al.* [26]
Wafers	Mitoxantrone	chemotherapy	glioma	2002	DiMeco *et al.* [25]
Wafers	BCNU Gliadel	chemotherapy	glioma	2003	Westpahl *et al.* [31]
Wafers	Minocycline (with or without systemic BCNU)	anti-angiogenic factor with systemic chemotherapy	glioma	2003	Frazier *et al.* [8]
Wafers	Doxorubicin	chemotherapy	glioma	2005	Lesniak *et*

					al. [86]
Wafers	Interleukin-2 and adriamycin	immunotherapy and chemotherapy	glioma	2005	Hsu *et al.* [27]
Wafers	Genetically engineered tumor cells that produce IL-2 with BCNU or carboplatin	immunotherapy and chemotherapy	glioma	1999	Sampath *et al.*[88]
Wafers	Interleukin-2 and BCNU	immunotherapy and chemotherapy	glioma	2003	Rhines *et al.*[89]
Wafers	Synthetic endostatin fragment (with or without systemic BCNU)	anti-angiogenic factor with systemic chemotherapy	glioma	2005	Pradilla *et al.* [29]
Wafers	Minocycline (with or without systemic Temozolomide or radiotherapy)	anti-angiogenic factor with systemic chemotherapy	glioma	2014	Bow *et al.*[23]
Wafers	Cancer-cell glycolytic inhibitors (3-bromopyruvate (3-BrPA) and Dichloroacetate (DCA) (with or without temezolomide or radiotherapy)	chemotherapy	glioma	2015	Wicks *et al.*[32]
Fatty acid dimer – sebacic acid copolymer (FAD-SA)					
Disc	4-hydroperoxycyclophosphamide (4HC)	chemotherapy	glioma	1995	Judy *et al.* [33]
Poly(lactic-*co*-glycolic acid) copolymer (PLGA)					
Thin film	5-[^{125}I]iodo-2'-deoxyuridine	radiation	glioma	2000	Mairs *et al.* [35]
Wafers	BCNU	chemotherapy	glioma	2002	Seong *et al.*[102]
Wafers	BCNU	chemotherapy	glioma	2005	Lee *et al.* [34]
Electrospun meshes	Paclitaxel	chemotherapy	glioma	2006	Xie *et al.* [38]
Sheet	Doxurubicin	chemotherapy	glioma	2006	Manome *et al.*[36]
Electrospun discs and sheets	Paclitaxel	chemotherapy	glioma	2008	Ranganath *et al.* [37]
Scaffolds from	Chemokine CCL22-lentiviral vector	immunotherapy	breast cancer	2015	Azarin *et al.*[147]

microspheres					
Macroporous matrix	Granulocyte macrophage colony-stimulating factor (GM-CSF) and tumor lysates	immunotherapy	melanoma	2009	Ali *et al.*[139]
Macroporous matrix	Various combinations of an inflammatory cytokine, immune danger signal, and tumor lysates	immunotherapy	melanoma	2009	Ali *et al.*[140]
Macroporous matrix	Tumor lysates, GM-CSF and various Toll-like receptor (TLR) agonists	immunotherapy	melanoma	2014	Ali *et al.*[141]
Macroporous matrix	Tumor lysates, GM-CSF and CpG-ODN, used in combination with immune checkpoint antibodies	immunotherapy	melanoma	2016	Ali *et al.*[142]
Poly(ε-caprolactone) (PCL)					
Surgical paste	Paclitaxel	chemotherapy	Not designed for a specific type of cancer	1996	Winternitz *et al.*[105]
Surgical paste (with or without MePEG)	Bis(maltolato)oxovanadium (BMOV)	chemotherapy	Not designed for a specific type of cancer: tested *in vitro* on colon, breast and non-small-cell lung cancer human cell lines, *in vivo* on murine radiation-induce fibrosarcoma (RIF-1) tumor model	1996	Jackson *et al.* [39]
Surgical paste (blends of low MW PDLLA:PCL[#])	Paclitaxel	chemotherapy	Not designed for a specific type of cancer: tested *in vivo* on lymphoma cell tumor model	1996	Zhang *et al.* [40]
Surgical paste	Gelatin microparticles/ Paclitaxel	chemotherapy	Not designed for a specific type of cancer: tested *in vivo* on lymphoma cell tumor model	1997	Dordunoo *et al.*[41]

