About the Editor

Norbert Sewald

Norbert Sewald was born in Munich in 1961 and studied Chemistry at the Technical University of Munich. Having finished his PhD thesis in Organic Chemistry in 1991 he joined the group of Sir JE Baldwin at the Dyson Perrins Laboratory, University of Oxford from 1991 to 1992. In 1998 he finished his habilitation at the University of Leipzig and became Full Professor of Organic and Bioorganic Chemistry at Bielefeld University in 1999.

His research interests lie at the borderline between Chemistry and Life Sciences. The research activities of the Sewald group comprise chemically-modified bioactive peptides, natural product isolation, natural product total synthesis, antibody–drug conjugates and peptide–drug conjugates, peptide–protein and peptide–DNA interactions, molecular tools for proteome research, enzymatic halogenation and structure determination with NMR and molecular dynamics calculations.

For reprint orders, please contact reprints@future-science.com

Foreword

Optimizing antibody–drug conjugates for targeted delivery of therapeutics

Norbert Sewald

Despite a remarkable improvement of our knowledge in cancer biology and the successful approval of novel therapies, long term disease control or cure remain the exception rather than the rule in oncology. In most cases tumors develop resistance to therapeutic agents. In addition, many antitumor agents display high systemic toxicity and most advanced solid tumors remain essentially incurable. This need for better medication renders anticancer drugs a continuously attractive field of research. Thus, for facing the demand of high drug efficacy and safety, the development of targeted cytotoxic drugs has revived interest in pharmaceutical research. Many tumor cells are characterized by the overexpression of certain receptors, enzymes or antigens. Hence, molecules that specifically recognize these structures are suitable as homing devices in tumor therapy.

The Nobel laureate Paul Ehrlich (1854–1915) had the early vision that a compound could be made to selectively target a disease-causing organism or a tumor. A toxin should be delivered to a particular organism or tissue by an agent of selectivity. Such an ideal therapeutic agent would be a ‘magic bullet’ that killed only the target cells. This vision in part became true with the development and approval of therapeutic monoclonal antibodies. However, many therapeutic monoclonal antibodies that showed promise in preclinical studies when used on their own failed in the clinic because of insufficient cancer cell toxicity [1]. To overcome this problem, there has been an exponential growth in the field of antibody–drug conjugates (ADCs), where a monoclonal antibody is linked to a highly cytotoxic drug.

The structure of an ADC can be described as being formed by three different components: an antibody, which recognizes the tumor, is connected across a linker to an anticancer agent. The ADC is usually taken up by endocytosis and the anticancer agent is released inside the tumor cell according to a well-designed chemical mechanism or upon degradation of the immunoglobulin. Three ADCs have been approved by the US FDA: Mylotarg (2000, withdrawn in 2010), Adcetris (2011) and Kadcyla (2013), while approximately 30 ADCs are currently in clinical trials [2].

In this e-book, contributions by scientists both from industry and academia have been compiled to provide a comprehensive overview on the current development status of ADCs also covering the historical development and mode of action. Essential details are given on the development of new drugs, antibody–drug stoichiometry, and linker technologies including release mechanisms. Strategies for target selection, approaches to optimize antibody specificity, and ways to circumvent multidrug resistance are described. Aspects of pharmacology, pharmacokinetics and pharmacodynamics as well as the clinical development are covered and, finally, case studies shed light on the ADCs already approved for treatment and on current development candidates.

Acknowledgements

It has been a privilege and pleasure to edit this e-book on the exciting development of ADCs and I have to acknowledge all contributors for their high-quality manuscripts as well as Ryan De Vooght-Johnson and Duc Hong Le who took care of the administrative and technical issues in the publishing process.

Financial & competing interests disclosure

The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending or royalties.

No writing assistance was utilized in the production of this manuscript.

References

1. Firer MA, Gellerman G. Targeted drug delivery for cancer therapy: the other side of antibodies. *J. Hematol. Oncol.* 5, 70 (2012).
2. Mullard A. Maturing antibody–drug conjugate pipeline hits 30. *Nat. Rev. Drug Discov.* 12, 329–332 (2013).