

# Preface

The first description of bispecific antibodies dates back 50 years, when Nisonoff and Rivers described the recombination of a mixture of univalent antibody fragments of different specificity. However, it took another 20 years before bispecific antibodies were proposed for therapeutic applications, mainly for the retargeting of effector T cells to tumor cells. These early studies implied already the use of bispecific antibodies to extend the functions beyond that normally executed by antibodies. Limited by the availability of monoclonal antibodies obtained from animal sources, bispecific antibodies of this early phase were generated by somatic hybridization of two hybridomas or by chemical conjugation of two IgG molecules. The high expectations on these bispecific antibodies were, however, not fulfilled, mainly because of low efficacy, immunogenicity, and severe adverse effects seen in clinical trials. This resulted in a loss of interest in this kind of molecules during the last decade of the last century. However, with advancements in antibody engineering and the establishment of novel applications, bispecific antibodies experienced a revival at the beginning of this century. Besides effector cell retargeting for cancer immunotherapy, applications include, among others, pre-targeting strategies in radioimmunotherapy and more recently dual-targeting strategies simultaneously attacking two disease-relevant targets. Genetic engineering allows nowadays to generate recombinant bispecific antibodies of defined composition, as well as with improved stability and producibility. Hence, bispecific antibodies have regained interest by the pharmaceutical industry, and many companies have meanwhile established their own bispecific antibody program. The first bispecific antibody for the retargeting of effector cells to EpCAM-positive tumor cells was approved in 2009 for the treatment of malignant ascites, and an increasing number of bispecific antibodies is currently in preclinical and clinical development.

Today, approaches to generate bispecific antibodies cover a broad spectrum including chemical conjugation, somatic hybridization, and genetic engineering. The latter has resulted in a multitude of recombinant IgG-like but also small-size bispecific antibody formats. Importantly, applications have been extended in the same manner. With many bispecific antibodies, especially of the second generation,

in development, this class of molecules is rapidly advancing. This book is intended to provide a comprehensive overview of the various techniques and formats to generate bispecific antibodies and to give insights into the various applications which have emerged during the last two decades and which are actively explored for therapeutic and diagnostic purposes.

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