Poly(glycerol monostearate-*co*-caprolactone)					
Films	10-hydroxycamptothecin (HCPT)	chemotherapy	Lung cancer	2010	Wolinsky *et al.* [69]
Films	Paclitaxel	chemotherapy	Non-small-cell lung cancer (NSCLC)	2010	Liu *et al.* [70]
Films	Paclitaxel	chemotherapy	sarcoma	2012	Liu *et al.* [68]
Alginate					
Injectable hydrogel	Immune cells, proteins/cytokines or other immunoregulatory factors	immunotherapy	ova-expressing B16F0 murine melanoma	2009	Hori *et al.*[146]
Discs (synthetic collagen-modified alginate)	T-cells (lymphocytes), cytokine loaded lipid-coated silica microspheres	immunotherapy	mouse breast cancer tumor model, multifocal ovarian cancer model	2015	Stephan *et al.*[135]
Injectable shape-memory cryogel	GM-CSF and CpG-ODN, irradiated B16-F10 cells	immunotherapy	melanoma	2015	Bencherif *et al.*[143]
Silica					
Injectable mesoporous silica rods	GM-CSF, ovalbumin, CpG-ODN	immunotherapy	EG7.OVA lymphoma	2015	Kim *et al.*[145]

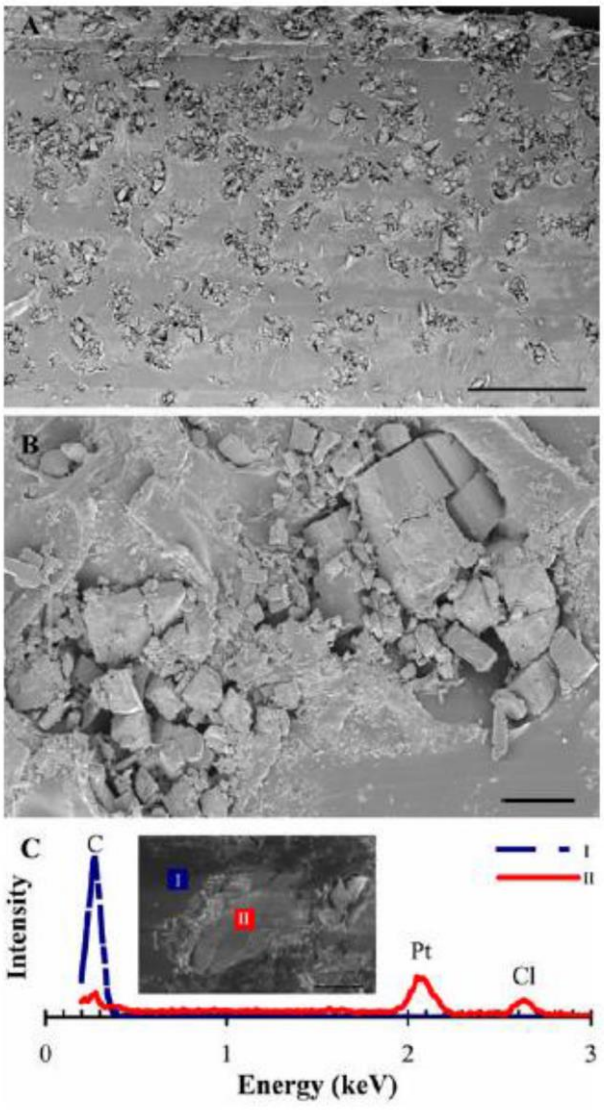

Figure 1. Representative SEM images of lateral sections of an EVAc scaffold loaded with cisplatin at (A) low magnification (scale bar = 500 μm) and (B) higher magnification (scale bar = 25 μm) which show two clear phases. (C) Energy Dispersive X-Ray Spectroscopy (EDS) spectra at the two indicated locations indicated in the inset scanning electron, polymer matrix (, I) and cisplatin crystals (, II). Reproduced with permission.[19] 2006, Elsevier.

