TUBERCULOSIS AND THE TUBERCLE BACILLUS
2ND EDITION
Cover images: Cording M. tuberculosis infected by fluorescent reporter phage φDRM9, courtesy of Paras Jain and Torin Weisbrod, Albert Einstein College of Medicine, Bronx, NY.

Copyright © 2018 by ASM Press. ASM Press is a registered trademark of the American Society for Microbiology. All rights reserved. No part of this publication may be reproduced or transmitted in whole or in part or reutilized in any form or by any means, electronic or mechanical, including photocopying and recording, or by any information storage and retrieval system, without permission in writing from the publisher.

Disclaimer: To the best of the publisher’s knowledge, this publication provides information concerning the subject matter covered that is accurate as of the date of publication. The publisher is not providing legal, medical, or other professional services. Any reference herein to any specific commercial products, procedures, or services by trade name, trademark, manufacturer, or otherwise does not constitute or imply endorsement, recommendation, or favored status by the American Society for Microbiology (ASM). The views and opinions of the author(s) expressed in this publication do not necessarily state or reflect those of ASM, and they shall not be used to advertise or endorse any product.

Library of Congress Cataloging-in-Publication Data
Names: Jacobs, William R., Jr., editor.
Title: Tuberculosis and the tubercle bacillus / edited by William R. Jacobs, Jr., Department of Immunology and Microbiology, Albert Einstein School of Medicine, Bronx, New York, Helen McShane, Cellular Immunology and Vaccine Development Group, Nuffield Department of Medicine, Jenner Institute, University of Oxford, Oxford, United Kingdom, Valerie Mizrahi, Institute of Infectious Disease and Molecular Medicine, University of Cape Town, Faculty of Health Sciences, Rondebosch, South Africa, Ian M. Orme, Department of Microbiology, Immunology, and Pathology, Colorado State University, Fort Collins, Colorado.
Identifiers: LCCN 2017038089 (print) | LCCN 2017040375 (ebook) | ISBN 9781555819569 (ebook) | ISBN 9781555819552 (print)
Subjects: LCSH: Tuberculosis.
Classification: LCC QR201.T6 (ebook) | LCC QR201.T6 T83 2018 (print) | DDC 614.5/42--dc23
LC record available at https://lccn.loc.gov/2017038089
doi:10.1128/9781555819569
Printed in Canada
10 9 8 7 6 5 4 3 2 1

Address editorial correspondence to: ASM Press, 1752 N St., N.W., Washington, DC 20036-2904, USA.
Send orders to: ASM Press, P.O. Box 605, Herndon, VA 20172, USA.
Phone: 800-546-2416; 703-661-1593. Fax: 703-661-1501.
E-mail: books@asmusa.org
Online: http://www.asmscience.org
12 The Immune Interaction between HIV-1 Infection and Mycobacterium tuberculosis / 239
Elsa du Bruyn and Robert John Wilkinson

SECTION II

DRUG DISCOVERY AND DEVELOPMENT: STATE OF THE ART AND FUTURE DIRECTIONS / 269

13 Preclinical Efficacy Testing of New Drug Candidates / 271
Eric L. Nuermberger

14 Oxidative Phosphorylation as a Target Space for Tuberculosis: Success, Caution, and Future Directions / 295
Gregory M. Cook, Kiel Hards, Elyse Dunn, Adam Heikal, Yoshio Nakatani, Chris Greening, Dean C. Crick, Fabio L. Fontes, Kevin Pethe, Erik Hasenoehrl, and Michael Berney

15 Targeting Phenotypically Tolerant Mycobacterium tuberculosis / 317
Ben Gold and Carl Nathan

SECTION III

BIOMARKERS AND DIAGNOSTICS / 361

16 Tuberculosis Diagnostics: State of the Art and Future Directions / 363
Madhukar Pai, Mark P. Nicol, and Catharina C. Boehme

17 Latent Mycobacterium tuberculosis Infection and Interferon-Gamma Release Assays / 379
Madhukar Pai and Marcel Behr

18 Impact of the GeneXpert MTB/RIF Technology on Tuberculosis Control / 389
Wendy Susan Stevens, Lesley Scott, Lara Noble, Natasha Gous, and Keertan Dheda

SECTION IV

HOST AND STRAIN DIVERSITY / 411

19 The Role of Host Genetics (and Genomics) in Tuberculosis / 413
Vivek Naranbhai

20 The Evolutionary History, Demography, and Spread of the Mycobacterium tuberculosis Complex / 453
Maxime Barbier and Thierry Wirth

21 Impact of Genetic Diversity on the Biology of Mycobacterium tuberculosis Complex Strains / 475
Stefan Niemann, Matthias Merker, Thomas Kohl, and Philip Supply

22 Evolution of Mycobacterium tuberculosis: New Insights into Pathogenicity and Drug Resistance / 495
Eva C. Boritsch and Roland Brosch

SECTION V

THE SIGNATURE PROBLEM OF TUBERCULOSIS PERSISTENCE / 517

23 Acid-Fast Positive and Acid-Fast Negative Mycobacterium tuberculosis: The Koch Paradox / 519
Catherine Vilchèze and Laurent Kremer

24 Mycobacterial Biofilms: Revisiting Tuberculosis Bacilli in Extracellular Necrotizing Lesions / 533
Randall J. Basaraba and Anil K. Ojha

25 Killing Mycobacterium tuberculosis In Vitro: What Model Systems Can Teach Us / 541
Tracy L. Keiser and Georgiana E. Purdy

26 Epigenetic Phosphorylation Control of Mycobacterium tuberculosis Infection and Persistence / 557
Melissa Richard-Greenblatt and Yossef Av-Gay

27 DNA Replication in Mycobacterium tuberculosis / 581
Zanele Ditse, Meindert H. Lamers, and Digby F. Warner

28 The Sec Pathways and Exportomes of Mycobacterium tuberculosis / 607
Brittany K. Miller, Katelyn E. Zulauf, and Miriam Braunstein

29 The Role of ESX-1 in Mycobacterium tuberculosis Pathogenesis / 627
Ka-Wing Wong
<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Pages</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>The Minimal Unit of Infection: <em>Mycobacterium tuberculosis</em> in the Macrophage</td>
<td>635</td>
</tr>
<tr>
<td></td>
<td>Brian C. VanderVen, Lu Huang, Kyle H. Rohde, and David G. Russell</td>
<td></td>
</tr>
<tr>
<td>31</td>
<td>Metabolic Perspectives on Persistence</td>
<td>653</td>
</tr>
<tr>
<td></td>
<td>Travis E. Hartman, Zhe Wang, Robert S. Jansen, Susana Gardete, and Kyu Y. Rhee</td>
<td></td>
</tr>
<tr>
<td>32</td>
<td>Phenotypic Heterogeneity in <em>Mycobacterium tuberculosis</em></td>
<td>671</td>
</tr>
<tr>
<td></td>
<td>Neeraj Dhar, John McKinney, and Giulia Manina</td>
<td></td>
</tr>
<tr>
<td>33</td>
<td><em>Mycobacterium tuberculosis</em> in the Face of Host-Imposed Nutrient Limitation</td>
<td>699</td>
</tr>
<tr>
<td></td>
<td>Michael Berney and Linda Berney-Meyer</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Index</td>
<td>717</td>
</tr>
</tbody>
</table>
Contributors

Else Marie Agger
Department of Infectious Disease Immunology, Statens
Serum Institut, Artilerivej 5, Copenhagen, Denmark

Yossef Av-Gay
Division of Infectious Diseases, Department of Medicine,
University of British Columbia, Vancouver, Canada

