

Lipid A in Cancer Therapy

ADVANCES IN EXPERIMENTAL MEDICINE AND BIOLOGY

Editorial Board:

NATHAN BACK, *State University of New York at Buffalo*

IRUN R. COHEN, *The Weizmann Institute of Science*

ABEL LAJTHA, *N.S. Kline Institute for Psychiatric Research*

JOHN D. LAMBRIS, *University of Pennsylvania*

RODOLFO PAOLETTI, *University of Milan*

Recent Volumes in this Series

Volume 660

PARAOXONASES IN INFLAMMATION, INFECTION, AND TOXICOLOGY

Edited by Srinu Reddy

Volume 661

**MEMBRANE RECEPTORS, CHANNELS AND TRANSPORTERS IN
PULMONARY CIRCULATION**

Edited by Jason X. -J. Yuan, and Jeremy P.T. Ward

Volume 662

OXYGEN TRANSPORT TO TISSUE XXXI

Edited by Duane F. Bruley and Eiji Takahasi

Volume 663

**STRUCTURE AND FUNCTION OF THE NEURAL CELLADHESION
MOLECULE NCAM**

Edited by Vladimir Berezin

Volume 664

RETINAL DEGENERATIVE DISEASES

Edited by Robert E. Anderson, Joe G. Hollyfield, and Matthew M. LaVail

Volume 665

FORKHEAD TRANSCRIPTION FACTORS

Edited by Kenneth Maiese

Volume 666

PATHOGEN-DERIVED IMMUNOMODULATORY MOLECULES

Edited by Padraic G. Fallon

Volume 667

LIPID A IN CANCER THERAPY

Edited by Jean-François Jeannin

A Continuation Order Plan is available for this series. A continuation order will bring delivery of each new volume immediately upon publication. Volumes are billed only upon actual shipment. For further information please contact the publisher.

Lipid A in Cancer Therapy

Edited by

Jean-François Jeannin

Tumor Immunology and Immunotherapy Laboratory

Ecole Pratique des Hautes Etudes

Inserm U866, University of Burgundy, Dijon, France

Springer Science+Business Media, LLC

Landes Bioscience

Springer Science+Business Media, LLC
Landes Bioscience

Copyright ©2009 Landes Bioscience and Springer Science+Business Media, LLC

All rights reserved.

No part of this book may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopy, recording, or any information storage and retrieval system, without permission in writing from the publisher, with the exception of any material supplied specifically for the purpose of being entered and executed on a computer system; for exclusive use by the Purchaser of the work.

Printed in the USA.

Springer Science+Business Media, LLC, 233 Spring Street, New York, New York 10013, USA
<http://www.springer.com>

Please address all inquiries to the publishers:
Landes Bioscience, 1002 West Avenue, Austin, Texas 78701, USA
Phone: 512/ 637 6050; FAX: 512/ 637 6079
<http://www.landesbioscience.com>

The chapters in this book are available in the Madame Curie Bioscience Database.
<http://www.landesbioscience.com/curie>

Lipid A in Cancer Therapy, edited by Jean-François Jeannin. Landes Bioscience / Springer Science+Business Media, LLC dual imprint / Springer series: Advances in Experimental Medicine and Biology.

ISBN: 978-1-4419-1602-0

While the authors, editors and publisher believe that drug selection and dosage and the specifications and usage of equipment and devices, as set forth in this book, are in accord with current recommendations and practice at the time of publication, they make no warranty, expressed or implied, with respect to material described in this book. In view of the ongoing research, equipment development, changes in governmental regulations and the rapid accumulation of information relating to the biomedical sciences, the reader is urged to carefully review and evaluate the information provided herein.

Library of Congress Cataloging-in-Publication Data

Lipid A in cancer therapy / edited by Jean-François Jeannin.
p. ; cm. -- (Advances in experimental medicine and biology ; 667)

Includes bibliographical references and index.

ISBN 978-1-4419-1602-0

1. Cancer--Immunotherapy. 2. Microbial lipids--Therapeutic use. 3. Endotoxins--Therapeutic use.
I. Jeannin, Jean-François, 1948- II. Series: Advances in experimental medicine and biology, v. 667.
0065-2598 ;

[DNLM: 1. Lipid A--pharmacology. 2. Lipid A--therapeutic use. 3. Neoplasms--drug therapy. W1
AD559 v.667 2009 / QU 85 L7605 2009]

RC271.I45L57 2009

616.99'4061--dc22

2009035583

FOREWORD

Cancer remains a major challenge for modern society. Not only does cancer rank among the first three causes of mortality in most population groups but also the therapeutic options available for most tumor types are limited. The existing ones have limited efficacy, lack specificity and their administration carry major side effects. Hence the urgent need for novel cancer therapies. One of the most promising avenues in research is the use of specific immunotherapy.

