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Biomaterials and Emerging Anticancer Therapeutics: Engineering the Microenvironment

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Abstract

The microenvironment is increasingly recognized to play key roles in cancer, and biomaterials provide a means to engineer microenvironments both *in vitro* and *in vivo* to study and manipulate cancer. *In vitro* cancer models using 3D matrices recapitulate key elements of the tumor microenvironment and have revealed new aspects of cancer biology. Cancer vaccines based on some of the same biomaterials have, in parallel, allowed for the engineering of durable prophylactic and therapeutic anticancer activity in preclinical studies, and some of these vaccines have moved to clinical trials. The impact of biomaterials engineering on cancer treatment is expected to further increase in importance in the years to come.

Introduction

The complexity, diversity, and dynamic nature of cancer pose many challenges to both its study and treatment. For example, the tumor microenvironment and stromal cells contribute to tumor progression as well as its escape from host immune surveillance[1–3]. Cancer cells originated from the same tumor of a patient may also be genetically heterogeneous[4–6], solid tumors tend to have leaky vasculature that allow drug access[7,8] but also have elevated interstitial fluid pressure (IFP) to impede penetration of therapeutics[9,10], and cancer cells can develop drug resistance through multiple mechanisms[11,12].

To confront these and additional challenges, many engineering tools and techniques have been created and utilized to both study cancer *in vitro*, and to develop new anticancer therapeutics. In particular, complex *in vitro* culturing systems, engineered protein or cell-based diagnostic and therapeutic agents, and sophisticated molecular or cellular delivery devices are in various stages of development. Integration of bioengineering into cancer research and therapy is not only improving the efficacy of traditional cancer treatments such as surgery[13,14] and chemotherapy[15,16], but is also opening up entirely new modalities of cancer therapy. This Perspective will discuss the current contributions of bioengineering, especially biomaterials engineering, to our understanding of cancer biology and to the

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development of emerging therapeutic strategies such as cancer immunotherapy. Biomaterial-based delivery systems for chemotherapeutics are now routinely used to treat patients (see Text Box 1), but as there have been many excellent reviews on this topic[17–20], it will not be reviewed here.

Biomaterials, traditionally defined as materials used in medical devices, provide a highly versatile tool to create defined macro and microenvironments, and manipulate cells and tissues *in vitro* and *in vivo*. They have been used since antiquity as simple prosthetics to replace damaged tissues[21], but their degree of sophistication has increased rapidly in recent years. New characterization[22–24] and synthetic methods[25,26], combined with advances in our understanding of biological processes, have greatly extended the variety as well as the size scale at which biomaterials can be designed and synthesized, and how they specifically impact signal transduction pathways. Together, these have transformed biomaterials from being simple structural supports to sophisticated devices that can interact with cells and tissues through well-defined molecular pathways at various size scales to create highly defined microenvironments to direct biological responses. As such, the same materials can now provide both a basis for *in vitro* mimics of tumors in order to better screen therapeutic approaches and identify new therapeutic targets, and a means to modulate the microenvironment *in vivo* and direct therapeutic responses against cancerous cells and tumors (Fig. 1).

This perspective will focus on two highly interrelated areas where biomaterials engineering may have a substantial impact on the development of new cancer therapies in the future. The use of biomaterials to engineer 3D human tumors *in vitro* with defined microenvironments will first be reviewed, as these may both further our understanding of cancer and provide new models for drug screening and identification. We will then discuss how biomaterials can be used to manipulate the microenvironment *in vivo* to alter the immune system, in the context of immunotherapy for cancer.

Biomaterials to create 3D tumor models

One of the most prevalent challenges in cancer research and therapeutic screening is the limitations of current *in vitro* models[27,28], which relate in part to their inability to accurately reflect microenvironmental cues found *in vivo*. Conventional two-dimensional (2D) monolayer models of human cancers have been important tools for studying cancer biology and developing anticancer therapeutics, and provide a valuable addition to what can be learned using animal models. However, it is becoming increasingly clear that conventional 2D culture models are insufficient to recapitulate many important characteristics of tumors *in vivo* and are often poorly predictive of drug response in humans[29–31]. In contrast to 2D monolayer culture models, tumor cells *in vivo* are supported by a 3D extracellular matrix (ECM) and non-tumor cells, including endothelial cells, immune cells, and other stromal cells[1,32]. Early studies have demonstrated that changing the culture of cancer cells from 2D to 3D markedly affects cell behaviors, and that 3D cultures often better resemble tumors than conventional 2D monolayers and can improve our understanding of cancer biology[33,34]. For example, coupled interactions were found between β-1 integrin and epidermal growth factor receptor (EGFR) signaling in 3D cultures of malignant human mammary epithelial

cells but not in 2D culture[35]. For drug testing, it is important that the cells in the *in vitro* assay mimic the phenotype within tumors to produce biomedically relevant responses. Although 3D tumor models have not yet had a direct impact on clinical translation at this time point, we expect that more sophisticated 3D models will become important tools for anticancer drug discovery and testing in the future. In order to better mimic different aspects of the microenvironment of human cancers, various 3D culture models have been developed. We here discuss biomaterials engineering approaches to modeling the tumor microenvironment, particularly its mechanical and structural functions, and their potential influence on testing of anticancer drugs (Fig. 2).

Engineered 3D tumors to better model cancer biology

In order to recapitulate the 3D organization and ECM of tumors, various natural and synthetic materials have been developed to provide architectural support to interacting cells[26,33]. Natural ECM-derived biomaterials such as collagen, laminin, hyaluronic acid, and reconstituted basement membrane (rBM or Matrigel) were the first and are still the most commonly used materials for 3D culture of cancer cells due to their inherent cytocompatibility, intrinsic cell adhesion properties, and ability to be remodeled by cells[33,36]. However, the batch-to-batch variability, complex molecular composition, and uncontrolled degradation of these materials often make it difficult to study the influence of a particular property of the ECM on tumor cells while maintaining other variables unaltered. Synthetic materials such as poly(ethylene glycol) (PEG) and poly(lactide-co-glycolide) (PLG) can provide more precise experimental control over biochemical and mechanical properties in modeling the tumor ECM. However, as these synthetic materials lack natural cell adhesion sites and are not readily remodeled by cells, cell adhesion ligands and biodegradable crosslinkers are often grafted to the polymers. For example, PEG hydrogels containing the integrin-binding RGD peptide and matrix metalloproteinase (MMP)-degradable peptide crosslinkers promoted 3D epithelial morphogenesis of lung adenocarcinoma cells similarly to Matrigel[37]. Another class of biomaterials that is increasingly being used in 3D tumor models is naturally-derived polysaccharides such as alginate and chitosan. They are biocompatible and have a broad range of chemical and mechanical properties, but they also lack mammalian cell adhesion sites and often require chemical modification for crosslinking to form gels with desirable physical properties[26].