Maxime Barbier
Laboratoire Biologie Intégrative des Populations,
Evolution Moléculaire; Institut de Systématique, Evolution,
Biodiversité, UMR-CNRS 7205, Muséum National
d'Histoire Naturelle, Univ. Pierre et Marie Curie, EPHE,
Sorbonne Universités, Paris, France

Randall J. Basaraba
Department of Microbiology, Immunology, and Pathology,
College of Veterinary Medicine and Biomedical Sciences,
Colorado State University, Fort Collins, Colorado

Marcel Behr
McGill International TB Centre & Department of
Epidemiology & Biostatistics, McGill University,
Montreal, Canada

Michael Berney
Albert Einstein College of Medicine, Department of
Microbiology and Immunology, New York, New York

Linda Berney-Meyer
Albert Einstein College of Medicine, Department of
Microbiology and Immunology, New York, New York

Catharina C. Boehme
FIND, Geneva, Switzerland

Eva C. Boritsch
Institut Pasteur, Unit for Integrated Mycobacterial
Pathogenomics, Paris, France

Miriam Braunstein
Department of Microbiology and Immunology, University of
North Carolina – Chapel Hill, Chapel Hill, North Carolina

Susanna Brighenti
Center for Infectious Medicine (CIM), F59, Department
of Medicine, Karolinska Institutet, Karolinska University
Hospital Huddinge, Stockholm, Sweden

Roland Brosch
Institut Pasteur, Unit for Integrated Mycobacterial
Pathogenomics, Paris, France

Bryce M. Buddle
AgResearch, Hopkirk Research Institute, Palmerston North,
New Zealand

Gregory M. Cook
University of Otago, Department of Microbiology and
Immunology, Otago School of Medical Sciences, Dunedin,
New Zealand, and Maurice Wilkins Center for Molecular
Biodiscovery, The University of Auckland, Auckland, New
Zealand

Andrea Cooper
University of Leicester, Infection Immunity and
Inflammation, Leicester, Leicestershire, United Kingdom

Anna K. Coussens
Clinical Infectious Diseases Research Initiative, Division
of Medical Microbiology, Department of Pathology, and
Institute of Infectious Disease and Molecular Medicine,
University of Cape Town, Cape Town, South Africa

Dean C. Crick
Colorado State University, Department of Microbiology,
Immunology, and Pathology, Fort Collins, Colorado

Neeraj Dhar
Global Health Institute, École Polytechnique Fédérale de
Lausanne, Lausanne, Switzerland

Keertan Dheda
Lung Infection and Immunity Unit, Division of Pulmonology
and UCT Lung Institute, Department of Medicine,
University of Cape Town, Cape Town, South Africa
Zanele Ditse
MRC/NHLS/UCT Molecular Mycobacteriology Research Unit, DST/NRF Centre of Excellence for Biomedical TB Research, Department of Pathology, Faculty of Health Sciences, University of Cape Town, Cape Town, South Africa

Racquel Domingo-Gonzalez
Department of Molecular Microbiology, Washington University in St. Louis, St. Louis, Missouri

Elsa du Bruyn
Clinical Infectious Diseases Research Initiative, Institute of Infectious Diseases and Molecular Medicine, University of Cape Town, Observatory, Republic of South Africa

Elyse Dunn
University of Otago, Department of Microbiology and Immunology, Otago School of Medical Sciences, Dunedin, New Zealand

Helen A. Fletcher
Immunology and Infection Department, London School of Hygiene & Tropical Medicine, London, United Kingdom

Fabio L. Fontes
Colorado State University, Department of Microbiology, Immunology, and Pathology, Fort Collins, Colorado

Susana Gardete
Department of Medicine, Division of Infectious Diseases, Weill Cornell Medical College, New York, New York

Ben Gold
Department of Microbiology and Immunology, Weill Cornell Medical College, New York, New York

Natasha Gous
Department of Molecular Medicine and Haematology, Faculty of Health Sciences, University of the Witwatersrand, National Health Laboratory Service and National Priority Program of the National Health Laboratory Service, Johannesburg, South Africa

Chris Greening
The Commonwealth Scientific and Industrial Research Organization, Land and Water Flagship, Acton, Australia, and Monash University, School of Biological Sciences, Clayton, Victoria, Australia

Kiel Hards
University of Otago, Department of Microbiology and Immunology, Otago School of Medical Sciences, Dunedin, New Zealand

Travis E. Hartman
Department of Medicine, Division of Infectious Diseases, Weill Cornell Medical College, New York, New York

Erik Hasenohrle
Albert Einstein College of Medicine, Department of Microbiology and Immunology, Bronx, New York

Mark Hatherill
South African Tuberculosis Vaccine Initiative (SATVI) and Institute of Infectious Disease & Molecular Medicine (IDM), University of Cape Town, Wernher & Beit South Building, Anzio Road, Observatory, Cape Town, South Africa

Adam Heikal
University of Otago, Department of Microbiology and Immunology, Otago School of Medical Sciences, Dunedin, New Zealand, and Maurice Wilkins Center for Molecular Biodiscovery, The University of Auckland, Auckland, New Zealand

Marcela I. Henao-Tamayo
Department of Microbiology, Immunology and Pathology, Mycobacteria Research Laboratory, Colorado State University, Fort Collins, Colorado

R. Glyn Hewinson
Animal and Plant Health Agency – Weybridge, Addlestone, Surrey, United Kingdom

Wen-Zhe Ho
Animal Biosafety Level III Laboratory, Center for Animal Experiment, State Key Laboratory of Virology, Wuhan University, Wuhan, China; Department of Pathology and Laboratory Medicine, Temple University Lewis Katz School of Medicine, Philadelphia, Pennsylvania

Lu Huang
Microbiology and Immunology, College of Veterinary Medicine, Cornell University, Ithaca, New York

Robert L. Hunter
Department of Pathology and Laboratory Medicine, McGovern Medical School, University of Texas Health Science Center at Houston, Houston, Texas

Robert S. Jansen
Department of Medicine, Division of Infectious Diseases, Weill Cornell Medical College, New York, New York

Tracy L. Keiser
Department of Microbiology and Immunology, Albert Einstein College of Medicine, Bronx, New York

Shabaana Khader
Department of Molecular Microbiology, Washington University in St. Louis, St. Louis, Missouri

Joanna R. Kirman
Department of Microbiology and Immunology, University of Otago, Dunedin, New Zealand

Thomas Kohl
Molecular Mycobacteriology, Forschungszentrum Borstel, Leibniz-Zentrum für Medizin und Biowissenschaften, Borstel, Germany

Laurent Kremer
IRIM (ex-CPBS) UMR 9004, Infectious Disease Research Institute of Montpellier (IDRIM), Université de Montpellier, CNRS, Montpellier, France

Giulia Manina
Microbial Individuality and Infection Group, Institut Pasteur, 25 rue du Docteur Roux, Paris, France
Contributors

John McKinney
Global Health Institute, École Polytechnique Fédérale de Lausanne, Lausanne, Switzerland

Helen McShane
The Jenner Institute, University of Oxford, Old Road Campus Research Building, Roosevelt Drive, Oxford, United Kingdom

Matthias Merker
Molecular Mycobacteriology, Forschungszentrum Borstel, Leibniz-Zentrum für Medizin und Biowissenschaften, Borstel, Germany

Brittany K. Miller
Department of Microbiology and Immunology, University of North Carolina – Chapel Hill, Chapel Hill, North Carolina

Yoshio Nakatani
University of Otago, Department of Microbiology and Immunology, Otago School of Medical Sciences, Dunedin, New Zealand, and Maurice Wilkins Center for Molecular Biodiscovery, The University of Auckland, Auckland, New Zealand

Vivek Naranbhai
Wellcome Trust Centre for Human Genetics, Nuffield Department of Medicine, University of Oxford, Oxford, United Kingdom, and Centre for the AIDS Programme of Research in South Africa, University of KwaZulu Natal, Durban, South Africa