The notion that the immune system may have important anti-tumor effects has been around for more than a century now. Every major progress in microbiology and immunology has been immediately followed by attempts to apply the new knowledge to the treatment of cancer. Progress has reached a point where it is well established that most cancer patients mount specific T cell responses against their tumors. The molecular identity of the antigens recognized by anti-tumor T cells has been elucidated and several hundreds of tumor-derived antigenic peptides have been discovered. Upon recognition of such peptides presented by self MHC molecules, both CD8 and CD4 T cells are activated, expand to high numbers and differentiate into effective anti-tumor agents. CD8 T cells directly destroy tumor cells and can cause even large tumors to completely regress in experimental mouse models. These observations have spurred intense research activity aimed at designing and testing cancer vaccines.

Over 100 years ago Coley successfully used intratumoral injection of killed bacteria to treat sarcomas. The important anti-tumor effects observed in a fraction of these patients fueled major research efforts. These led to major discoveries in the 80s and the 90s. It turns out that bacterial lipopolysaccharides stimulate the production of massive amounts of a cytokine still known today as tumor necrosis factor (TNF- α). They do so by engagement of a rather complex set of interactions culminating in the ligation of a Toll-like receptor, TLR-4. Ensuing signaling through this receptor initiates potent innate immune responses. Unfortunately the clinical use of both TNF- α and LPS can not be generalized due to their very narrow therapeutic margin. Importantly, synthetic Lipid A analogs have been identified that retain useful bioactivity and yet possess only mild toxicity.

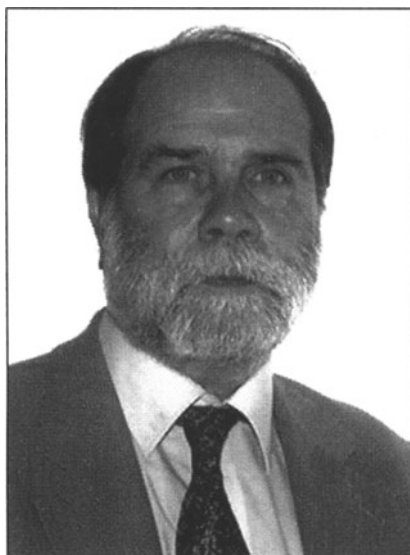
The relatively large body of information accumulated thus far on the molecular and cellular interactions set in motion by administration of LPS as well as by the synthetic Lipid A analogs allow to place this family of bacterially-derived molecules at the crossroads between innate and adaptive immunity. By virtue of this key position, the therapeutic applications being pursued aim at using these compounds either as direct anti-tumor agents or as vaccine adjuvants. The clinical experience acquired so far on these two avenues is asymmetric. Few clinical trials using Lipid A analogs as single anti-cancer agents involving less than 100 patients with advanced cancer have been reported. In contrast, Lipid A has been tested in over 300,000 individuals in various vaccines trials, including therapeutic cancer vaccines.

Clearly most of the work needed to develop Lipid A as effective anti-cancer agents and/or as vaccine adjuvant lies ahead in the near future. This book is a timely contribution and provides a much needed up-to-date overview of the chemical, biological and physiological aspects of Lipid A. It should be a beacon to all those involved in this field of research.

*Jean-Charles Cerottini, MD
University of Lausanne,
Former Director, Ludwig Institute for Cancer Research
Lausanne Branch*

*Pedro Romero, MD
University of Lausanne,
Member, Ludwig Institute for Cancer Research
Lausanne Branch*

ABOUT THE EDITOR...



JEAN-FRANÇOIS JEANNIN is Professor of Immunology at Ecole Pratique des Hautes Etudes (EPHE) and director of the EPHE Tumor Immunology and Immunotherapy Laboratory, an INSERM (National Institute of Health and Medical Research) team. His main research interests have included the effects of lipopolysaccharides in the tumor immune response and the immunotherapy of colon cancer with Lipid A. Now he is investigating mechanisms of immunotherapy with synthetic Lipid A analogs in cancer patients and animal cancer models. He is especially interested in the sensitization of tumor cell death by nitric oxide produced in tumors during Lipid A immunotherapy.