In addition to providing structural support to cancer cells, 3D matrices are also used to create spatially controlled cellular compartments, allowing the interactions between cancer cells and other cells, including immune cells, to be studied in various 3D contexts. For example, collagen and rBM-based 3D systems have been developed to study tumor-induced angiogenesis by co-culturing various types of cancer cells with human umbilical vein endothelial cells or arterial explants[38,39]. Interactions of cancer cells and stromal fibroblasts in 3D have also been modeled and investigated using collagen gels[40,41]. In an *in vitro* bone metastasis model, prostate cancer cells encapsulated in PEG hydrogels were co-cultured with primary human osteoblasts seeded in bone-mimicking polycaprolactone–tricalcium phosphate scaffolds, revealing the paracrine effect of osteoblasts in altering the androgen dependency of prostate cancer cells and supporting their survival[42]. In the context of tumor-immune cell interactions, it has been shown that melanoma cells cultured in 3D become

more resistant to cytotoxic T lymphocytes (CTL) compared to cells grown in 2D monolayers, owing to down regulation of tumor antigens and major histocompatibility complex class I (MHC I), and increased production of lactate[43,44]. Similarly, 3D culture of lung carcinoma cells diminished their susceptibility to CTL activity. However, this result was attributed to a decrease in heat shock protein 70 (HSP70) expression and associated defective tumor antigen presentation[45]. Glioma spheroids also appeared to have an increased resistance to natural killer (NK) cell cytotoxicity compared to glioma cells grown in 2D monolayers[46]. These findings support the importance of using 3D culture for developing *in vitro* models of tumor-immune cell interactions. While abovementioned 3D models for studying tumor-immune cell interactions primarily use unsupported tumor spheroids, biomaterial matrices mimicking various tumor microenvironments may also be utilized to investigate microenvironmental influences in such interactions. For example, porous scaffolds made from chitosan and alginate have been used to study interactions of human prostate cancer cells and lymphocytes. These scaffolds allow one to track immune cell penetration into tumor spheroids for a longer period of time in a 3D environment due to slower scaffold degradation, as compared to collagen or rBM matrices[47]. More sophisticated 3D co-culture models, particularly incorporating a model of the vasculature, can be fabricated using 3D printing. Sacrificial templates have been printed using glassy carbohydrate or temperature-responsive hydrogels. The templates are embedded within various cell-laden natural and synthetic hydrogels, and can be subsequently dissolved to generate vascular networks in the hydrogels[48,49]. Various photolithography[50,51] and soft lithography[52] methods using photo-crosslinked materials have also been developed to achieve *in vitro* mimics of 3D vascularized tissues. These sophisticated architectures have not been widely applied yet as 3D tumor models, but are likely to provide important tools for studying various aspects of cancer biology in the future.

As tumors have distinct mechanics compared to normal tissues, biomaterials have also been utilized in 3D culture to model the mechanical properties of the tumor microenvironment, and to study the effects of ECM mechanics on tumor development and progression. Mechanical cues regulate various cell behaviors through mechanotransduction, including proliferation, migration, and differentiation[53–55]. In the context of cancer, tumor cells remodel the ECM and change its mechanical properties, and the altered mechanical niche in turn is likely to influence tumor progression[32]. For example, breast cancer stroma is stiffer than normal stroma due to increased collagen deposition and ECM crosslinking. Using 3D *in vitro* models fabricated from rBM and collagen, it was discovered that high matrix stiffness together with increased collagen concentration or crosslinking induced a malignant phenotype in normal mammary epithelium[56,57]. To understand the specific role of increased matrix stiffness in this transformation independent of changes in matrix composition and architecture, an interpenetrating polymer network (IPN) of rBM and alginate matrix was developed[58]. The stiffness of these IPNs can be modulated by simply controlling the ionic crosslinking of alginate without changing the polymer concentration, cell-adhesion-ligand density, or the pore size of the matrix. Using this IPN model, it was found that the increased matrix stiffness was sensed through the β4 integrin, Rac1, and the PI3K pathway, leading to loss of apicobasal polarity, cell invasion into the basement membrane, increased proliferation, and other hallmarks of a malignant phenotype in mammary epithelium[58].

Other biomaterials have also been used to model the mechanical properties of different tumors. As hyaluronic acid is a major component of brain ECM, 3D glioblastoma models were developed using methacrylate modified hyaluronic acid hydrogels with different mechanical properties. These hydrogels mimic the stiffness encompassing normal and tumorigenic brain tissues, allowing one to study cancer cell invasion into different matrices[59]. Synthetic hydrogels based on PEG have been used in lung adenocarcinoma models to study the influence of matrix stiffness on the epithelial–mesenchymal transition. The PEG hydrogels were modular and had higher stiffness compared to collagen or rBM matrices[37].

Although the importance of ECM mechanics is increasingly recognized, the majority of the studies have focused on the elasticity (stiffness) of ECM, overlooking the potential role of the viscoelasticity (both viscous and elastic characteristics) of the ECM. A recent study showed that viscoelastic substrates could stimulate spreading of osteosarcoma cells to a greater extent than purely elastic substrates with the same initial elastic modulus[60]. Future 3D models using materials developed to mimic the viscoelasticity of various tumor niches will potentially help to better dissect the function of ECM mechanics on tumor progression.