Carl Nathan
Department of Microbiology and Immunology, Weill Cornell Medical College, New York, New York

Mark P. Nicol
University of Cape Town, Cape Town, South Africa

Stefan Niemann
Molecular Mycobacteriology, Forschungszentrum Borstel, Leibniz-Zentrum für Medizin und Biowissenschaften, and German Center for Infection Research (DZIF), partner site Borstel, Borstel, Germany

Lara Noble
Department of Molecular Medicine and Haematology, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, Gauteng, South Africa

Eric L. Nuermberger
Center for Tuberculosis Research, Department of Medicine, Johns Hopkins University School of Medicine, and Department of International Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland

Anil K. Ojha
Wadsworth Center, NY State Department of Health and University at Albany, Albany, New York

Diane J. Orway
Mycobacteria Research Laboratories, Department of Microbiology, Immunology and Pathology, Colorado State University, Fort Collins, Colorado

Ian M. Orme
Colorado State University, Fort Collins, Colorado

Madhukar Pai
McGill International TB Centre & Department of Epidemiology & Biostatistics, McGill University, Montreal, Canada

Juliet C. Peña
Department of Pathology and Laboratory Medicine, Temple University Lewis Katz School of Medicine, 3500 N. Broad St., MERB 843, Philadelphia, Pennsylvania

Kevin Pethe
Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore

Oliver Prince
Department of Molecular Microbiology, Washington University in St. Louis, St. Louis, Missouri

Georgiana E. Purdy
Department of Microbiology and Immunology, Oregon Health Sciences University, Portland, Oregon

Kyu Y. Rhee
Department of Medicine and Department of Microbiology & Immunology, Division of Infectious Diseases, Weill Cornell Medical College, New York, New York

Melissa Richard-Greenblatt
Division of Infectious Diseases, Department of Medicine, University of British Columbia, Vancouver, Canada

Kyle H. Rohde
Burnett School of Biomedical Sciences, College of Medicine, University of Central Florida, Orlando, Florida

David G. Russell
Microbiology and Immunology, College of Veterinary Medicine, Cornell University, Ithaca, New York

Larry S. Schlesinger
Department of Microbial Infection and Immunity, Center for Microbial Interface Biology, The Ohio State University, Columbus, Ohio

Jeffrey S. Schorey
Department of Biological Sciences, Eck Institute for Global Health, Center for Rare and Neglected Diseases, University of Notre Dame, Notre Dame, Indiana

Lesley Scott
Department of Molecular Medicine and Haematology, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, Gauteng, South Africa
Thomas J. Scriba
South African Tuberculosis Vaccine Initiative, Division of Immunology, Department of Pathology, and Institute of Infectious Disease and Molecular Medicine, University of Cape Town, Cape Town, South Africa

Wendy Susan Stevens
Department of Molecular Medicine and Haematology, Faculty of Health Sciences, University of the Witwatersrand, National Health Laboratory Service, and National Priority Program of the National Health Laboratory Service, Johannesburg, South Africa

Philip Supply
INSERM U1019; CNRS UMR 8204; Institut Pasteur de Lille, Center for Infection and Immunity of Lille; and Université Lille Nord de France, Lille, France

Dereck Tait
Aeras, Blackriver Park, First Floor, Observatory, Cape Town, South Africa

Brian C. VanderVen
Microbiology and Immunology, College of Veterinary Medicine, Cornell University, Ithaca, New York

Catherine Vilchèze
Howard Hughes Medical Institute, Department of Microbiology and Immunology, Albert Einstein College of Medicine, Bronx, New York

H. Martin Vordermeier
Animal and Plant Health Agency – Weybridge, Addlestone, Surrey, United Kingdom

Zhe Wang
Department of Medicine, Division of Infectious Diseases, Weill Cornell Medical College, New York, New York

Digby F. Warner
MRC/NHLS/UCT Molecular Mycobacteriology Research Unit, Department of Pathology, and Institute of Infectious Disease and Molecular Medicine, Faculty of Health Sciences, University of Cape Town, Rondebosch, South Africa

Robert John Wilkinson
Department of Medicine, Imperial College London, and The Francis Crick Institute Mill Hill Laboratory, London, United Kingdom

Ann Williams
Health UK, Porton Down, Salisbury, United Kingdom

Thierry Wirth
Laboratoire Biologie Intégrative des Populations, Evolution Moléculaire; Institut de Systématique, Evolution, Biodiversité, UMR-CNRS 7205, Muséum National d’Histoire Naturelle, Univ. Pierre et Marie Curie, EPHE, Sorbonne Universités, Paris, France

Ka-Wing Wong
Shanghai Public Health Clinical Center, Key Laboratory of Medical Molecular Virology, School of Basic Medical Sciences, Shanghai Medical College of Fudan University, Shanghai, People’s Republic of China

Katelyn E. Zulauf
Department of Microbiology and Immunology, University of North Carolina – Chapel Hill, Chapel Hill, North Carolina
It is the height of irony that the man who discovered the smallpox vaccine, Edward Jenner, lost both his wife and son to tuberculosis (TB). By the time smallpox was essentially eradicated, it is estimated that over 300 million people had died from this disease over the preceding century. Its eventual prevention—by a simple vaccine—clearly illustrates the power of scientific discovery and how its application can affect human health. Hundreds of millions of people have been spared death and suffering from infectious diseases because of the development of vaccines and chemotherapeutic agents in the last 100 years. Millions of lives have been saved with the use of the TB vaccine, BCG, and the development of chemotherapeutic regimens for TB. Depressingly, despite these effective interventions, TB remains one of the most challenging problems of global health, with over 9 million new cases and 1.6 million deaths each year. This crisis has been further compounded by the emergence of the HIV epidemic, as this explosive and deadly combination has dramatically increased the global spread of TB, including increasing numbers of cases of multidrug-resistant (MDR) and extensively drug-resistant (XDR) TB.

Historically, mycobacterial disease has long been at the forefront of scientific discovery for infectious diseases. The leprosy bacillus, Mycobacterium leprae, the first bacterium to be associated with human disease, was initially visualized by Gerhard Armauer Hansen in 1873. Earlier, Jean Antoine Villemin was the first person to realize that lung tubercles were infectious and not cancerous. By the 1880s, Robert Koch, aware of both of these discoveries, not only observed the tubercle bacilli in tubercles, but developed a growth medium of heated serum to cultivate the tubercle bacillus outside of humans. He went on to repeat the transfer experiment of Villemin and transferred the disease of TB to numerous animal species, establishing the experimental paradigm (“the postulates”) of how to prove that an infectious agent is a cause of a disease. Koch’s findings led Albert Calmette and Camille Guérin to follow Jenner’s approach of developing an attenuated pathogen for use as a vaccine, using the bovine tubercle bacillus to develop the bacille Calmette-Guérin (BCG) vaccine that bears their names and is still used to this day.

It is noteworthy that Paul Ehrlich was sitting in the lecture hall when Robert Koch presented his work in 1882; he later went on to help Koch improve his staining techniques. By observing the selective staining of various cell types, including human cells and different bacteria, Ehrlich also developed the idea of chemotherapy—“magic bullets” that could kill microbial pathogens. He tried for years to develop a chemical that could kill the tubercle bacillus, with little success, though at the same time was far more successful in developing a treatment for syphilis. In the 1930s, his protégé Gerhard Domagk discovered the first sulfonamide to treat bacterial infections such as streptococcus, and as this fledging field expanded, para-aminosalicylic acid and isoniazid were discovered to be active against the TB bacillus. Parallel studies by Salaman Waksman and Albert Schatz in the 1950s led to the discovery of streptomycin, the first bactericidal drug for the tubercle bacilli.