Jean-François Jeannin has been Dean and President of the Life Sciences faculty of EPHE and a member of numerous scientific organizations.

PARTICIPANTS

Shizuo Akira
Department of Host Defense
Research Institute for Microbial
Diseases
Osaka University
and
ERATO
Japan Science and Technology
Corporation
Osaka
Japan

Jörg Andrä
Biophysics Division
Research Center Borstel
Leibniz-Center for Medicine
and Biosciences
Borstel
Germany

Marc Bardou
Clinical Pharmacology Unit
and Laboratory of Cardiovascular
Experimental Physiology
and Pharmacology
Dijon
France

Ali Bettaieb
Tumor Immunology
and Immunotherapy Laboratory
Ecole Pratique des Hautes Etudes
Inserm U866
University of Burgundy
Dijon
France

Klaus Brandenburg
Division of Biophysics
Research Center Borstel
Leibniz-Center for Medicine
and Biosciences
Borstel
Germany

Jean-Charles Cerottini
University of Lausanne
Ludwig Institute for Cancer Research
Lausanne
Switzerland

Christopher W. Cluff
GlaxoSmithKline Biologicals
Hamilton, Montana
USA

Thomas Gutschmann
Department of Immunochemistry
and Biochemical Microbiology
Research Center Borstel
Leibniz-Center for Medicine
and Biosciences
Borstel
Germany

Masahito Hashimoto
Department of Nanostructure
and Advanced Materials
Graduate School of Science
and Engineering
Kagoshima University
Korimoto, Kagoshima
Japan

Jean-François Jeannin
Tumor Immunology
and Immunotherapy Laboratory
Ecole Pratique des Hautes Etudes
Inserm U866
University of Burgundy
Dijon
France

Kazuyoshi Kawahara
Department of Applied Material
and Life Science
College of Engineering
Kanto Gakuin University
Yokohama, Kanagawa
Japan

Shoichi Kusumoto
Suntary Institute for Bioorganic
Research
Shimamoto-cho
Mishima-gun, Osaka
Japan

Amandine Martin
Tumor Immunology
and Immunotherapy Laboratory
Inserm U866
University of Burgundy
Dijon
France

David C. Morrison
Department of Basic Medical Science
School of Medicine
Shock Trauma Research Center
University of Missouri
Kansas City, Missouri
USA

Mareike Müller
Department of Immunochemistry
and Biochemical Microbiology
Research Center Borstel
Leibniz-Center for Medicine
and Biosciences
Borstel
Germany

Nilofer Qureshi
Department of Basic Medical Science
School of Medicine
Shock Trauma Research Center
University of Missouri
Kansas City, Missouri
USA

Catherine Paul
Tumor Immunology
and Immunotherapy Laboratory
Inserm U866
University of Burgundy
Dijon
France

Daniele Reisser
Tumor Immunology
and Immunotherapy Laboratory
Inserm U866
University of Burgundy
Dijon
France

Cheryl E. Rockwell
Department of Basic Medical Science
School of Medicine
Shock Trauma Research Center
University of Missouri
Kansas City, Missouri
USA

Pedro Romero
University of Lausanne
Ludwig Institute for Cancer Research
Lausanne
Switzerland

Néjia Sassi
Tumor Immunology
and Immunotherapy Laboratory
Inserm U866
University of Burgundy
Dijon
France

Participants

Andra B. Schromm
Department of Immunochemistry
and Biochemical Microbiology
Research Center Borstel
Leibniz-Center for Medicine
and Biosciences
Borstel
Germany

Ulrich Seydel
Division of Biophysics
Research Center Borstel
Leibniz-Center for Medicine
and Biosciences
Borstel
Germany

Kiyoshi Takeda
Department of Molecular
Genetics
Medical Institute
of Bioregulation
Kyushu University
Fukuoka
Japan

Masahiro Yamamoto
Department of Host Defense
Research Institute for Microbial
Diseases
Osaka University
Osaka
Japan