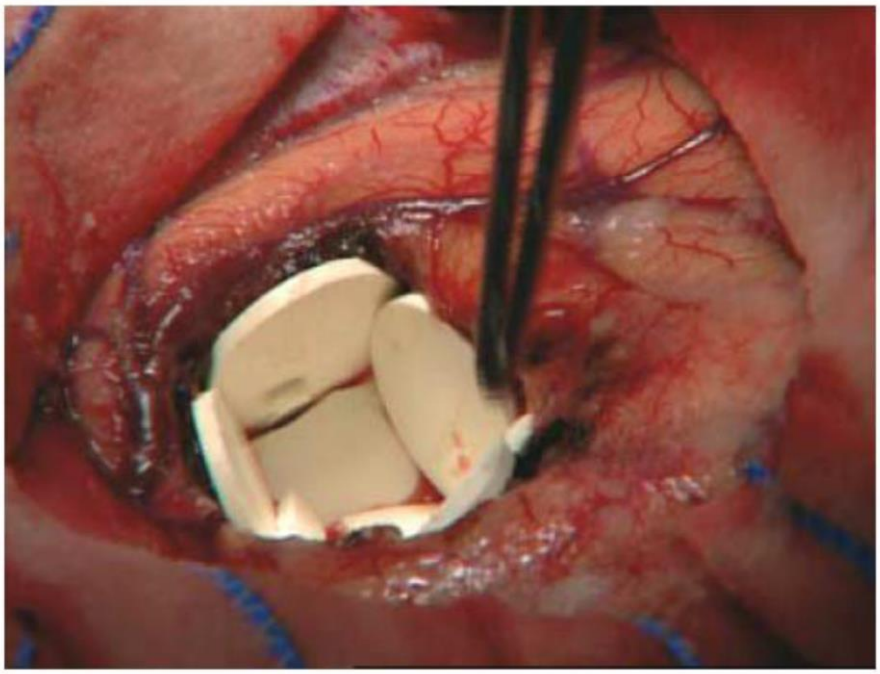

Figure 2. Photograph of the placement of GLIADEL wafers into a human brain following resection of a malignant glioma by lining 8 wafers on the walls of the tumor cavity. Reproduced with permission.[156] 2004, Nature Publishing Group.