Despite these many historical advances, the TB bacillus—Mycobacterium tuberculosis—has proven to be a formidable adversary against numerous interventions. Nevertheless, despite the arduous challenges of
working with this dangerous pathogen, the field continues to persevere, and our continued success in the pursuit of knowledge would, we suspect, be applauded by Koch, Ehrlich, Calmette, and many others, as we strive to find and apply more effective cures for this dreadful disease. In this spirit, this textbook is a collection of state-of-the-art research aimed at understanding the TB bacillus, the way it infects its host, the mechanisms by which it persists in the face of host immunity, and current intervention and therapeutic methods. The contributors of this book believe that such continued and dedicated research efforts will eventually lead to better vaccines, better chemotherapies, and ultimately the eradication of TB—Edward Jenner’s revenge.

William R. Jacobs, Jr.  
Helen McShane  
Valerie Mizrahi  
Ian M. Orme
Index

A

Acid-fast (AF) mycobacteria, 519, 528–529
AF-negative M. tuberculosis and cell wall alterations, 527–528
brief history of AF staining, 520–522
chemical structures of mycolic acids, 520
clinical diagnosis of TB, 522–523
importance of mycolic acids, 523–524
Koch paradox, 523
lipid accumulation, 526–527
loss of AF property, 526–527, 528
mycobacterial cell envelope, 523–526
non-mycolic acid-containing components, 524–526
process for loss of acid-fastness, 525
Acquired immunity, 35, 43
CD4 T cells in HIV-TB coinfection, 248–251
HIV-TB coinfection, 248–252
TB-immune reconstitution inflammatory syndrome (TB-IRIS), 255–256
Adjunctive therapeutic vaccination, TB disease, 196–197
Alveolar epithelial cells (AECs), 3, 4
Alveolar macrophage (AM), 3, 4–5; see also Macrophages
M. tuberculosis infection, 215–216
Alzheimer's disease, 630
Amikacin, drug resistance, 503, 505
Amino acids, auxotrophs, 701–706
Amyloid diseases, 630
Anhui Zhifei Longcom Biologic Pharmacy Co. Ltd., 202
Animal models, 131, 139; see also
Experimental infection models;
Guinea pigs; Mouse models
assessment of new drugs, 136–137
assessment of vaccines, 135
assay, 134
common experimental designs, 280
efficacy testing, 277–284
ethical and husbandry issues, 138–139
guinea pigs, 132
host response and pathogenesis, 134–135
innate immunity, 135
limitations of, 137–139
mechanism of protection, 136
mice, 132, 279–280
mini pigs, 134
non-human primates (NHP), 132–133
practical applications of, 134–137
primary host response to M. tuberculosis infection, 122–123
process and capacity, 135–136
rabbis, 133
rats, 133–134
Treg cell responses in experimental, 80–87
Treg cells in guinea pig model of TB, 85–86
Treg cells in mouse models of TB, 80–85
Treg cells in non-human primate models of TB, 86–87
tuberculosis disease progression in, 122
vaccine testing protocols, 136, 137
zebrafish, 133, 685, 686
Antibodies, 17
Antibiotics, golden era of, 317
Antibiotics treatment, extracellular M. tuberculosis in, 533
Antibiotic tolerance, 596
Antibodies
BCG vaccination and, 220
M. tuberculosis infection, 219–220, 221
role in anti-M. tuberculosis infection, 219
tuberculosis, 225–226
Antigen-presenting cells (APCs)
development of memory T cells, 98
function of, 74, 75
Antiretroviral therapy (ART), 389
HIV, 239
HIV-TB coinfection, 250
HIV-TB immune constitution inflammatory syndrome (IRIS), 252–253, 255–256
influence on T cell responses in coinfection, 251
Apoptosis, 563
Archaebacteria, 455
Archivel Farma SL, 202
Arginine auxotrophs, 702
Aristotle, 413
Asparagine auxotrophs, 702
Aspartate auxotrophs, 702
Association of Internal Medicine, 520
AstraZeneca, 282
ATP synthesis, 308–309
Auramine O, staining of M. tuberculosis, 522–523, 526–527
Austin, Robert, 597
Autophagy, 8, 10
Auxotrophies, 701; see also Nutrient use of pathogens 
amino acid, 701–706 
arginine, 702 
asparginases, 702 
aspartate, 702 
biotin (vitamin B7), 707 
cobalamin (vitamin B12), 707–708 
cofactor, 706–708 
cysteine, 702 
folate (vitamin B9), 707 
glutamate, 703–706 
glutamine, 705 
histidine, 703 
isooleucine, 704 
leucine, 704 
lysine, 703–704 
methionine, 702–703 
nicotinamide, 706 
pantothenate, 703 
purine, 708 
pyridoxamine (vitamin B6), 706–707 
serine, 704 
tryptophan, 704–705 
valine, 704

B 
Bacillus Calmette-Guérin (BCG), original vaccine, 95, 117 
Bacillus subtilis, 582, 673 
Bacterial cell biology, tuberculosis research, 185 
Bacterial clearance, 16–17 
Bacterial replisome, components of, 584–586

B cells 
M. tuberculosis infection, 217, 219–220 
tuberculosis (TB), 225–226

Bedaquiline 
animal model, 278 
drug candidate, 271, 273 
mice, 279 
proof-of-concept molecule, 333 

Biofilms, see Mycobacterial biofilms 
Biological 
animal- and human-associated MTBC lineages, 481–482 
genetic diversity of TB bacilli, 477–484 
M. canetti and MTBC, 482 
M. tuberculosis strains, 482–484 
variations from genomes, 480–481 

Biomarkers 
classes of TB, 371 
human tuberculosis (TB), 226–227 
transcriptomic profiling, 226–227 
treatment response, 227 

Biomedical Primate Research Center (Netherlands), 165, 167

Biosynthesis, menaquinone, 302–303, 304 
Biotin (vitamin B7), 707 
British Medical Research Council, 654

Bronchoalveolar lavage (BAL), 215, 242

C 
Callobrix jacobs (common marmoset), 172, 284 
Canadian Tuberculosis Standards, 379

Candida albicans, 321 
Canetti, Georges, 496 
Capreomycin, drug resistance, 503, 505 
Carbon starvation, screening, 341, 342 
Carbonyl cyanide m-chlorophenyl hydrazine (CCCP), 298 
Cattle 
animal model, 134 
experimental infection of, 177–178 
as model of TB in humans, 178 
new TB vaccines tested in, 181 
potential correlates of protection, 183 
Caulobacter crescentus, 594 
Cavity formation, pathology of tuberculosis, 119, 120 
CD4 T and T helper 1 (Th1) cells, memory immunity, 95–96, 102–104 
CD4 T and T helper 17 (Th17) cells, memory immunity, 104–105 
CD8 memory T cells, 105–106 
Cellular immunity, 143 
Centers for Disease Control and Prevention (CDC), 379 
Chagas’ disease, 454 
Chemokines 
CCR (CC receptors) and ligands, 49–52 
CCR1, 49–50 
CCR2, 50 
CCR5, 50–51 
CCR6, 51 
CCR7, 51–52 
CXC1R1, 52 
CXC2R1, 52 
CXC3R1, 52–53 
CXC3R3, 53 
CXC receptors and ligands, 52–53 
HIV-TB coinfection, 241 
M. tuberculosis infection, 49–53 
positive and negative roles in TB, 36 
role in adaptive response to M. tuberculosis infection, 38 
role in innate response to M. tuberculosis infection, 37 

Chemotherapy 
latent TB infection (LTBI), 284–286 
M. tuberculosis persistence, 653–658, 662 
Chicago Center for Biomedical Research, 171

