Mohammad A. Tabrizi
Gadi G. Bornstein
Scott L. Klakamp *Editors*

Development of Antibody-Based Therapeutics

Translational Considerations & Challenges

2nd Edition

Adis

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Introduction

1

Mohammad A. Tabrizi

"Life is like riding a bicycle. To keep your balance you must keep moving."

—Albert Einstein

Abstract

This book will expand on the content provided in the First Edition (*Development of Antibody-Based Therapeutics: Translational Considerations, 1st Edition, 2012*). Although the first publication provided a comprehensive review of the critical topics relevant for development of antibody-based therapeutics, this Second Edition will provide in-depth coverage of the key topics related to development of targeted therapeutics with key focus on the recent developments in the field. Recent advances span development of targeted modalities in exciting therapeutic areas such as immuno-oncology (IO) and application of combination therapies, novel technologies, and advances in therapeutic application of antibody-drug conjugates. We hope that this collection has successfully captured new advances relevant to the development of targeted therapeutics and will provide interested reader with an advanced knowledge of the field.

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1.1 Prelude

Biologics are one of the fastest growing subsets of pharmaceuticals today. In 2016, ten monoclonal antibodies were approved by the FDA for diverse conditions such as psoriasis and cancer. This high number of approvals followed the previous record number of approvals of ten monoclonal antibodies in 2015. The high approval rate for biologics is a testament to advances in antibody technology and the unique advantage that this class of therapeutics can offer. In addition to monoclonal antibodies, other biologics such as antibody-drug conjugates, multi-specific constructs, and antibody-derived modalities are also being considered as viable drug candidates for development. With so many players in the market, it becomes imperative to have an efficient and effective translational approach early on in the drug development process. Clarity on patient-related variables, construct manufacturing considerations, underlying pharmacology and pathophysiology, as well as integration of key translational considerations can accelerate drug development processes, ultimately benefiting patients in need of such therapies.

With advances in antibody technology, it is possible to rapidly and effectively generate highly tailored and specific antibody-based therapeutics that interact with a diverse array of soluble or cell-associated antigen targets. Biologics and antibody-based therapeutics are becoming progressively complex. With such complexities in the design of novel constructs, foundational and robust approaches in translation of preclinical data in support of the later stages of drug development are becoming increasingly vital. Understanding of target biology across species and application of a science-based approach for integration of pharmacology principles are an essential cornerstone for translational efficiency across species. Hence, an important question to be addressed from early stages of lead selection is to identify and establish an efficient translational strategy for successful development of such novel constructs.

Antibody-drug conjugates (ADCs) are increasingly employed as novel targeted therapies. Translational challenges important for ADCs are highly specific and require establishing an integrated approach for evaluation of many relevant variables. Antibody-drug conjugates combine the exquisite selectivity of targeted antibodies and the high potency of small molecule drugs with the aim of achieving durable responses in patients. As application of highly potent small molecule drugs can be limited by their undesirable toxicity, targeted delivery of highly potent small molecule drugs to specific cells is intended to augment the therapeutic window for the payload in the clinical setting. A successful transition of ADCs into the clinic will be highly dependent on effective translation of critical attributes governing exposure-response relationships across species. Similarly, combination therapies, using single agents, could benefit from the "synergistic" effect profile and offer a unique spatial configuration where each construct can engage the intended target in a flexible manner. However, multi-specific modalities may not benefit from a similar spatial flexibility to engage targets in a comparable manner. Therefore, translational challenges important for this class of molecules are highly specific and require establishing novel design and development approaches.

Inclusion of pharmacology principles in drug development is a foundational step for effective modality design and selection of antibody-based therapeutics. Clarity on patient-related variables, manufacturing considerations, underlying biology and pathophysiology, as well as integration of key translational variables can accelerate drug development processes, ultimately benefiting patients in need of such therapies. Establishing design goals with respect to antibody affinity is a necessary step and should be incorporated into the development strategies from the earliest stages of the discovery process for biologic modalities. Evaluation of affinity design goals is a complex process contingent on many critical variables. Knowledge of the target antigen biology and its role in the pathogenesis of disease is of high importance for achieving this objective. Selection of the adequate affinity for a functional biologic construct should allow achievement of the maximum therapeutic benefit at a dose associated with a manageable cost of goods.

Additionally, the post-genomic era has witnessed the emergence of new and improved state-of-the-art technologies to characterize structure-function relationships. The emergence of these technologies has been further facilitated by faster computer processors, expanded memory, increased storage capacity, and newer algorithms. The need to obtain critical information on protein structures has resulted in significant improvements in methods such as protein crystallography and NMR (nuclear magnetic resonance). Bi- and multi-specific molecules can be differentiated from traditional monoclonal antibodies as they are able to bind multiple antigen targets simultaneously. These modalities may offer additional advantages with respect to target engagement that may not be feasible by traditional combination therapies with single agents. Therefore, design of multi-specific constructs requires particular attention to target and drug selection for successful application of this class of therapeutics. In the past, progress in advancing bispecific molecules into the clinical arena was slow, mainly due to challenges associated with generating bispecific molecules in sufficient quality and quantity. However, due to recent progress in rapidly evolving technologies that encompass state-of-the-art engineering, production, and development of recombinant protein scaffolds, development of novel bispecific modalities has witnessed exponential growth.

