Introduction: Antibody-Targeted Therapy
Special Issue

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Lymphocytes are the crucial orchestrators of the adaptive immune system because the enormous flexibility of antibody or TCR gene expression and modification in B or T lymphocyte populations allows adaptive selection of individual lymphocytes that express antibodies or TCRs that can recognize and tag almost any candidate molecule and potentially trigger a range of effector functions.

Over a century ago, pioneering immunologists not only learned how antibodies function in immune responses to pathogens and tumors, but also applied this knowledge to use antibodies therapeutically. The first preparations were relatively crude, but still very effective, antisera; however, as our understanding of antibody structure and genetics and the available technologies have improved over time, so has the ability to manipulate and fine-tune antibody molecules. In particular, monoclonal antibodies of various formulations are proving to be increasingly valuable therapeutic reagents for an ever-expanding range of diseases. In this Special Issue of review articles, our authors detail many of the current and future uses of antibodies in human diseases. We are very grateful to the authors for their excellent contributions and we hope that our readers find the articles both informative and inspirational.

Christian U. Blank and Alexander Enk (p.3) describe the expression of CTLA-4, which is an inhibitor of T cell second signals, on T cells and tumors, then detail its mechanisms of action and their inhibition by anti-CTLA-4 antibodies. They next summarize the use of two anti-CTLA-4 antibodies (tremelimumab or ipilimumab) as monotherapy or in combination with other agents as therapy for several cancers, in particular melanoma. Ipilimumab was the first immunotherapy approved for late-stage melanoma as monotherapy and its inhibition by anti-CTLA-4 antibodies. The authors also discuss combining this targeting strategy with the successful use of natalizumab in multiple sclerosis. The targeting of the PD-1–PD-L1 pathway offers the opportunity to selectively target responses to within the tumor microenvironment. Using various monoclonal antibodies, this approach has proved successful in hematological malignancies, melanoma, renal cell carcinoma, non-small cell lung cancer, bladder cancer and head and neck squamous cell cancers. The authors also discuss combining this targeting strategy with a wide range of currently available and potential therapies. Finally, they outline some problems in detecting expression of PD-L1 as a predictive biomarker.

Sujin Kang, Toshio Tanaka and Tadamitsu Kishimoto (p.21) describe the discovery and cloning of the cytokine IL-6 and its receptor; they detail the regulation of IL-6 production and its many roles in a wide range of cells types and protective immune responses. They go on to outline the roles of IL-6 in various diseases and the highly successful clinical use of the anti-IL-6R antibody tocilizumab in Castleman disease, rheumatoid arthritis and juvenile idiopathic arthritis. Tocilizumab is also being tested as therapy for several other chronic diseases, for example neuromyelitis optica, as well as for acute, life-threatening conditions such as systemic inflammatory response syndrome and cytokine-release syndrome.

Zachary Zimmerman, Tapan Maniar and Dirk Nagorsen (p.31) describe a strategy that combines two separate antibody specificities in a single, dual-specificity construct that recognizes CD3 on T cells and a second molecule on target tumor cells. The authors focus on blinatumomab, which cross-links T cells with B cell malignancies that express CD19, thereby recruiting cytotoxic T lymphocytes precisely to the tumor; CD19 has the advantage of very limited expression on hematopoietic cells. The authors detail the characteristics of T cell recruitment and the mechanisms used by them to kill tumor cells. Blinatumomab is being successfully used for relapsed/refractory non-Hodgkin’s lymphoma, diffuse large B cell lymphoma and acute lymphoblastic lymphoma.

George K. Philips and Michael Atkins (p.39) describe therapies that target PD-1 (and its ligand PD-L1), which is a ‘checkpoint inhibitor’ during TCR signaling. Tumors may express PD-L1 to down-regulate immune responses, so the targeting of the PD-1–PD-L1 pathway offers the opportunity to selectivity target responses to within the tumor microenvironment. Using various monoclonal antibodies, this approach has proved successful in hematological malignancies, melanoma, renal cell carcinoma, non-small cell lung cancer, bladder cancer and head and neck squamous cell cancers. The authors also discuss combining this targeting strategy with a wide range of currently available and potential therapies. Finally, they outline some problems in detecting expression of PD-L1 as a predictive biomarker.

Nicolas Schwab, Tilman Schneider-Hohendorf and Heinz Wiendli (p.47) discuss anti-α4-integrin antibodies, focusing on the successful use of natalizumab in multiple sclerosis (MS). Integrins comprise a wide range of heterodimers composed of various integrin α and β chains: α4-integrin can combine with β1-integrin to form VLA-4, or with β7-integrin to form LPAM-1. Natalizumab is effective not only in MS but also, for example, in Crohn’s disease (CD); however, the occasional
adverse events of virus (JCV)-mediated progressive multifocal leukoencephalopathy and immune reconstitution inflammatory syndrome preclude its use for CD. The authors detail the risk-management strategy to minimize these adverse events and discuss the wider insights that the development and use of natalizumab has given into MS pathogenesis.

Claudia Monaco, Jagdeep Nanchahal, Peter Taylor and Marc Feldmann (p.55) outline the development of antibodies as novel but highly effective drugs, focusing on how TNF was identified as a pivotal cytokine controlling the cascade of cytokines in chronic inflammation, and the spectacular success of anti-TNF in rheumatoid arthritis. The mechanism of action and its effects on disease pathogenesis are now well established. As well as whole-antibody molecules recognizing TNF, a F\textsubscript{ab} fragment of anti-TNF and a fusion protein containing TNFR2 have been approved for clinical use; in addition, the success of this approach means that many similar drugs are being developed and tested in a wide range of conditions, including acute as well as chronic diseases.