Chlamydia trachomatis, 609 
Chlorpromazine, 299 
Cholesterol, M. tuberculosis in macrophages, 645, 646

Ciprofloxacin, drug resistance, 505 
Clinical testing, see Vaccine candidates

Clofazimine 
animal models, 278–279 
drug candidate, 272, 300 
mice, 281 
Clostridium difficile, 611 
Cobalamin (vitamin B12), 707–708 
Cofactors, auxotrophies, 706–708 
Collaborative Drug Discovery, 329 
Commercial liquid culture, 364 
Comparative genomic analysis, 185 
Comparative transcriptome analysis, 185 
Computed tomography (CT), 171 
Congenic mice, 145 
Consumption, 453 
Cox models, cumulative risk curves, 405

Crohn’s disease, 428 
Cyclophosphamide, 97 
CYCLO (cyclosporine), 97 
Cytokines 
enhancing HIV-1 replication, 246, 247 
HIV-1 replication, 246, 247 
IL-6 (interleukin-6), 40–41 
IL-10, 48–49 
IL-12 family, 44–45 
IL-18, 42 
IL-1R1/IL18R/MyD88, 41 
IL-22, 46 
IL-23, 44 
IL-23-dependent, 45–46 
IL-27, 44–45 
IL-35, 45 
interferons, 37–40

M. tuberculosis infection, 34–49 
positive and negative roles in TB, 35 
proinflammatory IL-1, 41–42 
regulatory, 47–49 
role in adaptive response to M. tuberculosis infection, 38 
role in innate response to M. tuberculosis infection, 37 
transforming growth factor β (TGFβ), 48 
tumor necrosis factor alpha (TNFα), 34–37 
type II interferon (INFγ), 38–39 
type I INF, 39–40

Cytomegalovirus (CMV) infection, 249, 251, 255

D 
Damage-associated molecular pattern molecules (DAMPs), 11 
Dannenberg, Arthur, 680 
Dartmouth University, 202 
Deer, experimental infection of, 177, 179 
Dehydrogenases 
NADH:menaquinone oxidoreductases, 299–300 
oxidative phosphorylation, 301–302 
succinate:quinone oxidoreductase, 300–301

Delamanid, drug candidate, 271, 273 
Dendritic cells (DCs) 
development of memory T cells, 98 
HIV-TB coinfection, 241, 244 
lung, 5 
M. tuberculosis infection, 11–12 
Diabetes mellitus, 222–223, 630 

Diagnosics for TB 
acid-fast (AF) staining in clinical diagnosis, 522–523 
classes of TB biomarkers, 371 
commercial liquid culture, 364 
current, for active TB, 363–366 
current, for drug-resistant TB, 366–369 
line probe assays for detecting resistance, 367–368
Genetics and genomics

Genetic diversity

- biological impact of, 480
- intrapatient, 479–480
- M. tuberculosis complex (MTBC), 477–484

Genetic deficiency, mycobacterial disease, 38

Gabbett, H. S., 520–521

Genome-wide association studies (GWAS)

- candidate gene studies, 417–418,
  complex (MTBC), 489–490
- M. tuberculosis
  - intrapatient, 479–480
  - biological impact of, 480

Mendelian susceptibility to mycobacterial disease (MSMD), 413, 415, 416

- linkage studies, 416–417
- identification of genetic variants with TB, 418–419
- host "omics" in TB, 414
- genome-wide association studies (GWAS), 414–418
  - epigenetic variation, 414
  - DNA sequence variation, 414
- clinical translation of host genomic insights, 427
- karyogram of host-genetic correlates, 427
- linkage studies, 416–417
- role of Mendelian randomization studies, 430
- sequence-based approaches to identifying loci, 428
- therapeutic tools, 430
- transcriptomic assays, 430
- preclinical models, 430
- twin studies, 413, 415

GeneXpert MTB/RIF technology

- background, 391
- challenges and opportunities during national implementation, 394–396
- cumulative risk curves, 405
- expansion in other countries, 399
- failures in, 399
- financial modeling, 398
- future for, 401
- historical context of national implementation, 391–396
- impact on diagnostics, 399–401
- impact on national programs, 396–398
- innovations in South Africa, 397
- nucleic acid amplification testing (NAAT) strategies, 390, 391, 392
- procurement strategies, 398
- South African national implementation of, 416–417
- treatment outcomes, 401, 402–404
- Xpert Omni, 392, 401, 405
- Xpert ULTRA, 392, 395, 397, 401
- GeneXpert Omni, 365
- Genome-wide association studies (GWAS)
  - host-genetic evidence, 417

revisiting heritability in post-GWAS era, 416
- TB susceptibility, 413, 418–419
- Genomics, see Genetics and genomics
- Genotype, 671
- GlaxoSmithKline, 199
- Global TB epidemic, 389–390
- Glutamate auxotroph, 705–706
- Glutamine synthetase (GS), 705
- Goats, experimental infection of, 177, 178–179
- Gordonia otitidis, 498
- Granulocyte-macrophage colony-stimulating factor (GM-CSF), 144
- Granulocytes, M. tuberculosis infection, 14–16
- Granulomas
  - development, 680–681
  - lung of human with primary tuberculosis, 118, 120–121
  - morphological features of, 533
- M. tuberculosis infection, 217, 636
  - progressive caseating, 126
  - restricting M. tuberculosis movement, 35–36
- term, 16
- Granulomatous inflammation, 123
- Guinea pigs, 150–155;
  - TB disease progression, 122
  - response to infection, 123, 124
  - TB disease progression, 122
  - biomarkers in human TB, 226–227
  - antibody responses, 219–220
  - Treg cell responses in, 74–80
- vaccines, 153–154

H

H37Rv strain of Mycobacterium tuberculosis, 166, 167, 168, 170, 172, 215
- Harvard School of Public Health, 467
- Helicobacter pylori, 462, 464, 594
- Heritability, see Genetics and genomics
- Heterogeneity, see Phenotypic heterogeneity
- Histidine auxotroph, 703
- HIV-1 (human immunodeficiency virus type 1)
  - functional impairment of CD4 T cells, 250–251
  - heterogeneity at site of M. tuberculosis disease, 247
  - immunity to TB, 50
  - infected people, 239
  - interferons and, 39
  - mediating immunosuppression, 239–241
  - M. tuberculosis infection risk, 172, 475
  - replication at site of M. tuberculosis disease, 243–247
- tuberculosis epidemic and, 389
- tuberculosis resurgence, 222
- HIV-TB-associated immune reconstitution inflammatory syndrome (IRIS)
  - acquired immunity and, 255–256
  - hypercytokinemia in TB-IRIS, 233, 253
  - innate immunity and TB-IRIS, 252–253
- model of innate receptor signaling in TB-IRIS, 254
- HIV-TB coinfection
  - acquired immunity, 248–252
  - CD4 T cells in, 248–251
  - dendritic cells in, 244
- disseminations and mycobacteremia in, 248
- immune activation in, 247–248
- immune reconstitution inflammatory syndrome (IRIS), 252–256
- macrophages in, 241–243
- natural killer (NK) cells in, 244–245
- neutrophils in, 243–244
- spectrum of disease in, 240
- Hollow fiber systems
  - diagram, 276
- tuberculosis (TB) model, 275–277
- Host genetic studies, tuberculosis, 429
- Histamine, 685–686
- Host-pathogen coevolution, 428
- Host response, application of animal models, 134–135
- Human immunology of tuberculosis acquisition of M. tuberculosis infection, 213, 215–221
- adaptive responses and spectrum of infection, 217–220
- alveolar macrophages, 215–216
- antibody responses, 219–220
- B cells, 217, 219–220
- biomarkers in human TB, 226–227
- granuloma, 2178
- immunity to M. tuberculosis, 213
- innate T cells, 216–217
- neutrophils, 216
- progression from infection to TB disease, 222–226
- spectrum of pulmonary TB lesions, 218
- stages of response to infection, 214
- T cells, 217–218
- Human models
  - challenge models, 205
    - in vitro, 345–346
- Human tuberculosis (TB)
  - balance of Treg activity, 77
  - cavity formation in lungs, 119, 120
  - CD39+ Treg cell subsets in, 77–78
  - granuloma in lungs, 118, 120–121
  - in vitro expansion of mycobacteria-specific Treg cells, 76–77
  - novel TB vaccine candidate MVA85A, 77–78
  - post-primary lung reinfestation, 124–125
  - TB disease progression, 122
  - Treg at site of infection, 79–80
  - Treg cell responses in, 74–80
Interleukin-23 (IL–23) dependent cytokines, 44–45
Interleukin-1 cytokine family, 41–42
Interleukin 17 (IL-17), memory immunity, 79–80
Treg responses in tissue, 79
Husbandry issues, animal models, 138–139
Hypercytokinemia, TB-immune reconstitution inflammatory syndrome (TB-IRIS), 233, 235
Hypoxia, 341
redox homeostasis during, 307–308
relationship to metronidazole activity, 318
screening, 341, 342