Engineered 3D matrices have also been developed to recapitulate the spatiotemporal complexity of soluble factors (e.g. oxygen and growth factor gradients) found in tumors, and study their contribution to tumor growth. Conventional 2D culture in reduced oxygen environments has helped to improve our understanding of the role of hypoxia, but does not recapitulate the spatial variation of oxygen in tumors. The use of stacked layers of chromatography paper infused with suspensions of cancer cells in Matrigel was shown to generate defined oxygen gradients in the 3D culture, and necrotic cells as well as overexpression of vascular endothelial growth factor (VEGF) and insulin-like growth factor binding protein 3 (IGFBP3) were observed at the hypoxic core of the 3D culture[61]. Alginate hydrogels have also been used to modulate oxygen concentration. This 3D system was able to model various uniform or gradient hypoxic conditions by controlling the hydrogel spatial configuration, which allowed studies of the secretion of pro-angiogenic factors (VEGF and interleukin 8 (IL-8)) from cancer cells in response to ECM cues such as integrin-matrix engagement under different hypoxia conditions[62,63]. To control the spatiotemporal availability of growth factors in a 3D tumor model, controlled drug delivery technologies have been exploited. For example, a hyaluronic acid hydrogel bilayer system was developed to study the function of heparin-binding EGF-like growth factor (HB-EGF) on the growth of prostate cancer spheroids. As HB-EGF is found in prostate stroma and bound to ECM, HB-EGF was encapsulated in microparticles to control its availability. Sustained release of HB-EGF from microparticles embedded in the top-layer hydrogel promoted the growth of tumor spheroids in the bottom layer, and increased VEGF and IL-8 expression in the cancer cells[64]. Microfluidic[65] and photo-patterning[66] methods may be useful to achieve more precise spatiotemporal control of soluble factors in 3D culture models through controlling the flow of fluids containing the factors, and photo-induced coupling or cleavage of factors, respectively. These approaches are likely to also be useful to study tumor cell responses to spatiotemporally controlled cytokines in the context of immunotherapy.

Engineered in vitro models for testing anticancer therapeutics

As it is desired to better mimic human biology and dismiss potentially ineffective or unacceptably toxic therapeutic candidates as early as possible, 3D *in vitro* human tumor models are being increasingly explored for evaluation of new therapies[67]. While 2D cell culture models have been an invaluable tool to identify potential anticancer agents at the early stages of drug discovery, they provide little information on drug responses influenced by tumor heterogeneity and microenvironment. In contrast, simple tumor spheroid models have shown drug responses more similar to that of tumors *in vivo* as compared to 2D models, and are increasingly being used to evaluate anticancer agents under 3D conditions[68–70]. For example, 3D tumor spheroids created through hanging drop methods have been commercialized by companies such as 3D Biomatrix and InSphero, and are being explored for high-throughput drug screening by pharmaceutical companies. To integrate additional influences of the tumor microenvironment, collagen gels containing heterospheroids of liver carcinoma cells and fibroblasts were used to study changes in drug resistance and metabolism associated with culture dimensionality, stromal cells, and the ECM. This study found that suspended 3D heterospheroids had higher drug resistance than 2D monolayers and suspended homospheroids containing only cancer cells, and placing either type of spheroid in a collagen matrix further increased drug resistance[71]. A 3D model of Ewing sarcoma has also been developed using biodegradable, highly porous polycaprolactone scaffolds fabricated by electrospinning. This 3D culture model showed closer resemblance to xenograft tumors in phenotype and drug resistance as compared to a 2D monolayer model. In addition, cancer cells in the 3D system also had a slower proliferation rate and better mimicked *in vivo* tumor growth, which allowed investigation of the long-term impact of drug exposure[72]. While patient-derived xenograft (PDX) cancer models have been established by engrafting and maintaining patient-derived tumor tissues in immunocompromised animals[73], the complexity of these models and long latency following engraftment has slowed their broad adoption. To circumvent these and other potential problems (e.g. drift of PDX stromal components from human to host species), patient-derived prostate xenograft tumor cells have been cultured in hyaluronic acid-based hydrogels to mimic the microenvironment of bone metastases in prostate cancer. This 3D system was shown to maintain the cancer cells' native androgen receptor expression, and a higher docetaxel resistance was observed with patient-derived cells compared to a commonly utilized prostate cancer cell line, although the relevance to patient drug response still needs to be varified[74]. *In vitro* 3D models to test immunotherapies are also being developed. For example, a 3D model of mouse mammary carcinoma cells cultured in porous chitosan-alginate scaffolds was used to evaluate CTL function in the presence or absence of tumor-associated fibroblasts. It was found fibroblasts decreased tumor necrosis factor α (TNFα) secretion by CTLs, likely due to elevated production of IL-10 and transforming growth factor beta (TGF-β) in the co-cluture[75]. In another study, drug inhibition of tumor cell-macrophage paracrine interactions was analyzed using co-culture of breast adenocarcinoma cells and macrophages in alginate hydrogel fibers. Gefitinib, an EGFR inhibitor, and a Rac1 inhibitor were both able to impair macrophage migration to cancer cells, and the 3D cell distribution and cancer cell-macrophage ratio affected drug responses[76]. Although generally faster than *in vivo* models, 3D tumor models for drug testing typically require increased processing time relative to 2D cell monolayers. In order to address this problem, automated

techniques such as microfluidics have been utilized to achieve high-throughput compound screening in 3D tumor models. For example, a microfluidic-based platform has been developed to fabricate “microtissues” that can encapsulate desired combination of cancer cells, stromal cells, and ECM components. These 3D microtissues allow one to probe cancer cell responses to various microenvironmental cues, as the specific matrices, soluble factors, and stromal cells are changed, and to test drug candidates[77].

Engineered 3D tumor models may also potentially help to improve animal models for drug development. Xenograft animal models are typically established by inoculation of cancer cells previously cultured on stiff 2D substrates. However, culture conditions can substantially alter cell gene expression and phenotype[78], and certain effects may persist for a long period of time even after altering conditions[73,79,80]. For example, soft fibrin gels were shown to promote growth and possibly “priming” of stem-cell-like cancer cells in 3D culture, and enhance their ability to form tumors in mice[81]. Similarly, culture in PLG or chitosan-alginate 3D matrices enhanced the subsequent ability of cancer cells to grow tumors and promote angiogenesis in mice, compared to cells from 2D culture[82,83]. Although still in a very early stage, further development and evaluation of these approaches may potentially help to create xenograft animal models that can better recapitulate the phenotypes of actual human tumors for drug testing.

Future directions and considerations

Since 3D cancer models are still in the early stages of development, a number of issues still remain to be addressed. First, factors such as specific disease relevance and processing efficiency will need to be evaluated and optimized in large-scale studies in order to fully establish and exploit 3D tumor models for drug discovery and screening. To date, few, if any, of the discoveries made in 3D cancer models have been validated in human cancer patients. This calls for closer collaborations among researchers, physicians, and pharmaceutical industry. Also looking forward, there is a substantial potential for advanced microfluidic 3D cell culture devices that more closely mimic the physiological function of human organs (organs-on-chips) in drug screening than static 3D model systems[84]. A ‘human-body-on-a-chip’ that combines several different, fluidically linked organs-on-chips[85] is a particularly appealing concept for testing new anticancer therapeutics including immunotherapies, as it could provide a human test bed that encompasses the dynamic, multiple cellular interactions required to mount an effective immune response to cancer. This approach may also potentially provide an *in vitro* platform for personalized therapy evaluation by using cells or tissues directly from patients[86]. However, the potential benefits of all 3D human cancer models must be balanced with the increased complexity and difficulty of performing large-scale discovery science or drug screening, as compared to the classic 2D systems.

