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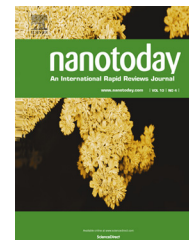
REVIEW

Engineered materials for cancer immunotherapy

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Summary   Immunotherapy is a promising treatment modality for cancer as it can promote specific and durable anti-cancer responses. However, limitations to current approaches remain. Therapeutics administered as soluble injections often require high doses and frequent re-dosing, which can result in systemic toxicities. Soluble bolus-based vaccine formulations typically elicit weak cellular immune responses, limiting their use for cancer. Current methods for *ex vivo* T cell expansion for adoptive T cell therapies are suboptimal, and achieving high T cell persistence and sustained functionality with limited systemic toxicity following transfer remains challenging. Biomaterials can play important roles in addressing some of these limitations. For example, nanomaterials can be employed as vehicles to deliver immune modulating payloads to specific tissues, cells, and cellular compartments with minimal off-target toxicity, or to co-deliver antigen and danger signal in therapeutic vaccine formulations. Alternatively, micro- to macroscale materials can be employed as devices for controlled molecular and cellular delivery, or as engineered microenvironments for recruiting and programming immune cells *in situ*. Recent work has demonstrated the potential for combining cancer immunotherapy and biomaterials, and the application of biomaterials to cancer immunotherapy is likely to enable the development of effective next-generation platforms. This review discusses the application of engineered materials for the delivery of immune modulating agents to the tumor microenvironment, therapeutic cancer vaccination, and adoptive T cell therapy.
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Introduction

Cancers are among the leading causes of morbidity and mortality worldwide with incidence expected to rise by 70% over the next two decades [1]. Current treatments for cancer, such as chemotherapy and radiation therapy which are characterized by a lack of specificity and response durability,

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are insufficient. There is a need for therapies that can target cancer cells with a high degree of specificity, leading to lower treatment-related morbidity, and that can facilitate long-term remission.

Cancer immunotherapy refers to any intervention that leverages the immune system to eliminate a malignancy. Successful cancer immunotherapies generate an anti-cancer response that is systemic, specific, and durable, overcoming the primary limitations of traditional cancer treatment modalities. Recent progress in our understanding of the immune system has enabled the development of effective platforms for promoting anti-cancer immunity, particularly in the areas of biologics for reversing immunosuppression in the tumor microenvironment (TME) [2,3], therapeutic cancer vaccines [4—6], and adoptive T cell therapies (ACT) [7—9]. For example, checkpoint inhibitors, monoclonal antibodies that block cell surface co-inhibitory receptors that disable the ability of T cells to destroy cancer cells, have shown unprecedented clinical success in a wide range of advanced stage malignancies [2,3,10—12]. To date, monoclonal antibodies for cytotoxic T-lymphocyte-associated protein 4 (CTLA-4; Ipilimumab) and programmed cell death protein 1 (PD-1; Pembrolizumab and Nivolumab) have been FDA approved for metastatic melanoma with the PD-1 antibodies given ''breakthrough therapy'' designation by the FDA. The discovery of key molecular players in the generation of immune responses, including pattern recognition receptors (PRRs) such as Toll-like receptors (TLRs) and their respective ligands, has provided us with a vast toolbox of danger signals for precisely tuning the immune response. These cues, in combination with an improved understanding of dendritic cells (DCs), the most potent antigen-presenting cells (APCs), have enabled the design of promising therapeutic cancer vaccines, many of which are under investigation in various stages of clinical trials [4—6]. Importantly, these developments also lead to the first approval of a therapeutic cancer vaccine by the FDA in 2010 (Sipuleucel-T) [13]. Although Sipuleucel-T showed only modest therapeutic benefit and was associated with a high treatment cost, its approval set a precedence in the therapeutic cancer vaccine field and will likely lead to the development of more effective and efficient cancer vaccine approaches in the future. Advancements in our understanding of the cellular and molecular biology of T cells and antigen recognition has allowed for the development of highly efficacious ACTs, including tumor-infiltrating lymphocyte (TIL)-based therapies for advanced melanoma [9], and high-affinity/avidity T cell receptor (TCR)- [8] and chimeric antigen receptor (CAR)-transduced T cell-based therapies [7] for a wide range of hematologic malignancies.

Despite these advancements, drawbacks to current cancer immunotherapy strategies remain. Therapeutics are commonly administered as soluble injections, typically necessitating high doses and frequent re-dosing to achieve biologically relevant concentrations in target tissues, which often results in systemic toxicities [14,15]. Soluble bolus-based vaccine formulations typically elicit weak cellular immune responses [16,17], limiting their effective use for cancer. Current methods for *ex vivo* cell expansion for ACT are suboptimal and do not always facilitate the generation of high quality T cells [18,19], and achieving high

T cell persistence and sustained functionality with limited systemic toxicity following transfer remains challenging [20,21]. The use of biomaterials as platforms for cancer immunotherapy could allow for some of these limitations to be overcome. Although beyond the scope of this review, there are also promising virus-based approaches for cancer vaccination being explored, and this is described elsewhere [22,23].

To date, a wide range of material systems have been developed as molecular and cellular delivery vehicles in biomedical applications ranging from diagnostics [24—26] to therapeutics [27—29]. As delivery vehicles, biomaterials allow for a level of spatiotemporal control over payload delivery that is difficult to recapitulate with a bolus. For example, nanomaterials can be used to deliver diverse combinations of bioactive payloads to specific tissues [25,30], cell types [31,32], and intracellular compartments [33—35] in a controlled manner and with a high degree of specificity, curtailing off-target toxicity and allowing for dose-sparing. Micro- to macroscale materials can be designed as depots for the sustained local delivery of bioactive payloads with high spatiotemporal resolution [36—38], or as artificial cellular microenvironments displaying complex combinations of cues [39—43]. This review will point out some of the challenges associated with various current immunotherapy modalities, and will discuss how the application of biomaterials as delivery vehicles or engineered microenvironments can potentially aid in overcoming some of these challenges. Specifically, this review will discuss the use of nano- to microscale materials for modulation of immunosuppression in the TME, therapeutic vaccination, and for promoting *in vitro* and *in vivo* T cell survival and expansion, and the use of 3-D macroscale materials as engineered microenvironments for programming immune cells, and as cellular delivery devices.

Brief review of cancer and the immune system

The generation of a productive anti-cancer immune response resulting in the elimination of cancer cells is dependent on a coordinated series of events that must take place in an iterative and self-sustaining manner (Figure 1). This process, termed the ''cancer-immunity cycle'', has been reviewed in detail elsewhere [44]. Briefly, antigens are released from cancer cells and captured by DCs, the primary mediators of adaptive immunity (step 1). DC activation, which is associated with the upregulation of cell surface co-stimulatory molecules and cytokine production, is necessary for efficient downstream priming of a T cell response, and may be promoted in the endogenous situation by factors released by dying cancer cells, broadly termed ''danger associated molecular patterns''. DC activation facilitates efficient processing of the uptaken antigen and subsequent presentation of antigenic peptides on cell surface MHC molecules (step 2). In the draining lymph nodes, activated DCs present cancer antigens to naïve T cells, resulting in the priming and activation of cancer antigen-specific T cells, a subset of which will differentiate into long-lived memory cells (step 3). Activated T cells, in particular, effector CD8+ cytotoxic T lymphocytes (CTLs), subsequently traffic to (step