I
Imidapyridine amide, TB drug, 300, 305
Immunee response, see Memory immune response
Immunity, see also Regulation of TB immunity
cytokines and chemokines in, 33–34
HIV infection and TB, 30
interleukin-6 (IL-6), 40–41
working model of, 42, 45
Immunodeficient mice, 145
Immunopathology, guinea pig model, 152
Immunosuppression, HIV-1 mediating, 239–241
Immunotherapy, vaccine development, 197
Inactivated whole-cell and fragmented TB vaccines, 202
Infectious Diseases Research Institute, 199
Inflammation, TB progression, 224–225
Infliximab, 36
Innate immunity, 16–17, 35, 106–107
HIV-TB coinfection, 241–245
mouse model, 145
TB-immune reconstitution inflammatory syndrome (TB-IRIS), 252–253, 254
Institut Pasteur, 496
Interferon gamma (IFN-γ) response assay
IGRA, 16, 193, 214, 220, 221, 225
latent TB infection, 381–385
reducing test variability with, 385
Interferons (IFN-γ)
M. tuberculosis infection, 37–40
protection against TB, 102–104
roles in TB, 35
type I, 39–40
type II IFN-γ, 38–39
Interleukin-12 (IL-12) cytokine family, 42–45
IL-12, 43–44
IL-23, 44
IL-27, 44–45
IL-35, 45

Interleukin 17 (IL-17), memory immunity, 104–105
Interleukin-1 cytokine family, 41–42
IL-1, 41–42
IL-18, 42
IL-1R/IL18R/MyD88, 41
Interleukin-23 (IL-23) dependent cytokines, 45–46
IL-17, 45–46, 104–105
IL-22, 46
Interleukin-6 (IL-6) cytokine, 40–41
roles in tuberculosis (TB), 35
International Tuberculosis Host Genetics Consortium (ITHGC), 413, 416, 428
Intracellular receptors, M. tuberculosis infection, 10
In vitro models
granuloma models, 549–550
human, 545–546
investigating MTB infection, 548–550
mouse, 542–544
non-human primate (NHP), 544–545
zebrafish, 550
IFN-γ syndrome (immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome), 73, 74
Isocitrate lyase (Icl), M. tuberculosis in macrophages, 644, 645–647
Isoleucine auxotroph, 704
Isoniazid, 86
animal models for testing, 278–280
drug candidate, 272, 274
drug resistance, 503, 504, 505, 506
guinea pigs, 282
latent TB infection, 285–286
line probe assays for detecting resistance, 367–368
non-human primates, 283–284
phenotypic heterogeneity of M. tuberculosis with, 674, 677
staining of M. tuberculosis, 519, 523
tolerance of infected cells, 639–641
Isoniazid preventive therapy (IPT), HIV, 239

J
Jeffreys, Sir Alec, 455
Johannsen, Wilhelm, 671

K
Kanamycin, drug resistance, 503, 505
Kaplan-Meier analysis, vaccine, 138
Kinyoun, J., 521–522
Koch, Robert, 224, 390, 520
Koch paradox, 519, 523
Koch phenomena, 126

L
Laënnec, Rene, 121
Lamers, Meindert H., 581–599
Lansoprazole, TB drug, 300, 305
Latency, definition, 654

Latent TB infection (LTBI), 217, 226, 227, 239, 379, 385–386
human model, 593–594
IGRAs, 381–385
immunological principles underlying IGRA, 382
modeling chemotherapy of, 284–286
mouse model and clinical guidelines, 285
new skin tests, 385
puriﬁed protein derivative (PPD)-based test, 381
testing methods for, 380
Leishmania, 146
Legionella pneumophila, 699, 709
Lentivirus, 146
Lenvivirus genus, 239
Leucine auxotroph, 704
Levofloxacin, drug candidate, 272–273
Line probe assays (LPAs)
detecting resistance to anti-TB drugs, 367–368
detecting resistance to second-line anti-TB drugs, 368–369
Linezolid drug candidate, 272
mice, 279
non-human primates, 283
Lipidomics, 683–684
Lipid synthesis, 332–334
Lipid utilization, M. tuberculosis in macrophages, 644, 647
Lipoarabinomannan (LAM)
immproving detection, 369
rapid urine test, 366
Liquid culture, TB diagnostics, 364
Listeria monocytogenes, 102, 203, 609, 611, 699, 709
Little, Clarence, 143
Loop-mediated amplification test, 365–366
Low oxygen recovery assay (LORA), 323
Lung, 3–6
cellular components, 4–5
M. tuberculosis interaction with, 6–16
cytokines and chemokines in, 33–34
HIV infection and TB, 30
interleukin-6 (IL-6), 40–41
working model of, 42, 45
non-human primates, 5
pathology of C3HeB/FeJ mice, 281
post-primary reinfection, 124–125
post-primary TB in human, 125–127
schematic of, 4
soluble components in surfactant
spectrum of human pulmonary TB lesions, 218
Lung macrophages, 4–5
cell death, 11
release of exosomes, 10–11
Lymphotactin (XCL1), 144
Lysine auxotroph, 703–704

M
Macaca fascicularis (cynomolgus macaque), 163, 172
Macaca mulatta (rhesus macaque), 163, 173
Macaque models
Golden Age of TB research, 163, 165
historical use of, 163–165
M. tuberculosis/simian immunodeficiency virus coinfection, 171–172
TB drug evaluation, 170–171
TB pathogenesis study, 171
TB vaccine evaluation, 167, 170
Treg cells in macaques, 86–87
validation of, 163
Macrophages, see also Mycobacterium tuberculosis in macrophage; Mycobacterium tuberculosis–macrophage biology
basic principles of macrophage biology, 546–548
cell death, 11
exosome release from, 10–11
HIV-TB coinfection, 241–243
human in vitro models, 545–546
lung, 4–5
mouse in vitro models, 542–544
M. tuberculosis and, 541–542
M. tuberculosis growth in, 700–701