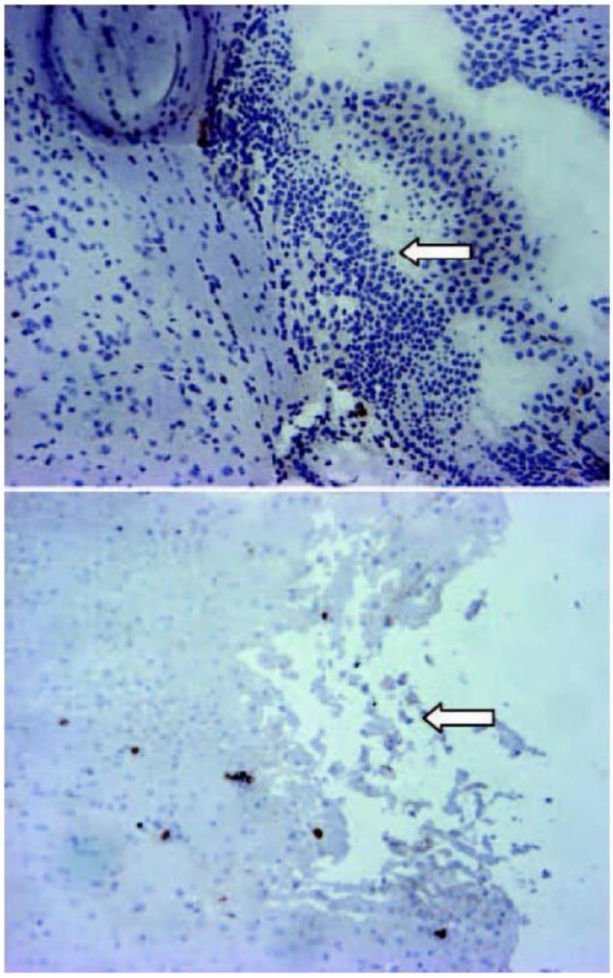

Figure 3. Representative histological images of animal brain of control group and (B) doxorubicin loaded pCPP:SA scaffold group. Arrow in A and B shows the presence of tumor cells and tissue necrosis, respectively. Reproduced with permission.[86] 2005, International Institute of Anticancer Research (IIAR).

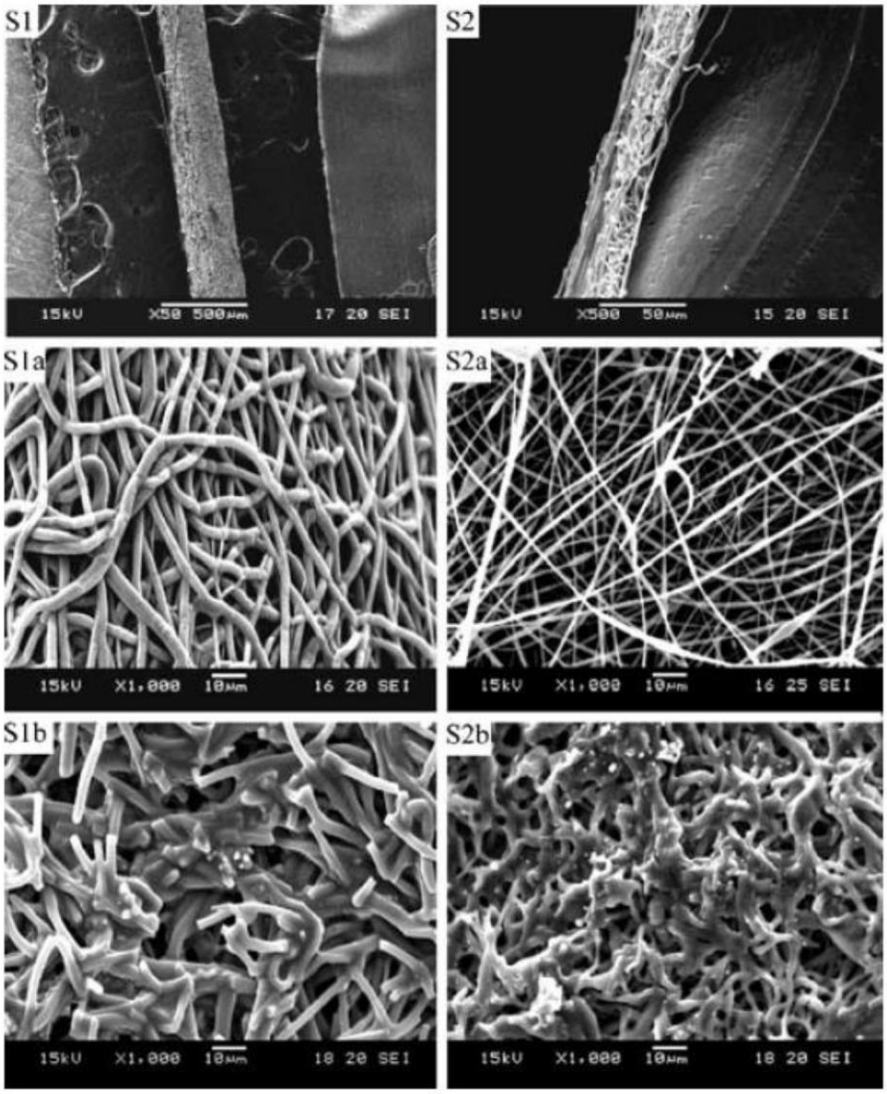

Figure 4. Representative SEM images of paclitaxel-loaded PLGA microfiber film: (S1) non-woven fabric, (S1a) before release and after 61-day release and paclitaxel-loaded PLGA nanofiber film: (S2) non-woven fabric, (S2a) before release and (S2b) after 61-day release. Reproduced with permission.[38] 2006, Springer.