Biomaterials in cancer immunotherapy

Harnessing the immune system to treat cancer has been a goal in medicine for over a century, driven by the potential of providing specific, durable, and adaptive reactivity towards tumors[87,88]. Recently, the benefit and efficacy of certain cancer immunotherapies, including checkpoint blockade antibodies, were successfully established in large clinical

trials[89–92], and adoptive cell transfer (ACT) is also extremely promising[93,94]. Biomaterials may enhance the efficacy of many of these new therapies or other immunotherapies (e.g. cancer vaccines) via control over the microenvironment in which immune cells encounter antigen, stimulatory signals, cancerous cells, or other immunomodulatory cells (Fig. 3). Therapeutic viral particles can also be considered biomaterials, but are not covered here as they are typically not intended to directly alter the microenvironmental conditions of immune cells and have been discussed in previous reviews[95].

Biomaterial-based cancer vaccines

Therapeutic cancer vaccines aim to generate immune reactivity against existing tumors in the host. Through vaccination, antigen presenting cells (APCs) such as dendritic cells (DCs) are activated to elicit tumor specific CTLs[87]. The activation of APCs can be achieved either *ex vivo* or *in vivo*. Provenge, the first cell-based therapeutic cancer vaccine approved by the US Food and Drug Administration (FDA), demonstrated the potential of adaptive immunity in combating cancer, but the complexity of the treatment (e.g. *ex-vivo* cell manipulation, transportation of living cells between clinic and production facility) and its associated high cost hampered its reach to patients[96]. In contrast, cancer vaccines based on peptides, viruses, or DNA encoding tumor antigens historically have shown low overall objective response rates in clinical trials[97,98], perhaps due to inappropriate temporal or spatial control over antigen presentation and immune cell activation, and a limited ability to overcome the immune inhibitory mechanisms of tumors. To generate tumor specific CTLs, it is critical to activate APCs in a stimulatory microenvironment that induces antigen-specific immunity rather than tolerance[99,100]. The kinetics of antigen exposure are also important, as too short of a low-dose or too long of a high-dose of antigen exposure, at least in infectious diseases, may either fail to result in a T cell response or cause T cell exhaustion, respectively[101–104].

Biomaterial-based vaccines may achieve more precise immune modulation due to their ability to control delivery of antigens and adjuvants in space and time, to regulate immune cell trafficking through their physical and chemical characteristics, and to mimic stimulatory signals of innate immunity. For example, in contrast to the *ex-vivo* cell manipulation approach of Provenge, implantable cancer vaccines fabricated from porous PLG scaffolds, similar to those used in 3D cancer models *in vitro*[82], have been designed to control immune cell trafficking and activation kinetics *in situ*. Also different from traditional bolus vaccination, this biomaterial-based vaccine creates a new physical environment in the body that accumulates, activates, and presents antigens and stimulatory signals to DCs over a period of at least 2 weeks[105]. Specifically, the macroporous PLG vaccine system has a sustained release of granulocyte macrophage-colony stimulating factor (GM-CSF), which promotes DC accumulation at the vaccine scaffold. The vaccine is loaded with tumor lysate as an antigen source and also presents nanoparticles of CpG oligodeoxynucleotides (or CpG for short), which are agonists of toll-like receptor 9 (TLR9) and serve as a “danger signal” for DC activation. The activated and antigen-loaded DCs subsequently migrate to lymph nodes[105]. This vaccine leads to a strong CTL response against established melanoma (syngeneic B16-F10 model), causing complete regression of tumors in ~47% of mice in preclinical studies[106]. A human version of this vaccine (called WDVAX) is currently in a Phase I clinical trial for stage IV melanoma (https://clinicaltrials.gov/ct2/show/

NCT01753089). Importantly, this type of biomaterial design for a cancer vaccine is modular, and a variety of immunostimulatory agents can be incorporated. For example, inflammatory cytokines such as chemokine (C-C motif) ligand 20 (CCL20) or Fms-related tyrosine kinase 3 ligand (Flt3L) can be used in place of GM-CSF in the vaccine to alter DC subset recruitment and activation, and these also generate anti-tumor responses in a preclinical melanoma model[107]. Altering the source of tumor lysate used as the antigen allows the PLG vaccine system to demonstrate therapeutic activity in mouse lung carcinoma and rat glioma models[108,109]. Local immunogenic niches that control immune cell trafficking and activation have also been created using other materials such as gelatin, alginate hydrogels, and mesoporous silica rods[110–113]. As these materials are either highly deformable or self-organizing, they can be administered by injection, instead of the surgical implantation required for WDVAX. Many of the scaffold vaccine systems use tumor lysates or irradiated tumor cells as the antigen source. This design can create personalized vaccines to address tumor heterogeneity and potentially hit multiple tumor antigens simultaneously. However, this approach may also lead to increased complexity in clinical translation, as compared to using defined antigens. One alternative approach that could be pursued in the future is to use synthetic neoantigens identified by exome sequencing of cancer cells from individual patients[114].

Biomaterials, owing to their tunable sizes at the nanoscale, can also be transported to lymph nodes, where they alter the microenvironment of the targeted immune cells. As large numbers of DCs reside in the secondary lymphoid organs, delivery of vaccines to lymph nodes is an attractive alternative to recruiting the migratory DCs to a vaccination site. It has been shown that interstitial particles (e.g. administered subcutaneously or intramuscularly) in the size range of 10–100 nm, depending on the type of material and animal model, are optimal for lymph node targeting through lymphatic drainage[102,115,116]. Small (25 nm) pluronic copolymer-coated nanoparticles that were intradermally injected were efficiently transported to draining lymph nodes through interstitial flow and retained for at least 120 h. The nanoparticles were readily internalized by DCs and macrophages in the lymph nodes. In comparison, 100 nm nanoparticles appeared only ~10% as efficient. When used to deliver the model antigen ovalbumin (OVA), the 25 nm nanoparticles also induced higher humoral immune responses compared to 100 nm nanoparticles[115]. A study using another type of nanoparticles (inert polystyrene beads) showed that 40 nm was optimal for targeting DCs in the lymph nodes and generating antitumor immunity in an OVA-expressing mouse lymphoma model (EG7-OVA)[117].