With the progress in cancer immunotherapy, it is now evident that antigen-specific activation of patients' immune responses can be utilized for achieving significant therapeutic benefits. Novel molecules have been developed, and promising advances have been achieved in cancer therapy. The latest success of cancer immunotherapy clearly reflects the novelty of the approach and importance of this class of therapeutics. Due to the nature of immunotherapy, i.e., harnessing the patient's immune system, it becomes critical to evaluate the important variables that can guide preclinical development, translational strategies, patient selection, and effective clinical dosing paradigms following single and combination therapies. There is now considerable interest in evaluation of the key regulatory mechanisms involved in activation of the immune system while identifying sources of variability in the clinical response to such therapies. Hence, it is evident that application of quantitative approaches can highly enhance knowledge regarding the underlying variables important for designing effective dosing strategies in IO therapies.

A critical consideration during the development of antibody-based therapeutics is selection and evaluation of relevant biomarkers during early preclinical stages. Effective application of biomarkers not only lessens the time and cost associated with the drug development process but also fosters implementation of rational development progress throughout various development phases. When appropriate immunoassay methodologies are available, relationships between antibody pharmacokinetics (PK) and the ensuing effects on biomarkers can be effectively examined. Evaluation of exposure-response relationships in vivo can provide invaluable information with respect to antibody potency and the pharmacodynamic response efficiency. Additionally, development of appropriate safety markers early in drug development can result in a higher probability of success for new drug candidates. As the overarching goal of cancer therapy is to effectively eradicate cancer in a manner that is tolerable and safe for use in the intended patient population, application of biomarkers can facilitate effective patient selection with a positive impact on the final therapeutic outcome. Additionally, combination therapies for the treatment of cancer have emerged as an effective way to anticipate and overcome cancer heterogeneity and resistance**.** With the emergence of cancer immune therapy, clinical trials for the combination of traditional oncology drugs and immune checkpoint inhibitors are ongoing.

Drug discovery and development, much like Einstein's quote on "life adventures similarity to riding a bicycle", are an analogous process. Despite numerous setbacks, we as scientists "must keep moving." In this book, we have attempted to provide a comprehensive discussion of various topics that highlight the progress in the field and are critical for establishing successful strategies for the development of antibody-based therapeutics. An understanding of the relationship between the "unit dose" and "unit effect" with respect to both beneficial and deleterious effects is essential for developing an effective translational strategy that will deliver a superior therapeutic candidate into clinical development. With this objective in mind, we have carefully assembled topics that highlight a science-based approach with the underlying theme of "translatability" throughout the various drug development phases. The ensuing chapters were prepared by scientific experts in the field to whom we are greatly indebted for their valuable contributions to enable publication of this unique book. Each chapter has a particular focus on a specific relevant topic for the development of antibody-based therapeutics. Although some topics may not appear to be directly concerned with translational considerations or are technical in nature, addressing the ancillary aspects of antibody-drug discovery and development provides the reader with a broader understanding of the strategies involved in the drug development process of these agents. We envision that someone who has little if any current knowledge about therapeutic antibodies will be able to use both publications as valuable references and glean substantial insights from leading scientists across a broad range of expertise.

Let the beauty of what we love be what we do.
—Rumi

Translational Considerations and Challenges: An Overview

2

Vaishnavi Ganti and Mohammad A. Tabrizi

Abstract

Biologics are one of the fastest growing subsets of pharmaceuticals today. In 2016, ten monoclonal antibodies were approved by the FDA for diverse conditions such as psoriasis and cancer. This high number of approvals followed the previous record number of approvals of ten monoclonal antibodies in 2015. Such high approval rate for biologics is a testament to advances in antibody technology and the unique advantage that this class of therapeutics offers. In addition to monoclonal antibodies, other biologics such as antibody-drug conjugates, multi-specific constructs, and antibody-derived modalities are also being considered as viable drug candidates for development. With so many players in the market, it becomes imperative to have an efficient and effective translational approach early on in the drug development process. Clarity on patient-related variables, construct manufacturing considerations, underlying pharmacology and pathophysiology, as well as integration of key translational considerations can accelerate drug development processes, ultimately benefiting patients in need of such therapies. In the previous edition of this book (First Edition), translational considerations for development of antibody-based therapeutics were discussed. This publication deals with topics related to novel and more complex modalities.

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2.1 Introduction

Biologics are one of the fastest growing subsets of pharmaceuticals today. In 2016, various monoclonal antibodies were approved by the FDA for diverse conditions such as psoriasis and cancer. This trend followed the previous record number of approvals of many monoclonal antibodies in 2015. Such high approval rate for biologics is a testament to advances in antibody technology and the unique advantage that this class of therapeutics offers. Biologics and antibody-based therapeutics are becoming progressively more complex. Increasingly, drug candidates are designed to address multiple targets simultaneously. With such complexities in the design of novel constructs (Fig. 2.1), foundational and robust approaches in translation of preclinical data in support of the later stages of drug development are becoming increasingly vital. Understanding of target biology across species and application of a science-based approach for integration of pharmacology principles are essential cornerstones for translational efficiency across species. Hence, an important question to be addressed from early days of lead selection is to identify and establish an efficient translational strategy for successful development of such novel constructs.

