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Editorial

New Opportunities in Cancer Immunotherapy and Theranostics

Guest Editorial for the Accounts of Chemical Research special issue "Chemistry in Cancer Immunotheranostics".

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As exemplified by the recent clinical success of immune checkpoint blockers (ICBs) and chimeric antigen receptor (CAR) T-cell therapy, cancer immunotherapy is heralded as the next-generation therapeutics. In particular, ICBs and CAR T-cells have led to a paradigm shift in current oncology practices and provided new treatment options for patients. Compared with traditional cancer therapies that have only transient and limited efficacy against advanced cancer, ICBs can completely eliminate tumors in some patients with advanced disease, thus further raising the stakes for the field to broaden the target indications and improve patient survival while reducing side effects. In principle, cancer immunotherapy aims to educate the host immune cells to prime and expand antitumor immunity or to reinvigorate exhausted T-cells. Sufficient antitumor immunity induced by immunotherapy could promote systemic immune surveillance and eradicate advanced cancer. Successful application of cancer immunotherapy also has an additional benefit of inducing long-term memory responses against tumor relapse.

Nevertheless, critical issues remain for cancer immunotherapy. The latest data from the clinic suggest that only a small portion of patients respond to ICBs. Patients with "cold" tumors with a low frequency of T-cells or low expression of programmed death-ligand 1 (PD-L1) on tumor cells respond poorly to ICBs. In contrast, "hot" tumors, characterized by preexisting immunity with a high frequency of tumor-infiltrating T-cells and high PD-L1 expression by cancer cells, benefit from ICBs with durable clinical responses. Additionally, the current clinical practice of immunotherapy involves the systemic administration of monoclonal antibodies, which can induce activation of self-antigen reactive T-cells and cause off-target side effects. Indeed, one of the major side effects of ICB therapy is overt autoimmune responses generally categorized as immune-related adverse events. Similarly, while CAR T-cell therapy has been used in the clinic for the treatment of hematological malignancies, there are still manufacturing and regulatory hurdles to overcome for the production of personalized CAR T-cells. In addition, the application of CAR T-cell therapy for the treatment of solid cancers has been hampered by poor infiltration of T-cells into tumors. Thus, in order to maximize the potential of cancer immunotherapy, there is an urgent need for new approaches that can expand and reinvigorate exhausted T-cells, promote T-cell infiltration into tumors, and increase the patient response rates in a safe and effective manner.

Chemistry plays a critical role in the molecular understanding of the complex immune system and the development of new therapeutic approaches. In parallel, there has been rapid development of imaging biomarkers to allow immune-related criteria to assess the efficacy of immunotherapy. In particular, theranostics has shown a great potential to improve the diagnosis of these diseases and to personalize, evaluate, and boost the efficacy of immunotherapy. Hence, it is now prime time to rethink how chemistry can improve the efficacy and reduce the side effects of immunotherapies.

In this special issue of *Accounts of Chemical Research*, we highlight emerging strategies and new opportunities to design and improve cancer immunotherapies. We discuss how nanomedicine is applied to advance cancer vaccine design and delivery of immunostimulatory agents and immunotherapies to targeted tissues. We also present how biomaterials, including scaffolds, hydrogels, and stimuli-responsive polymers, are applied to achieve sustained release of immunomodulatory agents, including small molecules, antibodies, growth factors, and cytokines, and in a localized and targeted manner for maximizing the therapeutic potential of immunotherapies while limiting their systemic exposure for reducing side effects. We also present how recent advances in our understanding of T-cell biology and mechanobiology are applied to advance manufacturing, activation, genetic modification, and in vivo deployment of CAR T-cells. Lastly, we highlight new avenues for amplifying the therapeutic potential of cancer immunotherapy by achieving combination immunotherapy, including immunotherapies with theranostics, chemotherapy, radiotherapy, phototherapy, and photodynamic therapy.

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