Downloaded from www.asmscience.org by
IP:  54.70.40.11
On: Sun, 26 May 2019 11:20:46
Macrophages (Continued)
mycobacterial growth and HIV-1 viral replication, 243
non-human primate in vitro models, 544–545
Magnetic resonance imaging (MRI), infected guinea pig lungs, 153
Major histocompatibility complex (MHC), 38, 39, 49, 74, 97
Malnutrition, 223–224
Marmosets (Callithrix jacchus), 172, 284
McMaster (Ad5Ag85A), 201
Memory immune response against tuberculosis (TB), 96–97
alternative mediators of memory immunity, 105–107
CD4T and TH17 cells, 104–105
CD4T and T helper (Th) 1 cells, 95–96, 102–104
CDB T cells, 105–106
development after TB infection or vaccination, 98
γδ T cells, 106
generation of memory T cells, 97–99
innate memory, 106–107
memory T cell heterogeneity, 99–102
models of T cell fate, 98–99
natural killer (NK) cell memory, 107
novel TB vaccines, 107–108
resident memory T cells, 101–102
stem cell-like memory T cells, 102
T cell memory and TB vaccination, 107–108
T cell memory phenotypes, 100
trained immunity in monocytes, 107
Memory T cells, 95
CDB, 105–106
development after infection or vaccination, 98
enzyme-linked immunospot (ELISPOT) method, 182
generation of, 97–99
heterogeneity, 99–102
models of fate, 98–99
phenotypes, 100
proposed models of differentiation, 99
resident, 101–102
stem cell-like, 102
TB vaccination and, 107–108
vaccine efficacy, 182
Menaquinone biosynthesis, 302–303, 304
Mendelian susceptibility to mycobacterial disease (MSMD), 413, 415, 416, 417
Merck Research Laboratories, 596
Metabolomics, 683–684, 700–701
Methionine auxotrophs, 702–703
Methyl citrate cycle, M. tuberculosis in macrophages, 644, 645–647
Metronidazole, 278
hypoxia and activity of, 318
mice, 279, 286
non-human primates, 283
proof-of-concept molecule, 333
rabbits, 283
Microbiolology, explorative tools and methodologies, 682–686
Micrococcus luteus, 611
Microfluidics, 684–685
MicroRNAs (miRNAs), 10
Microscopy, time-lapse, 684–685
Millennium Development Goals, 389
Minimal unit of infection, 635, 648
Mini pigs, animal model, 134
Modified Henderson apparatus, 167, 173
Monocytes
trained immunity in, 107
tuberculosis, 224–225
Morella, 458
Morbidity, impact of GeneXpert MTB/RIF, 400
Mortality, impact of GeneXpert MTB/RIF, 400–401
Mouse models, 143–150, 278–280; see also Animal models
animal model, 132, 137
anti-TB treatment, 85
C3HeB/FeJ mice, 280–281
clinical M. tuberculosis strains, 83
common experimental designs, 280
Cornell model, 284–286
devices for aerosol exposure, 147
experimental infection of mice, 279–280
gene-disrupted mice, 144–145
immunodeficient, transgenic and congenic mice, 145
innate immunity, 145
in vitro, 542–544
latent TB infection (LTBI), 285
low-dose aerosol exposure to M. tuberculosis, 148
lung inflammatory response, 149
Mycobacterium biofilms, 533, 535, 536
Mycobacterium bovis bacille Calmette-Guérin (BCG), 6, 12, 13, 15, 703
BCG vaccine-induced protection, 43, 46
C3HeB/FeJ mice, 281
cattle model, 134
expansions of Treg cells, 76
responses of innate immune cells to, 12
vaccine, 95, 115, 179–180, 627
drug resistance, 502
lessons to learn from, 496–498
Mycobacterium caprae, 460, 461, 477, 479, 496
Mycobacterium flavescens, 382
Mycobacterium haemophilum, 495
Mycobacterium kansasii, 382, 495
Mycobacterium leprae, 382, 428, 495, 709
replicase components, 584–586, 587
Mycobacterium lepromatosis, 495
Mycobacterium marinum, 14, 382, 495, 679
mycolic acids, 523
virulence, 610
zebrafish model, 36, 133, 699
Mycobacterium mungi, 461, 496
Mycobacterium orygis, 460, 476, 479, 496, 498
Mycobacterium phlei, 6, 295
Mycobacterium pinnipedii, 460, 461, 476, 477, 479
Mycobacterium protatuberculosis, 458
Mycobacterium smegmatis, 10, 308–309, 535, 536, 609, 673, 675, 679, 703
Mycobacterium suricatae, 496
Mycobacterium szulgai, 382
Mycobacterium tuberculosis, 3;
see also HIV-TB coinfection
ATP synthesis by F$_1$F$_0$ ATP synthase, 308–309
biological differences between
chemokines and cytokines in adaptive response to, 38
chemokines and cytokines in innate response to, 37
chemokines in, infection, 49–53
cytokines in, infection, 34–49
emerging strains inducing regulatory T cells in lungs, 150
Erdman strain, 166, 167, 168, 170, 171–172
fate upon macrophage infection, 9
H37Rv strain, 166, 167, 168, 170, 172
HIV-1 heterogeneity at site of disease, 247
HIV-1 replication at site of disease, 243–244
hypothesized states of response to infection, 214
immune system, 95
interactions with macrophages, 6–8, 10–11
interaction with granulocytes, 14–16
interaction with lung, 6–16
latent TB infection (LTBI), 217, 226, 227
macrophage receptors, 7
mouse response to infection, 146–150
mutagenesis in, 595
oxidative phosphorylation in, 295
pathology of, 117–121, 125–127, 172
physiology for nonreplicating persistence, 567–571
prevention of infection, 193–195
primary host response to infection, 122–123
protein phosphorylation in, 557, 559–560
pulmonary innate immune cells during infection, 4
replisome components, 584–586, 587
respiration overview in, 295
responses of innate immune cells to, 12
schematic of electron transfer components, 296
spectrum of infection, 379–380
targeting primary dehydrogenases in, 299–302
targeting proton motive force (PMF) in, 299–299
vaccination, 95–96
Mycobacterium tuberculosis complex (MTBC), see also Evolution of MTBC
biological differences among
M. tuberculosis strains, 482–484
biological differences between animal and human MTBC lineages, 481–482
biological differences between M. canettii and, 482
biological impact of genetic diversity, 480
evidence for potential of biological variation, 480–481
global emergence of multidrug-resistant TB strains, 475–477
global genetic diversity, 477–484
global phylogenetic structure of MTBC strains, 476
global phylogeny of MTBC isolates, 465
intrapatient diversity, 479–480
phylogenetic reconstruction of MTBC
Beijing lineage population, 478
Mycobacterium tuberculosis infection, see also Protein phosphorylation
apoptosis, 563
cell wall remodeling, 569–570
defense against host-generated reactive oxygen and nitrogen species, 563–564
growth arrest, 567–569
Surv/Thr protein kinases (STPKs)
 coordinatineg physiology of, 567–571
slowing central metabolism, 570–571
STPK cell signaling network, 568
subversion of innate immune response, 560–564
Mycobacterium tuberculosis in macrophage bottleneck response, 637
chemical genetics of infection, 643–644
cholesterol, 645, 646
construction of reporter strains, 638–639, 640
drug sensitivity of, 641
environmental cues and responses, 638
fatty acids, 644–645
flow cytometry gating strategy, 642
flow sorting strategy, 641
guilt-by-association analysis, 637
life and death dynamics, 637
lipid acquisition from host cell, 647
lipid utilization by, 644
manipulating host cell for nutritional purposes, 647–648
minimal unit of infection, 635, 648
phagocytosis, 636
replication clock plasmid, 637
response of M. tuberculosis to intracellular environment, 636–638
role of isocitrate lyase (icl) and methyl citrate cycle (MCC), 645–647
single-cell suspension, 639–642
Mycobacterium tuberculosis-macrophage biology
downstream proinflammatory signaling, 547–548