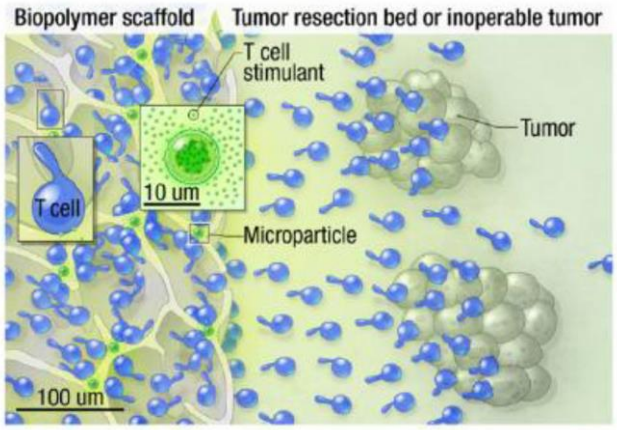

Figure 5. Schematic of Stephen et al's scaffold loaded with T cell in a tumor resection bed or inoperatable tumor site. Stimulatory lipid-coated silica microspheres incorporated into porous alginate scaffolds trigger T cell expansion and result in the exit of the cells into surrounding tissue. Reproduced with permission.[135] 2015, Nature Publishing Group.

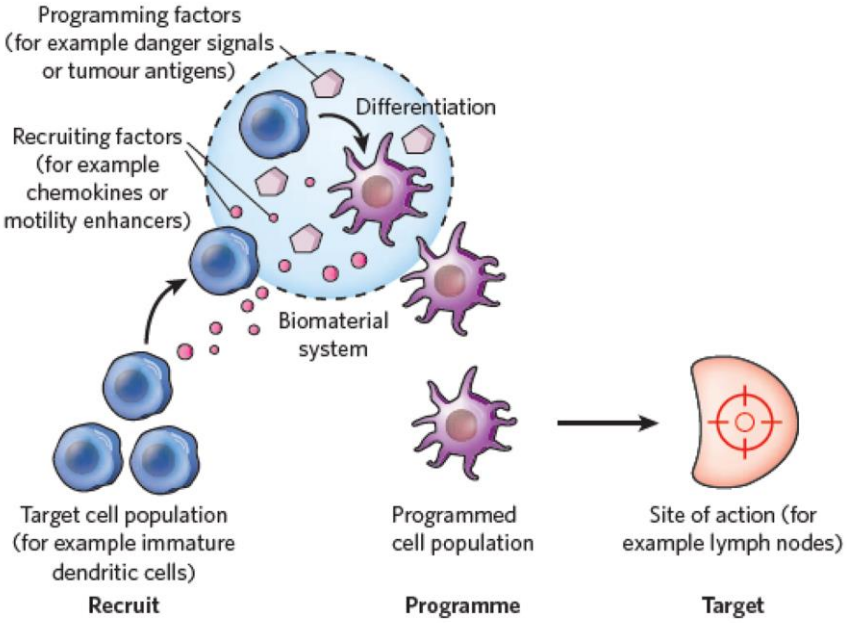

Figure 6. Schematic of an implantable biomaterial scaffolds which may mimic a vaccine site against an infection or tumor. The biomaterials contain both recruiting and programming factors for a cell population of interest, such as immature dendritic cells. This biomaterial acts as a niche by providing signals for cell differentiation and release towards the target organ, namely the lymph node, in which programmed dendritic cells finally activate the lymphocytes. Reproduced with permission.[137] 2009, Nature Publishing Group.