CONTENTS

FOREWORD	v
Jean-Charles Cerottini and Pedro Romero	
1. INTRODUCTION: HISTORICAL BACKGROUND	1
Jean-François Jeannin	
2. STRUCTURE AND SYNTHESIS OF LIPID A	5
Shoichi Kusumoto, Masahito Hashimoto and Kazuyoshi Kawahara	
Introduction	5
General Architecture of Lipid A	6
Structural Variations of Lipid A	9
Chemical Synthesis of Lipid A	17
Conclusion	19
3. CONFORMATION AND SUPRAMOLECULAR STRUCTURE OF LIPID A	25
Klaus Brandenburg and Ulrich Seydel	
Abstract	25
Introduction	25
Aggregate Structure and Molecular Conformation	27
Intramolecular Conformation	28
Phase States and Transitions between Them	29
Molecular Modelling	31
Physicochemical Data in Relation to Biological Activity	32
Conformational Concept of Lipid A Action: How Does Endotoxin Interact with Immune Cells?	33

4. INTERACTIONS BETWEEN LIPID A AND SERUM PROTEINS..... 39

Jörg Andrä, Thomas Gutsmann, Mareike Müller and Andra B. Schromm

Abstract.....	39
Proteins Involved in Lipid A/LPS—Mediated Immune Cell Activation.....	39
Detection of Lipid A by Immunoglobulins.....	41
Proteins Involved in Lipid A/LPS Transport.....	41
Lipoproteins.....	42
Proteins Neutralizing the Immune-Cell Activating Properties of Lipid A/LPS.....	44
Conclusion	46

5. THE LIPID A RECEPTOR 53

Kiyoshi Takeda

Abstract.....	53
Introduction.....	53
Components of the Lipid A Receptor	53
Conclusion	56

6. LIPID A RECEPTOR TLR4-MEDIATED SIGNALING PATHWAYS 59

Masahiro Yamamoto and Shizuo Akira

Abstract.....	59
Introduction.....	59
The MyD88-Dependent and MyD88-Independent Pathways.....	60
TRIF: The TIR Domain-Containing Signal Transducer for the MyD88-Independent Pathway.....	60
TIRAP and TRAM: Another Two TIR Domain-Containing Molecules	62
Negative Regulation of LPS-Induced Signaling Pathways.....	62
Two-Step Gene Induction Program in TLR4-Mediated Immune Responses.....	64
Conclusion	66

7. LIPID A-INDUCED RESPONSES IN VIVO..... 69Néjia Sassi, Catherine Paul, Amandine Martin, Ali Bettaieb
and Jean-François Jeannin

Abstract.....	69
Fate of Lipid A in the Bloodstream.....	69
General Immune Responses to Lipid A.....	70
Systemic Toxicity.....	71
Lipid A Tolerance	72
Tumor Immune Responses	73
Vascular Response.....	75
Conclusion	76

8. LIPID A-MEDIATED TOLERANCE AND CANCER THERAPY..... 81

Cheryl E. Rockwell, David. C. Morrison and Nilofer Qureshi

Abstract..... 81
Early, Late and Cross Tolerance..... 81
The Isolation of Various Lipid A Structures and Synthesis of Analogs 82
Relevance of Tolerance to the Use of LPS/Lipid A in Cancer 83
Mechanisms of Early LPS/Lipid A-Mediated Tolerance..... 86
Mechanisms of Tolerance of Other Lipid A Structures and LPS Antagonists 91
Conclusion 91

9. LIPID A IN CANCER THERAPIES: PRECLINICAL RESULTS 101

Daniele Reisser and Jean-François Jeannin

Abstract..... 101
Introduction..... 101
LPS Treatments..... 101
Lipids A Treatments..... 102
DT-5461 103
ONO-4007 104
OM-174 106
Conclusion 107

**10. MONOPHOSPHORYL LIPID A (MPL) AS AN ADJUVANT
 FOR ANTI-CANCER VACCINES: CLINICAL RESULTS..... 111**

Christopher W. Cluff

Abstract..... 111
Section 1: Vaccines Targeting Specific Cancer Types 112
**Section 2: Vaccines Targeting Specific TAAs Expressed on Multiple Tumor
 Types..... 115**
Conclusion 119

**11. ANTITUMORAL EFFECTS OF LIPIDS A,
 CLINICAL STUDIES..... 125**

Marc Bardou and Danièle Reisser

Abstract..... 125
Introduction..... 125
Immunological Background Underlying the Clinical Potential Interest 126
Clinical Studies..... 127
Conclusion 129

12. CONCLUSION 133

Jean-François Jeannin

INDEX..... 135