Besides exploiting size-dependent targeting to the lymph nodes, biomaterial-based vaccines have also used binding ligands of DC receptors or hitchhiked natural transportation mechanisms in the body to actively target DCs. For example, both inorganic and polymeric nanoparticles have shown enhanced binding and uptake by DCs when coupled with antibodies to CD40 or DEC-205 (also known as CD205 or LY75) receptors[118–121]. A recent study[122] exploited the clinical finding that injected dyes that bind avidly to endogenous albumin were efficiently transported to lymph nodes and filtered by resident APCs[123,124]. Inspired by this “albumin hitchhiking”, amphiphilic macromolecules were developed to deliver peptide antigens to lymph nodes. The structure comprised a peptide antigen linked to a lipophilic albumin-binding tail, with a hydrophilic PEG polymer chain as the linker to

improve solubility. When injected subcutaneously in mice, these amphiphilic macromolecules were efficiently transported with endogenous albumin to lymph nodes, targeting DCs and macrophages. Vaccination with the amphiphilic peptide antigens and CpG adjuvant significantly increased antigen specific CTL expansion and therapeutic efficacy against established tumors (B16F10 melanoma) compared to unmodified peptide and CpG immunizations[122]. Recent studies have shown that targeting tumor-draining lymph nodes specifically with nanoparticle-based cancer vaccines or adjuvants induced stronger cellular immune responses compared to targeting uninvolved lymph nodes, possibly due to altering the immunosuppressive environment of tumor-draining lymph nodes to a more stimulatory condition and to high exposure of immune cells in these lymph nodes to tumor-associated antigens[125,126]. An interesting direction for future studies would be to combine aforementioned APC targeting strategies to home in on specific immune cells in the tumordraining lymph nodes[127].

Particulate vaccine carriers can also promote a CTL response by controlling the intracellular delivery of antigens and modulating antigen processing. Normally, proteins in the cytosol of APCs (e.g. from invaded viruses) are degraded and loaded on MHC I for $CD8^+$ T cell activation, but soluble antigens which are endocytosed by APCs are typically presented on MHC II to activate $CD4^+$ T cells and induce a humoral response. However, phagocytosis of pathogens or particulate antigens by APCs, in contrast to the endocytosis of soluble antigen, can lead to loading of antigen on MHC I through cross-presentation[128]. Certain types of nanomaterial vaccine carriers can also actively destabilize endosomes through mechanisms such as altering endosomal osmotic pressure, and release antigen into the cytosol, promoting cross-presentation of antigen[129–132]. In addition, co-delivery of antigen and TLR agonists simultaneously to APCs can promote $CD8^+$ T cell responses. For example, multilamellar lipid nanoparticles have been loaded with a model antigen together with the TLR4 agonist monophosphoryl lipid A (MPLA). These nanoparticles consist of multiple concentric lipid bilayers that are crosslinked within the vesicle walls to stably retain antigen and MPLA. The nanoparticles elicited a high percentage of antigen specific $CD8^+$ T cell in the peripheral blood of mice after a prime injection and two boosters, and this response was dependent on co-delivery of the stably incorporated TLR agonist[133]. Similarly, enhanced cellular immunity against melanoma (B16F10) was also observed using other nanomaterial carriers when a melanoma antigen (tyrosinase-related protein 2 peptide) and various TLR agonists were co-delivered[134,135]. Interestingly, preclinical studies have shown that combined stimulation of multiple TLR or Nod-like receptors (NLRs) may have a synergistic effect and enhance vaccine efficacy[136–138]. A recent melanoma clinical trial using virus-like particle (VLP) vaccine containing CpG and the melan-A peptide antigen, given together with incomplete Freund's adjuvant (IFA) injection and imiquimod topical cream (a TLR7 agonist), significantly increased memory and effector $CD8^+$ T cell responses as compared to the vaccine alone[139]. This suggests that incorporating multiple TLR agonists simultaneously into nanoparticle-based cancer vaccines may also potentially improve the efficacy of therapeutic vaccines in humans.

Certain materials have intrinsic adjuvancy or the capacity to create an inflammatory microenvironment, which can be exploited in the design of cancer vaccines. Aluminum salts (alum), whose mechanism is not yet fully understood, were until recently the only type of

adjuvant approved for human vaccination[140]. Silica particles were recently shown to activate the innate immune response and promote cellular immunity, possibly due to inflammasome activation of APCs[112,141]. ISCOMATRIX adjuvant consists of cage-like nanoparticles comprising saponin, cholesterol, and phospholipid. It does not appear to activate TLRs, but it induces innate immune response by inflammasome-dependent and independent IL-18 production, possibly due to endosomal stress and cell damage[142]. Vaccination with ISCOMATRIX adjuvant and an HPV16 E6–E7 fusion protein demonstrated both antigen specific humoral and cellular immune responses in a Phase I clinical trial for cervical intraepithelial neoplasia[143]. Some materials can also generate danger signals of innate immunity by triggering the complement cascade. Studies using polypropylene sulfide nanoparticles coated with Pluronic copolymers showed that the surface terminal hydroxyl groups activated complement, eliciting DC maturation. When the model antigen OVA was coupled to these nanoparticles, effective humoral and cellular immune responses were observed[115]. It was further shown that the complement activation of these nanoparticles could be controlled by adjusting their core thiolation and surface carboxylation to affect the deposition of complement component C3b[144]. So far, our understanding of how biomaterials with various chemical and physical properties may interact with the innate immune system is still quite limited, and further knowledge would be invaluable for designing future cancer vaccines.

Biomaterials engineering in adoptive cell transfer

T cell-based ACT, including tumor infiltrating lymphocytes and chimeric antigen receptor (CAR) T cells, has become one of the most successful developments in cancer immunotherapy[93,94,145]. However, these promising treatments have some notable challenges, including expansion of T cells and maintaining their effector function, both during *ex vivo* cell production and *in vivo* after transplantation.