Translational considerations for development of drug candidates, small molecules or biologics, should encompass considerations as related to (a) therapeutic application and target patient population, (b) cost of goods, (c) relevance of species selection, and (d) nuances in the pharmacological system response that define the relationships between the "unit dose" and the "unit effect" across species (First Edition). Hence, a clear understanding of the target antigen biology and its role in

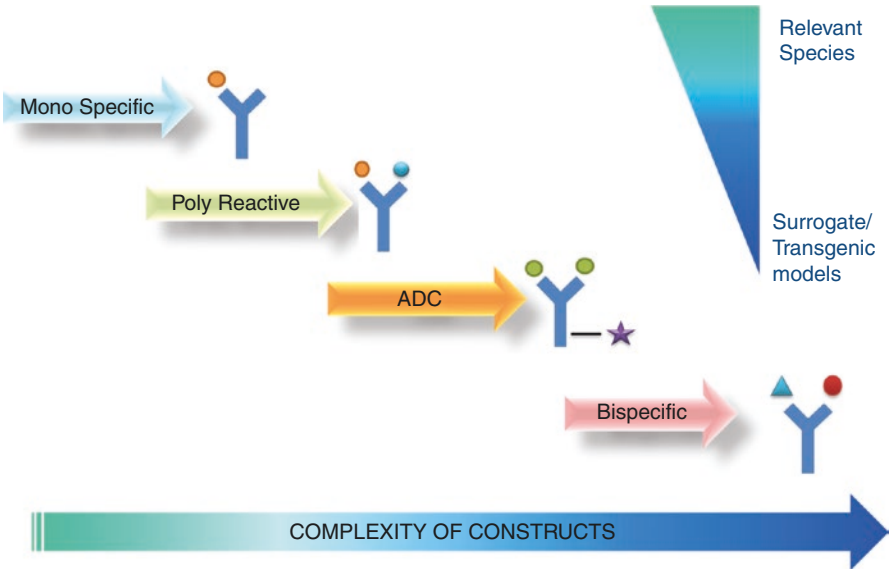

Fig. 2.1 Construct complexity and selection of the pharmacologically relevant species

the pathogenesis of disease is of primary importance. Surveying appropriate tissues for validation of target expression by immunohistochemistry, or equivalent methodologies, is vital to establishing disease linkage, and verifying the target antigen is not abundantly expressed in normal tissues. Also, functional validation of the target is critical in appropriate disease models. Functional redundancy of the target is an additional consideration; if the target antigen belongs to a conserved protein family, down-modulation of the target may not result in the desired phenotypic outcome. However, interpretation of the preclinical findings and implications for human disease obtained from preclinical models is rarely straightforward and is limited by various factors such as choice of species, target properties, drugs' mode of action (MOA; viz., construct-related factors: cytotoxic vs. cytostatic properties, immune modulation requirements, effect-site localization, biodistribution, and PD system efficiency). For example, with immuno-oncology drugs, the presence and comparability of the functional immune system are essential for translation of the immune-related effects; hence, considerations regarding the pharmacological differences in immune function and activation across species are of great significance.

Establishing relevant bioanalytical (BA) methodologies from early preclinical stages is necessary for implementation of effective strategies and successful translation of information into the later drug development phases (Tabrizi et al. 2010). Robust and effective BA methodologies assist in addressing important questions regarding PK, immunogenicity (IM), and PD of drug candidates. Moreover, BA methodologies are critical for translation of exposure-response data from preclinical efficacy and nonclinical safety studies in support of the effective design of first-in-human clinical programs. To achieve these objectives, BA methods must be well characterized and provide a certain degree of robustness even at early stages of preclinical development. Evaluation of relevant biomarkers in appropriate animal models can greatly enhance translation of exposure-response relationships across species. When appropriate immunoassay methodologies are available, relationships between construct exposure and the ensuing effects on proof-of-mechanism and proof-of-principle biomarkers can be effectively examined (see First Edition, Chap. 13). Application of biomarkers should guide the selection of safe and effective first-generation leads for advancement through various development stages. Additionally, relevant biomarkers can further provide a clear opportunity for evaluation of differentiating characteristics relevant to development of second-generation antibody-based candidates and drive lead evaluation during the preclinical phases.

Characterization of safety in relevant species is pivotal to effective translational strategies. The purpose of preclinical safety evaluation for small and large molecules is to identify potential risks to humans. These data are used to recommend a safe starting dose and guide dose escalation schemes, as well as other risk mitigation strategies during early clinical development. The objective is to reveal potential target organs of toxicity with an assessment of dose-response, reversibility, ability to monitor, as well as establishing adverse effect levels or minimally anticipated biological effect levels. It is essential that these pivotal preclinical studies are conducted in a pharmacologically relevant species. Safety concerns associated with many monoclonal antibodies are often an extension of their intended