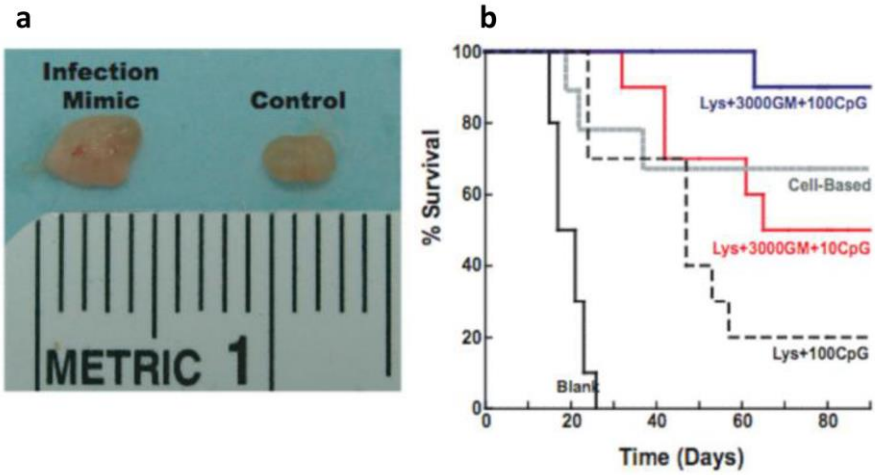

Figure 7. Results of Ali and coworkers' experiment in melanoma cell infected mice testing implanted PLG scaffolds, mimicking cancer infections that allow for recruitment, proliferation and activation of DCs, which trigger T cells in lymph nodes ultimately attacking melanoma cells. (**A**) Pictures of lymph node biopsies of mice treated with matrices incorporating 10 μg CG-ODN and 3000 ng of GM-CSF, versus untreated controls. (**B**) Comparison of survival time in mice treated with controls (blank scaffolds), tumor lysate + 100 μg CpG-ODN, tumor lysate + 3000 ng GM-CSF + 10 μg CpG-ODN, and tumor lysate + 3000 ng GM-CSF + 100 μg CpG-ODN. The mice were immunized using a cell-based vaccine. Reproduced with permission.[139] 2009, Nature Publishing Group.