Biomaterials may address many of challenges facing T cell-based ACT by providing a means to locally and specifically provide stimulatory cues. First, these therapies typically require large numbers of autologous tumor specific T cells, but T cells collected directly from patients' peripheral blood or tissues are normally low in number and can be hyporesponsive[146]. To activate and expand the cells *ex vivo*, microparticles coated with anti-CD3 and anti-CD28 antibodies have been developed as "artificial APCs" to provide primary and co-stimulatory signals. These macroparticles also contain superparamagnetic iron oxide for easy separation from cells by a magnetic field. This method has now become a common tool in immunology and is widely used in CAR T cell clinical studies[147]. More recently, it was reported that biodegradable PLG microparticles containing an additional signal, the T cell growth factor IL-2, further enhanced T cell expansion, especially of $CD8^+$ T cells. The sustained release of IL-2 from microparticles in the vicinity of T-cell contacts, in a paracrine fashion, appeared more effective than simply adding soluble IL-2 to the culture media[148]. Besides biochemical factors, the physical characteristics, such as the shape and size, of the microparticles also affect their T cell expansion efficiency[149]. For example, ellipsoidal PLG microparticles showed enhanced $CD8^+$ T cell expansion activity compared to spherical microparticles with the same volume and protein content, possibly due to increased interaction of T cells with the long axis of the ellipsoidal microparticles[150].

Biomaterials may also allow one to prevent the decline in viability and function of the transplanted cells in ACT by creating optimal cytokine presentation in the cellular microenvironment. To improve the persistence of the transplanted T cells, systemic administration of cytokines (e.g. IL-2, IL-15) is often used[145,151]. However, high-dose systemic cytokines can cause severe side effects due to their broad activities[152]. One can instead enhance transplanted T cell function by conjugating cytokine-loaded nanoparticles to the surface of the transplanted cells[153]. Stable attachment to the cells for at least 4 days can be achieved by covalent conjugation of liposomal nanoparticles to the surface thiols on T cells. In a B16F10 melanoma model, transplanted CTLs conjugated with nanoparticles that release the cytokines IL-15 superagonist and IL-21 demonstrated a marked improvement in tumor elimination compared to CTLs with systemic co-injection of the free cytokines[153]. Nanoparticles conjugated to the T cell surface can also be used to deliver small molecular inhibitors (e.g. an inhibitor of the SHP1 and SHP2 phosphatases, which normally down-regulate T-cell receptor activation) into the T-cell synapse, achieving a greater adoptive T cell expansion at the tumor site[154]. However, one caveat of such approaches is that the cell-bound nanoparticles will be diluted during T cell expansion in the body, limiting the duration of stimulation from the nanoparticles. A possible solution is to target transplanted T cells *in vivo* using nanoparticles coupled with ligands specific to these cells[155]. Alternatively, a recent study used a porous alginate scaffold, similar to those used in 3D *in vitro* cancer models[47,63], to expand and deliver CTLs *in situ* by implanting a CTL-loaded scaffold adjacent to tumors or at resection sites. Microspheres containing IL-15 superagonist and anti-CD3, anti-CD28 and anti-CD137 antibodies were also incorporated into the scaffold to provide a stimulatory microenvironment to the loaded CTLs[156].

Future directions and considerations

Biomaterials-based cancer vaccines are expected to complement and synergize with the checkpoint blockade and ACT therapies that are rapidly moving to the frontline of cancer treatment. This combination would address two key factors for effective immunotherapy: generation of robust tumor-specific CTLs and inhibition of tumor-induced immunosuppression. Personalized cancer vaccines are also an important direction due to heterogeneity of tumors between patients, especially from the immunotherapy standpoint. Incorporation of patient-specific neoantigens identified by genetic profiling may enhance the efficacy of biomaterials-based cancer vaccines[114].

Clinical adaptation of biomaterial-based immunotherapies will, though, require the pharmaceutical industry to incorporate a much greater emphasis on materials science and engineering than has been typical in the past. This includes the new approaches required to manufacture these types of therapies as contrasted to small molecule drugs and biologics, and altered regulatory and approval pathways relating to the resultant combinations of materials and drugs. The recent manufacturing difficulties for Doxil point to the challenges that can arise from material-drug combinations[157].

Conclusions

The ability of biomaterials to create defined microenvironments is expected to have a major impact on both the discovery and clinical translation processes in cancer, and to increase exponentially in the coming years. 3D *in vitro* models that better recapitulate *in vivo* tumor biology are beginning to replace 2D models in many areas of cancer research. The first personalized biomaterial-based cancer immunotherapy (WDVAX) has recently moved to a clinical trial[158]. The frequent use of the same polymers, and even scaffold architectures, in these two developing areas suggest that transfer of knowledge and technologies both within and between the two areas is expected to be rapid and fruitful. This will allow, for example, discoveries on one type of cancer to be quickly applied to another. Also, when the role of specific signals (e.g., local cytokine gradients) in regulating immune cell activation is identified in 3D *in vitro* systems, these findings could be recapitulated *in vivo* using the same or a similar material system for therapeutic purposes. Conversely, new understanding of complex immune responses, often involving multiple cell types, that result from therapeutic use of biomaterials will then feedback to the design of new 3D *in vitro* models. Overall, the addition of biomaterials engineering to cancer research and therapies contributes to an exciting time in the search for better cancer therapies.

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Text Box 1

Other applications of biomaterials in cancer

In order to overcome limitations of classic chemotherapy treatment (e.g., toxicity), nanoparticle carriers have been developed to modulate the pharmacokinetics (PK, including absorption, distribution, metabolism and elimination) of chemotherapeutic agents[7,17,159–165]. To date, several nanoparticle-based anticancer therapeutics have been clinically approved in the United States and the European Union (Doxil, Janssen Products; Lipodox, a generic version of Doxil from Sun Pharma Global; Myocet, Teva UK Limited; DaunoXome, Galen Limited; Marqibo, Spectrum Pharmaceuticals; DepoCyt, Sigma-Tau Pharmaceuticals; Abraxane, Celgene), and many more in various stages of clinical trials. These approved nanodrugs use liposomes, proteins, or synthetic polymers as delivery vehicles, taking advantage of the simple materials design and enhanced permeability and retention (EPR) effect of nanoscale particles (~10–200 nm in diameters) in solid tumors[7,159,166]. These nanodrugs have clinically demonstrated higher drug accumulation in tumors and reduced side effects compared to the free drugs[157,167–169]. Besides the early generations of nanodrugs, many exciting new nanomaterials and delivery strategies are being investigated in preclinical studies and clinical trials. For example, a higher patient response rate and overall survival have been shown when using nanoparticles to co-deliver multiple therapeutic agents with precise formulation to tumors compared to conventional administration of drug cocktails[170,171]. Nanoparticles decorated with ligands that recognize specific receptors of cancer cells[172], trigger tumor transport mechanisms[173,174], or camouflage as “markers of self”[175,176] can exploit cellular pathways to enhance tumor uptake and avoid immune clearance. Inorganic nanomaterials such as silicon, gold, and iron oxide nanoparticles with unique optical or magnetic properties are also being explored for simultaneous drug delivery and tracking[177–180]. In addition, although not discussed in this Perspective, it is worth mentioning that biomaterials engineering is also impacting cancer diagnostics, offering methods with substantially improved sensitivity and specificity[181,182].

