Preface

Monoclonal antibodies (MAbs) have rapidly developed into one of the major tools in our arsenal for fighting human diseases. Currently, about 25% of the biological therapeutics that are being developed are MAbs or some form thereof. This book was initially planned as a formulation/analytical volume on MAb development, but the editors realizing the huge proliferation of development of MAbs felt that therapeutics might be better served with a book that touches on a variety of topics essential to the development of this exciting class of drugs. Hopefully you, the reader, will concur with this assessment and appreciate the efforts of all our contributors to this volume. Thus, this book represents a compilation of chapters that summarizes some of the recent progress in the pharmaceutical development of MAbs. It is divided into several different sections that span design of MAbs to the upstream and downstream processing steps required for production and manufacture of MAb therapeutics.

A summary of novel techniques used to humanize MAbs by Dennis along with a chapter on design of single-domain antigen-binding fragments by Ghassabeh et al. are presented in the section on "Design of Therapeutic Antibodies." The former addresses some new ways that MAbs are being engineered to reduce the potential of the immune response to murine-derived MAbs. The latter deals with the novel design of single heavy chain MAb fragments with comparable affinity to their related full-length MAbs, but that may be less costly to produce.

In the section on "Expression and Production of MAbs" some of the latest advances in the use of mammalian cell culture systems to produce therapeutic MAbs are discussed. The first chapter of this section by Bleck discusses a versatile transfection technology utilizing replication deficient retroviral vectors that allows for rapid expression of MAbs in different mammalian cell types. The second chapter by Heath describes the experiences and advances made in mammalian cell culture technology at Amgen. Their goal is to develop a cell culture platform for process development of MAbs to increase speed to market while minimizing resource commitments during early phase development.

This section is followed by two chapters on recovery and purification technologies that emphasize the efforts to develop and scale-up chromatographic processes. The first chapter in this section by Myers et al. discusses a case study involving the challenges and issues of scale-up and transfer of the chimeric MAb Remicade to a second manufacturing site. A detailed account is provided on the process changes that occurred during transfer and the changes that were made to ensure comparability of the products produced at the two

facilities. The second chapter by Walter and Gottschalk addresses the recent uses of disposable devices for tangential flow filtration (TFF) and chromatography for downstream MAb processing. Advantages and limitations of the technology over fixed stainless steel equipment are discussed with an emphasis on the cost of using disposables.

In the section on "Formulation and Delivery" two previously well-cited review publications are reproduced. The first chapter in this section by Daugherty and Mrsny reviews the general challenges of formulating complex biomolecules such as MAbs and then discusses potential administration by several delivery routes. The second chapter by Shire et al. reviews the challenges of developing and manufacturing high concentration MAb formulations for SC administration. The third chapter in the section by Bechtold-Peters summarizes innovative alternate approaches to lyophilization for the production of formulated bulk and solid dosage forms of therapeutic MAbs.

Recent progress and experience in the analysis of these complex biomolecules is presented in the section entitled "Analytics and Specification Setting for MAbs." The first chapter by Klakamp, reproduced from a previous publication, discusses the use of BiaCore and KinExA technologies to characterize binding affinities and kinetics of binding of MAbs to their therapeutic targets. This chapter summarizes the technologies as well as the challenges and limitations of the methods. The second chapter in this section by Harris et al. discusses the contributions to microheterogeneity of MAbs. In particular, glycosylation and covalent modifications as well as experimental modalities to characterize these modifications are reviewed. This chapter is followed by a review of the use of analytical ultracentrifugation (AUC) by Andya et al. to characterize fragmentation and aggregation of MAbs. This chapter also includes suggested methods to improve the precision of the AUC measurements. The final chapter in this section by Harn et al. explores the use of several biophysical methods to characterize and compare MAbs from different biotechnology companies. This chapter demonstrates that the use of different biophysical methods combined with changes in solution conditions such as temperature, pH, and ionic strength can provide a sensitive way to monitor conformational stability of MAbs.

The next section deals with MAb pharmacokinetic and immunogenicity issues. In particular, the first chapter by Raju discusses the complex role of glycosylation of MAbs and how the glycosylation can impact potential degradation of the protein backbone by proteases. The second chapter by Stas et al. discusses the potential for immunogenic responses to the administered MAbs, and the risks for altered pharmacokinetics. General strategies and methods to assess immunogenicity during MAb development are also reviewed.

The final section of this book deals with new classes as well as production methods of MAbs. The first chapter by Yansura and Reilly discuss novel technology to express recombinant derived full-length MAbs in *E. coli*, which may have advantages in cost and faster production rates. The second chapter in this section by Senter addresses the development of drug-conjugated MAbs for cancer therapy whereby the MAb is used to target a small molecule drug to a specific site on a cancer cell resulting in greater specific activity with lower systemic toxicity. This chapter discusses the challenges of choosing an appropriate linker chemistry that is sufficiently stable to minimize cytotoxic drug exposure during MAb circulation, but is still capable of releasing the drug once the MAb is internalized into the target cell.

As mentioned earlier, we decided to expand the scope of this volume and hopefully we have been successful in touching on the many aspects of MAb development and manufacture. The successful completion of this book was made possible by the assistance of a large number of people to whom we are very grateful. In particular, we wish to thank and acknowledge the contributions from many in the industry and academia who took time from their very busy schedules to share their expertise with all of us. We also want to thank the publisher, in particular Kathleen Lyons and Renata Hutter for their wonderful support.

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