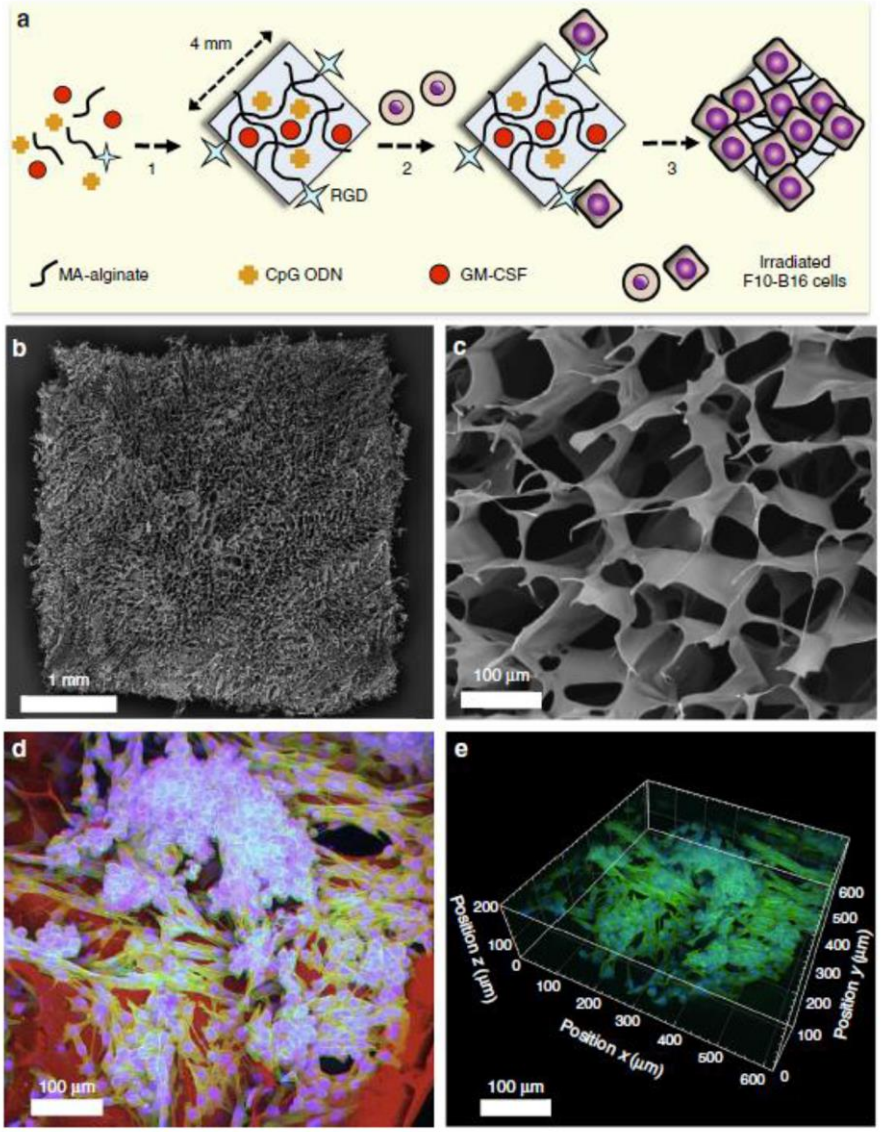

Figure 8. Alginate sponge loaded with irradiated B16-F10 cells as a vaccine strategy for melanoma. (**a**) Schematic of scaffold/cell construct preparation. The alginate matrix contains a TLR9-based immune adjuvant (CpG ODN), a cytokine adjuvant (GM-CSF) and RGD sequences. (**b**, **c**) SEM micrographs showing the scaffold: (**b**) top surface and (**c**) morphology, pores and pore interconnectivity in cross-section. (**d, e**) Laser scanning confocal microscopy images showing B16-F10 cells immobilized on the scaffold after 6 h. Actin filaments are imaged in green, cell nuclei in blue and polymer in red: (**d**) 2D micrograph and **(e**) 3D reconstruction. Reproduced with permission.[143] 2015, Nature Publishing Group.

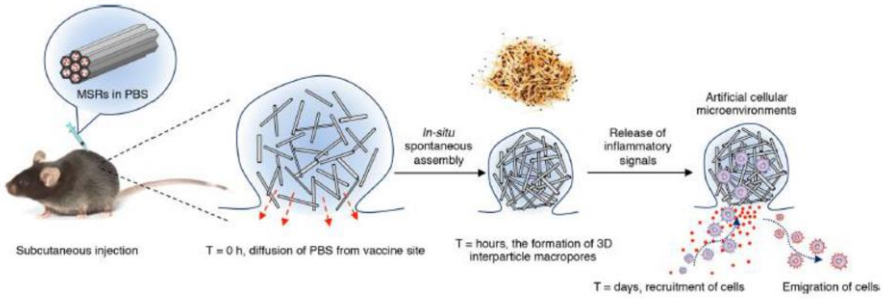

Figure 9. Schematic of the spontaneous assembly of mesoporous silica rods (MSRs) *in vivo.* MSRs dispersed in PBS are injected subcutaneously into mice. *In situ* spontaneous assemble of MSRs occurs after PBS diffusion from the vaccine site, resulting in the formation of 3D interparticle macropores. Recruited host cells are exposed to the inflammatory signals which then migrate from the device and interact with other immune cells. Reproduced with permission.[145] 2015, Nature Publishing Group.

