# **Cancer Drug Discovery and Development**

**Series Editor** 

Beverly A. Teicher, Bethesda, MD, USA

Cancer Drug Discovery and Development is the definitive book series in cancer research and oncology, providing comprehensive coverage of specific topics in the field. The aim of the series is to cover the process of drug discovery, preclinical models in cancer research, specific drug target groups and experimental and approved therapeutic agents across volumes.

Volumes are current and timely, anticipating areas where experimental agents are reaching FDA approval. Each volume is edited by an expert in the related field and chapters are authored by renowned scientists and physicians in their fields of interest. All volumes undergo single blind peer review and review by the series editor prior to acceptance and publication in the series. Cancer Drug Discovery & Development is indexed in SCOPUS.

More information about this series at https://link.springer.com/bookseries/7625

Armin Ghobadi • John F. DiPersio Editors

# Gene and Cellular Immunotherapy for Cancer

🔆 Humana Press

*Editors* Armin Ghobadi Department of Medicine, Division of Oncology Washington University School of Medicine St. Louis, MO, USA

John F. DiPersio Department of Medicine Pathology & Immunology, Division of Oncology Washington University School of Medicine Saint Louis, MO, USA

ISSN 2196-9906 ISSN 2196-9914 (electronic) Cancer Drug Discovery and Development ISBN 978-3-030-87848-1 ISBN 978-3-030-87849-8 (eBook) https://doi.org/10.1007/978-3-030-87849-8

#### © Springer Nature Switzerland AG 2022

This work is subject to copyright. All rights are reserved by the Publisher, whether the whole or part of the material is concerned, specifically the rights of translation, reprinting, reuse of illustrations, recitation, broadcasting, reproduction on microfilms or in any other physical way, and transmission or information storage and retrieval, electronic adaptation, computer software, or by similar or dissimilar methodology now known or hereafter developed.

The use of general descriptive names, registered names, trademarks, service marks, etc. in this publication does not imply, even in the absence of a specific statement, that such names are exempt from the relevant protective laws and regulations and therefore free for general use.

The publisher, the authors, and the editors are safe to assume that the advice and information in this book are believed to be true and accurate at the date of publication. Neither the publisher nor the authors or the editors give a warranty, expressed or implied, with respect to the material contained herein or for any errors or omissions that may have been made. The publisher remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

This Humana imprint is published by the registered company Springer Nature Switzerland AG The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

### Preface

Genetically modified cellular immunotherapies and T-cell bispecifics are changing the landscape of cancer treatment. Approval of five CAR-T products and a T-cell engager by the US Food and Drug Administration (FDA) for hematologic malignancies represents the start of a wave of cellular therapies that will dramatically change how we treat cancer in the near future. These advances have resulted in a high level of enthusiasm among scientific community, clinicians, and industry for developing effective immunotherapies for hematological malignancies and solid tumors. This book will cover two broad categories of gene and cellular therapies: (1) Cellular-based immunotherapies: CAR-T, TCR-T, TIL, viral CTLs, NK cells; (2) T/ NK cell engagers including BiTEs, DARTs, TanAbs, and others. The first two chapters present a review of the biologic basis of innate and adaptive immunity and a history of cellular therapy. We then review each treatment category comprehensively covering the whole spectrum of the bench to bedside preclinical and clinical studies. There is a substantial emphasis on CAR-T therapies followed by chapters focused on regulatory aspects of gene and cellular immunotherapy, manufacturing including point-of-care manufacturing of genetically modified cellular therapies and a roadmap to outpatient cellular therapy. This book provides a comprehensive source for readers involved in or interested in the nuts and bolts of gene and cellular therapies. We have prepared this book as a comprehensive review in a single volume for trainees and basic and clinical researchers in academic centers and the industry. In light of the rapid evolution of this field, we are planning to update this book every 4 years.

St. Louis, MO, USA St. Louis, MO, USA Armin Ghobadi John F. DiPersio

## Acknowledgments

We want to thank contributors who are all well-respected experts in the field of gene and cellular therapy. We appreciate Joel Eissenberg for the copy editing of multiple chapters, Larissa Albright, acquisitions editor, Springer; Deepak Ravi, product development editor; and Matt Wyczalkowski for illustrating the majority of figures for this book; they were instrumental in bringing this project to the finish line. Finally, we thank our wives and families for their support during the design, implementation, and completion of this project.

> Armin Ghobadi, MD John F. DiPersio, MD, PhD

## Contents

#### Part I Overview

The History of Cellular Therapies.Zachary D. Crees and Armin Ghobadi	3
Basics of Immunity Brian T. Edelson	13
Part II CAR-T	
<b>Biology of CAR-T Cells</b> Trisha R. Berger, Alexander Boardman, Renier Brentjens, and Marcela V. Maus	29
Cell Types Used for CAR Generation	57
Combination Therapeutics with CAR-T Cell Therapy Mohamad M. Adada, Elizabeth L. Siegler, and Saad S. Kenderian	69
Safety Switches Used for Cellular Therapies Lauren Smith and Antonio Di Stasi	91
<b>Off-the-Shelf CAR-T</b> Matthew L. Cooper, Giorgio Ottaviano, John F. DiPersio, and Waseem Qasim	109
Manufacturing of CAR-T Cells: The Assembly Line	121
Navigating Regulations in Gene and Cell Immunotherapy Jaikumar Duraiswamy, Courtney Johnson, and Karin M. Knudson	141
Bringing CAR-T to the Clinic Michael D. Jain, Pselane Coney, and Frederick L. Locke	165

CAR-T Cell Complications Emily C. Ayers, Dustin A. Cobb, and Daniel W. Lee	181
Mechanisms of Resistance and Relapse After CAR-T Cell Therapy Mehmet Emrah Selli, Prarthana Dalal, Sattva S. Neelapu, and Nathan Singh	207
Part III TIL	
<b>Tumor Infiltrating Lymphocytes (TIL): From Bench to Bedside</b> Jeffrey P. Ward	223
Part IV TCR	
T-Cell Receptor (TCR) Engineered Cells and Their Transition to the Clinic	251
Part V Viral CTLs	
Viral Cytotoxic T Lymphocytes (CTLs): From Bench to Bedside Susan E. Prockop and Sanam Shahid	269
Part VI NK Cell	
Biology of NK Cells and NK Cells in Clinic Grace C. Birch, Todd F. Fehniger, and Rizwan Romee	293
Part VII T/NK Cell Engagers	
Biology and Clinical Evaluation of T/NK Cell Engagers Rebecca Epperly, Stephen Gottschalk, and M. Paulina Velasquez	329
Part VIII Logistics	
Roadmap for Starting an Outpatient Cellular Therapy Program Mariana Lucena, Katie S. Gatwood, Bipin N. Savani, and Olalekan O. Oluwole	355
Index	369