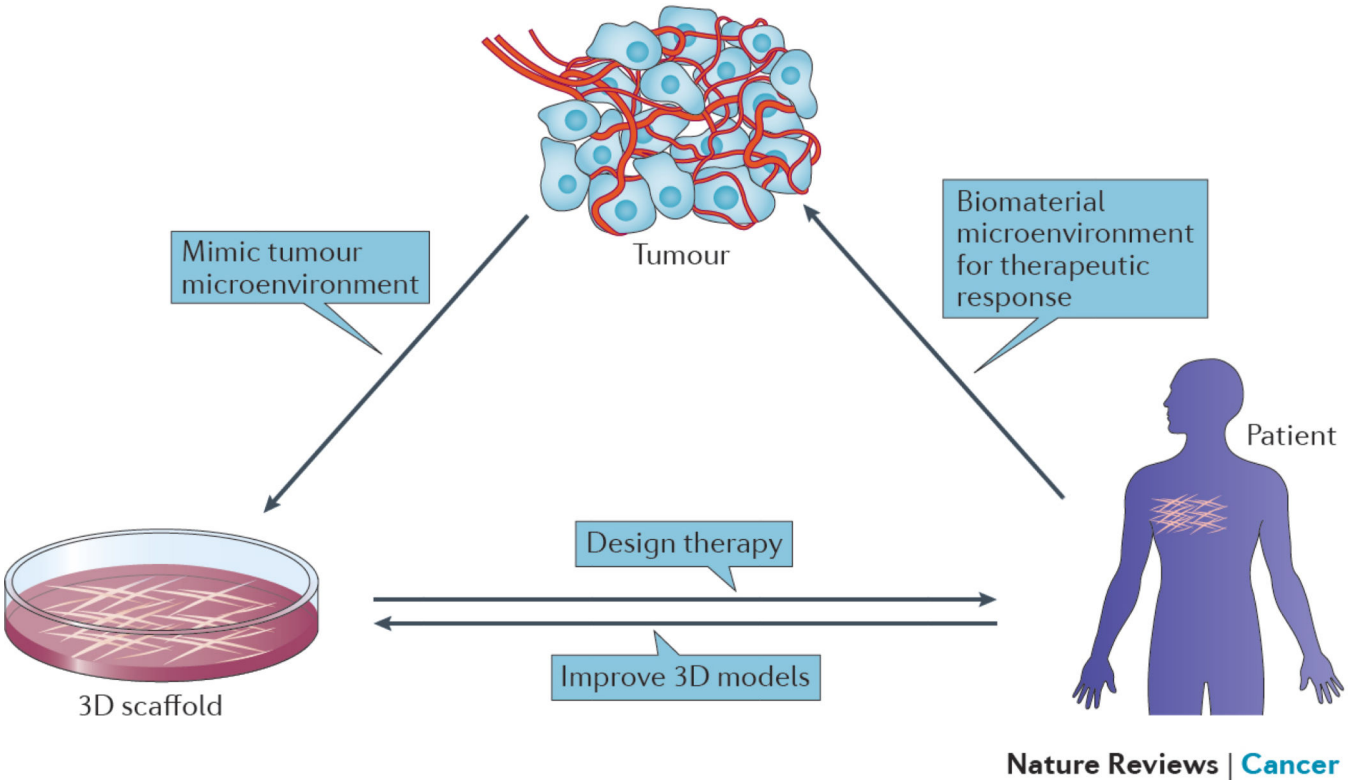

Figure 1. Creating new microenvironments *in vitro* and *in vivo* using biomaterials

Biomaterials are being used to both create 3D *in vitro* cancer models that mimic the microenvironmental conditions found in tumors, and to create new microenvironments within the body to allow effective immune cell activation and anti-tumor function. Knowledge gained from studies with 3D *in vitro* models can inform design of therapeutic biomaterials, while clinical experience resulting from use of biomaterials *in vivo* can inform the design of new 3D models that more faithfully mimic *in vivo* biology.