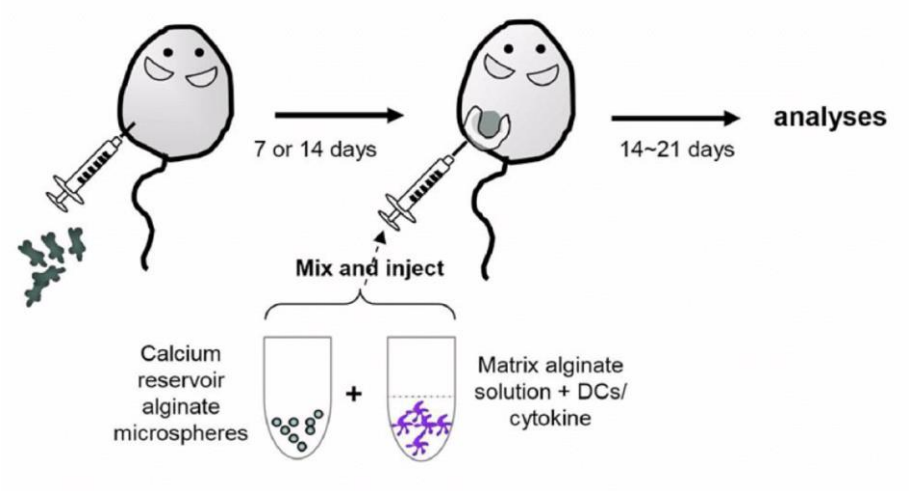

Figure 10. Schematic of the local immunotherapy system by Hori et al. B16-ova tumor cells were inoculated into C57B1/6 mice and the peritumoral injection of empty or loaded self-gelling (loaded with immune cells, proteins/cytokines or other immunoregulatory factors) alginate matrices 7 or 14 days later. After 14-21 days, the immune response and tumor growth were determined. Reproduced with permission.[146] 2009, Elsevier.

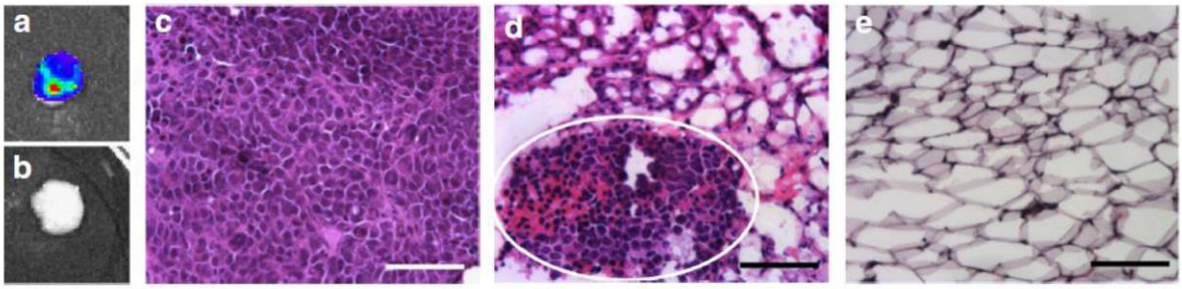

Figure 11. Representative bioluminescence and H&E stained histological images of peritoneal fat pads removed 28 days after tumor inoculation. Fat pads implanted with PLG scaffold resulted in the recruitment of metastatic cells (a,d) whereas sites without scaffolds did not accumulate tumor cells (b,e). The white circle indicates metastatic cluster. Figure c represent H&E staining of a primary tumor. Scale bars in c,d,e are 100 μm. Reproduced with permission.[147] 2015, Nature Publishing Group.

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Macroscale implantable biomaterials are recently being investigated as drug delivery systems and immunotherapy scaffolds for cancer therapy. They have shown remarkable results for tumor eradication where conventional chemotherapy, micro/nanoparticle systems and cell immunotherapy are poorly effective. The potential of biomaterial-based implantable devices, as well as their innovative and functional applications are reviewed and discussed.

Keywords: cancer; scaffolds; glioma; chemotherapy, immunotherapy.

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ToC Figure

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