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Editorial

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Introduction to the Special Issue

# Cancer Immunotherapy

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Advancements in our understanding of how tumor cells evade immune control have led to new therapeutic approaches, and the introduction of cancer immunotherapies into daily oncological practice. Inhibitors—most of the time blocking antibodies—of inhibitory receptors called immune checkpoints, including PD-1 and CTLA-4, can induce remissions even in patients with advanced disease (Chen and Mellman 2017). For example, patients with metastatic melanoma had a median survival of less than 12 months only 10 years ago, but treatment with blocking antibodies that target PD-1 and CTLA-4 results in 58% of patients with a 3-year survival (Wolchok et al. 2017). The success of these immune checkpoint inhibitors has spurred the development of new immunotherapies, including agents that block other immune checkpoints such as TIM-3, LAG3 or TIGIT, immune-stimulating agonistic antibodies that bind to activating immune receptors such as OX-40 or 4-1BB (CD137), and molecules that modulate the immunosuppressive microenvironment including adenosine receptor blockers or indolamine-dioxygenase inhibitors (Sharma and Allison 2015; Chen and Mellman 2017). In particular, combination therapies between different immunotherapies, or targeted therapies with immunotherapies, or even immune-stimulating chemotherapies, are showing exceptional promise (Melero et al. 2015; Chen and Mellman 2017). Even cancer vaccination therapies that have shown limited success are more effective when in combination with immune checkpoint inhibitors (Melero et al. 2015; Chen and Mellman 2017). Also, cellular therapies including naturally occurring T cells, and genetically modified T cells expressing chimeric antigen receptors (CAR T cells), show very promising activity in patients with previously only few therapeutic options, which includes patients with therapy-refractory, acute lymphoblastic leukemia or aggressive B-cell lymphoma (Schuster et al. 2017; Maude et al. 2018). While these new treatments are a proof of concept that the immune system can be used to fight cancer, only a minority of cancer patients benefit from currently available therapies, and new approaches are needed. The immune checkpoint ligands (and receptors) now targeted in the clinic, exist as a repertoire of glycoforms, sometimes highly disease specific. Therapeutic strategies that take advantage of this specificity of glycoforms may provide a successful new approach. Promising recent work on targeting a glycoform of PD-L1 supports such an approach (Li et al. 2018). In this special issue, we consider the mounting evidence to support targeting glycans and glycan-mediated interactions for future cancer immunotherapeutics.

Glycans play an important role in the modulation of immune responses, and several recent publications have highlighted the glycan–lectin interaction as a major facilitator of antitumor immunity (Hudak et al. 2014; Jandus et al. 2014; Beatson et al. 2016). We provide here a multidisciplinary view on current developments in cancer glycoimmunology, with reviews from clinicians, cancer biologists, biochemists and general glycobiologists. In order to hit cancer, the right target needs to be defined. Pearce (2018) provides an overview of changes of glycans during malignant transformation, their biosynthesis and their function. Antibodies are essential for cancer therapies, both for targeted therapy such as HER-2-targeted therapy with trastuzumab or pertuzumab, and also blocking of immune checkpoints such PD-1 directed therapy with nivolumab or pembrolizumab. Max Crispin et al. cover the role of glycosylation on antibodies, from their role in modulating function, to their engineering for eliciting more effective antibody therapy (Dalziel et al. 2018). Posey et al. discuss the potential of CAR T cells in general and also how they could be directed against tumor-specific glycan epitopes (Steentoft et al. 2018). Two reviews deal with the effects of aberrant sialylation or hypersialylation, and the consequences of cancer-associated hypersialylation on interactions with sialoglycan-binding lectins. Borsig (2018) discusses the role of sialoglycan-selectin interactions in antitumor immunity and cancer progression, and Adams et al. (2018) present an overview on sialoglycan–Siglec interactions in immune responses to cancer. These reviews describe only a small aspect of the part that glycans may play in cancer and cancer immunity. For example, galectins, which are crucial components in the immune response to tumor cells, have been recently covered in a special issue in *Glycobiology* (Thijssen and Rabinovich 2014) and are not specifically discussed in this issue. We hope that the reviews in this issue are stimulating for the reader, and will induce new ideas, and studies to generate new glycan-based approaches to

stimulate anticancer immunity, and improve the prognosis of our patients.

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