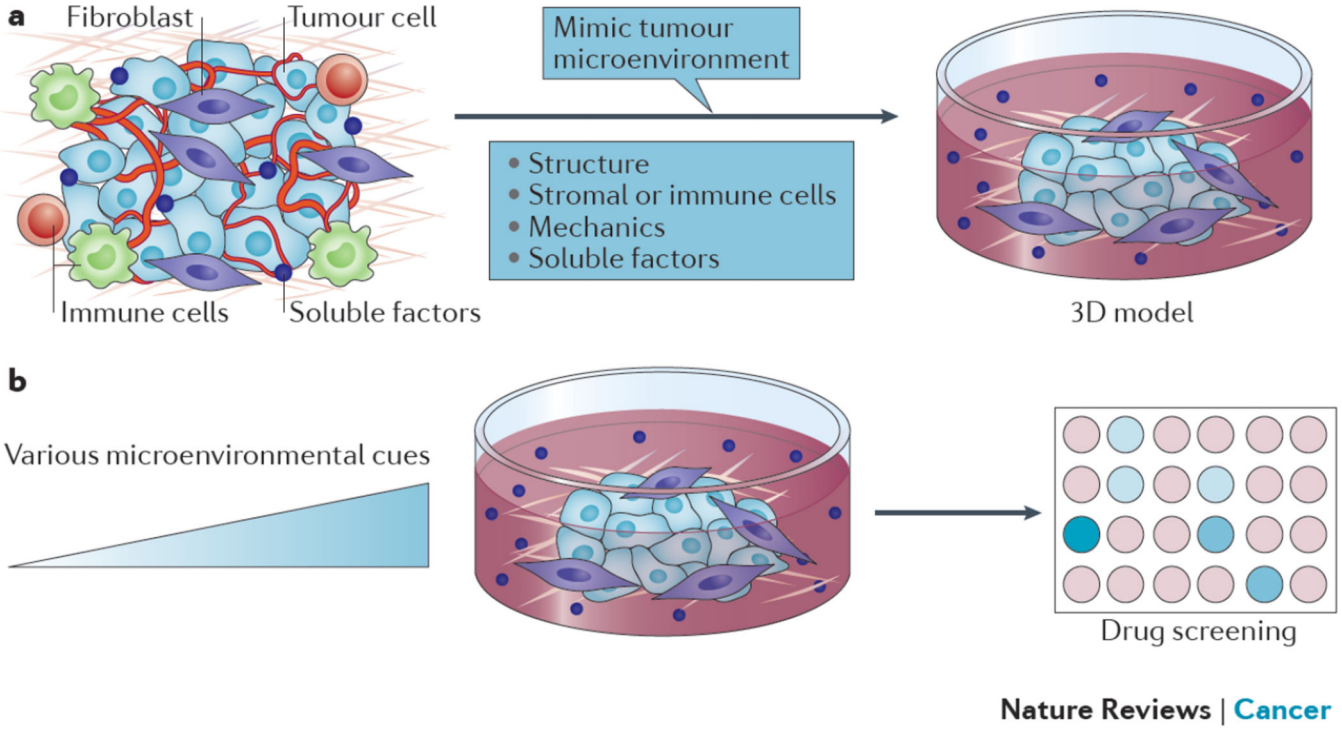

Figure 2. Biomaterials to create 3D *in vitro* human tumor models

a) Engineered 3D *in vitro* tumor models recapitulate various microenvironmental cues of human tumors. **b**) 3D *in vitro* tumor models can be used to screen anticancer therapeutics as various microenvironmental conditions are modulated, to determine the impact of each condition on efficacy of the therapeutic approach.

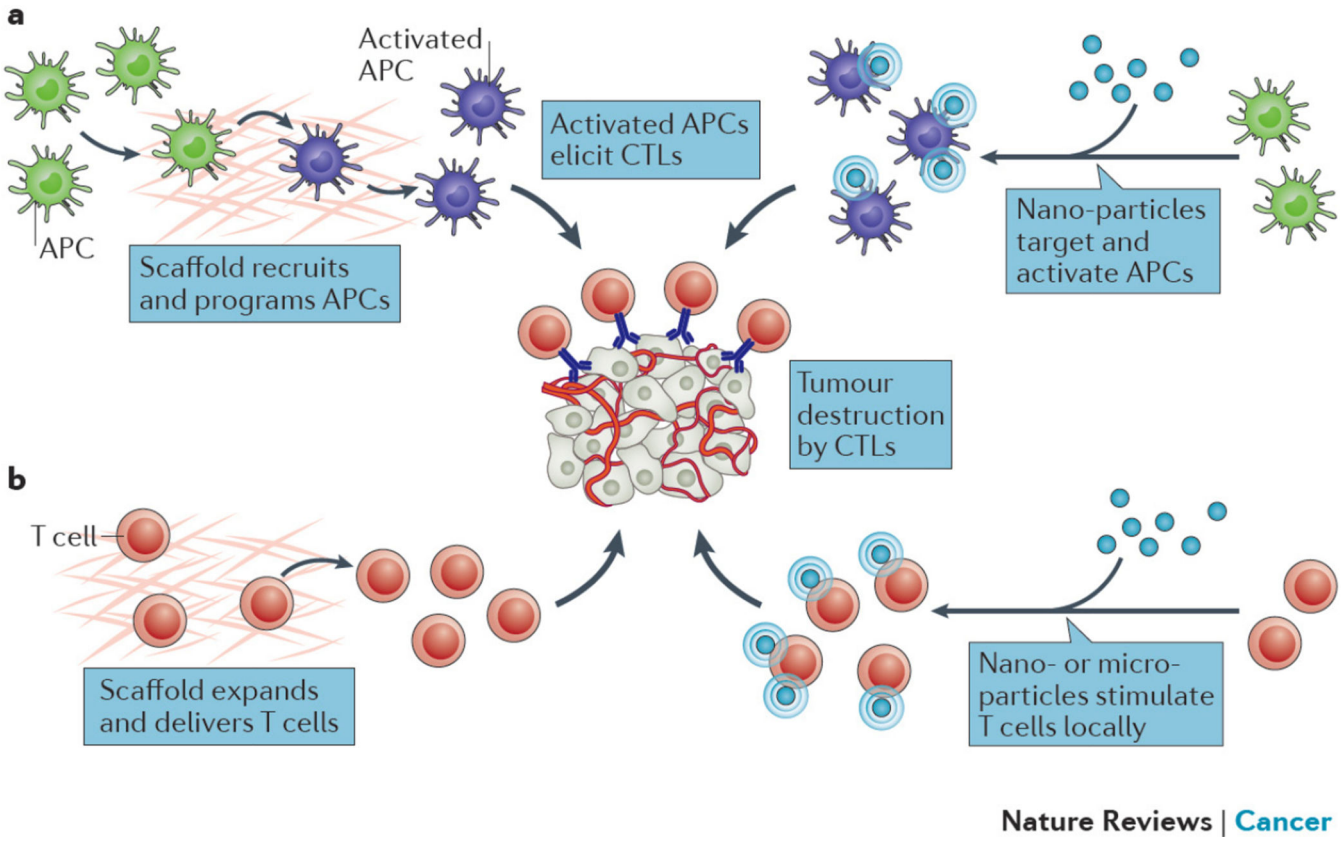

Figure 3. Biomaterials-based cancer immunotherapies

a) Biomaterial-based cancer vaccines. In one approach (left panel), a scaffold releases recruiting factors (e.g. GM-CSF) from the vaccine into surrounding tissue to direct host DCs to migrate into the device, where the DCs are exposed to tumor antigens and "danger signals" (e.g. CpG) that activate the DCs, and enable their homing to lymph nodes to elicit a cytotoxic T lymphocyte (CTL) anti-tumor response. Alternatively (right panel), nanoparticles are used to target DCs in lymph nodes, and deliver antigens and "danger signals" to again generate a CTL response. **b**) Biomaterial-based T cell manipulation. Either scaffolds (left panel), or nano- or micro-particles (right panel) are used to provide a stimulatory microenvironment to T cells for ACT in order to expand T cells and maintain their activity against tumors.