innate immune sensing, 547–548
modulation of cell death pathways, 547
phagosome maturation arrest, 546
principles of, 546–548
survival in the face of host
antimycobacterial molecules, 546–547
Mycobacterium tuberculosis sensu stricto, 454, 476, 477
Mycobacterium ulcerans, 495
Mycobacterium vaccae, 197
Mycolic acids
c hemical structures of, 520
importance of, 523–524
loss of acid-fastness, 519, 529
Mycobacterium xanthus, 673
N
NADH:menaquinone oxidoreductases, 299–300
National Institute for Health and Care Excellence (UK), 379
National Institute of Allergy and Infectious Diseases, 117
National Primate Research Centers (NPRCs), 164, 165, 166, 170, 171, 172
National TB Costing Model, 395, 398
Natural killer (NK) cells
HIV-TB coinfection, 244–245
memory, 107
M. tuberculosis infection, 12–14
Natural resistance-associated macrophage protein (Nramp), 146
Neanderthals, 467
Necrosis-associated extracellular clusters (NECs), 151, 153
Necrotizing lesions
biofilms as perspective of extracellular M. tuberculosis in, 533–536
characteristic of active pulmonary TB, 533–534
M. tuberculosis in, 534–535
Neelesen, E., 520
Neisseria meningitidis, 197
Neutrophils
HIV-TB coinfection, 243–244
lung, 5
M. tuberculosis infection, 12, 39, 216, 548
cell response to M. tuberculosis, 125
Niclosamide, 343–344, 346
Nicotinamide, 706
Nigericin, 297, 298
Nile red stain, 526–527
Nitro-containing compounds, dual- and nonreplicating active, 343, 344
3-Nitropropionate, 300, 301
Nocardia farcinica, 13
Nongrowing but metabolically active bacteria (NGMA), 676
diversity of, 678, 681, 683
Non-human primate models, see also Animal models
animal model, 132–133
comparison of rhesus and cynomolgus macaque models, 165–167
cynomolgus macaques, 166–167, 169
future research strategies, 172
historical use of macaque models, 163–165
in vitro, 544–545
macaque models for study of TB pathogenesis, 171
macaque models for TB drug evaluation, 170–171
macaque models for TB vaccine evaluation, 167, 170
M. tuberculosis/simian immunodeficiency virus coinfection, macaque models, 171–172
Non-human primate models (Continued)
preclinical efficacy models, 283–284
rhesus macaques, 165, 166, 168
Treg cells in, 80, 86–87
validation of macaques in TB research, 163
Nonreplicating (NR) models, selecting and designing, 323, 324
Nonreplicating persistence (NRP)
M. tuberculosis physiology for, 567–571
sensing when to exit NR, 571–572
Nonreplication, diversity in, 319–321
Nontuberculous mycobacteria (NTM), 495
Nucleic acid amplification testing (NAAT), 390, 391, 392; see also GeneXpert
MTB/RIF technology
Nutrient use of pathogens, see also
Auxotrophs
amino acid auxotrophies, 701–706
cofactor auxotrophies, 706–708
future perspectives, 708–710
lessons from auxotrophic strains, 701–708
lessons from metabolomics, 700–701
M. tuberculosis in host tissue, 701
M. tuberculosis in macrophages, 700–701
O
Ofloxacin, drug resistance, 505
Oxford University, 200
Oxidative phosphorylation
physiology for, 567–571
Oxidative stress in pathogenesis, 539
Oxidative stress response proteins, 567
Oxidoreduction potential, 552
Oxidoreduction potential, in vivo, 571
Phage therapy
Phage activity, 339
Phage therapy, 332
Phage, 330
Phagocytosis, 636
Phagosome maturation, 8, 9
Phagosome-lysosome fusion
Phagosomal pH
Phagosomal vesicles, 8, 9
Pharmacokinetics of drug candidates, 272–273
Pharmacology, 272–273
Pharmacokinetics, 272–273
Pharmacodynamics of drug candidates, 272–273
Pharmacodynamics, 272–273
Phenytoin
Phenytoin resistance
Phase 1 clinical trials, 331–332
Phase 2 clinical trials, 331–332
Phase 3 clinical trials, 331–332
Phenotypic drug resistance, 317
Phenotypic diversity, 321–322
Phenotypic heterogeneity, 671–672
asymmetric cell division and cell aging, 676–679
causes and consequences of, 673
flow cytometry and omics, 682–684
fluorescent recovery after photobleaching (FRAP), 678, 684
growth phase, 674–675
growth rate, 675–676
host microenvironment, 679–682
host-mimicking platforms, 683–686
in vivo investigation, 685–686
stochastic processes, 672–674
stress conditions enhancing, 677
time-lapse microscopy and microfluidics, 684–685
tools and methodology, 682–686
Phenotypic tolerance, 317
Phosphorylation, see Protein phosphorylation
Pneumonia, tuberculosis as obstructive lobular, 121, 123
Positron emission tomography/computed tomography (PET/CT), 171, 213, 283, 680–681, 686
Post-primary tuberculosis, 124–125
Preclinical efficacy testing, 271, 274
animal infection models of active TB, 277–278
drug candidates, 272–273
dynamic drug concentration models, 275–277
goals of, 274–275
guinea pigs, 282
hollow fiber system model of TB, 275–277
in vitro models, 275–277
mice, 278–281
modeling chemotherapy of latent TB infection (LTBI), 284–286
non-human primates, 283–284
rabbits, 283
rats, 281–282
static drug concentration models, 275
Preclinical studies, role in experimental medicine studies, 205–206
Pretomanid
drug candidate, 273
guinea pigs, 282
mice, 279
Prime, vaccine development, 197
Prime-boost, vaccine development, 197
Programmed cell death protein-1 (PD-1), 101–102
Proline auxotroph, 703
Proof-of-concept molecules
dual actives with in vivo efficacy, 331–332
nonreplicating actives with in vivo efficacy, 332
nonreplicating activity, 333
selective nonreplicating activity, 331
Protein-adjuvant TB vaccines, 198–200
Protein kinase activity, 557
Protein phosphorylation, see also
Mycobacterium tuberculosis infection
apoptosis, 563
biochemically verified substrates of M. tuberculosis serine/threonine protein kinases (STPKs), 358–359
effect on M. tuberculosis STPKs, 566
growth and persistence phenotypes of M. tuberculosis STPKs, 562
hierarchy of M. tuberculosis STPK activation, 561
inhibition of phagosomal-lysosome fusion, 561, 563
M. tuberculosis, 557, 559–560
STPKs coordinating M. tuberculosis physiology, 567–571
STPKs regulating M. tuberculosis morphology, 564–565, 567
Proteomics, 679, 683–684
Downloaded from www.asmscience.org by IP: 54.70.40.11
On: Sun, 26 May 2019 11:20:46
Index

Rats
animal model, 133
graftulomas in lungs, 126
preclinical efficacy models, 283
response to infection, 123, 124
TB disease progression, 122
Rapid speciation strip tests, 364
Rats
animal model, 133–134
preclinical efficacy models, 281–282
Recombinant mycobacterial vaccines, 202–203
Regulation of TB immunity, see also Animal models; Human tuberculosis (TB) antigen-presenting cells (APCs), 74, 75
human regulatory T (Treg) cells and anti-TB treatment, 78–79
human Treg cells and clinical M. tuberculosis strains, 78
in vitro expansion of mycobacteria-specific Treg cells, 76–77
mechanisms of Treg suppression, 74
naturally occurring and induced Treg cells, 73–74
Treg activity balance, 77
Treg cell, 73–74
Treg cell responses in experimental animal models of TB, 80–87
Treg cell responses in human TB, 74–80
Treg-mediated manipulation of immune cell activation, 75–79
Treg responses at M. tuberculosis infection site, 79–80
Treg suppression of APCs, 75
Regulatory cytokines
IL-4, IL-5, and IL-13, 47–48
interleukin IL-10, 48–49
transforming growth factor β (TGFβ), 48
Replication rate, 592; see also DNA replication
mycobacterial, 592–594
Research Institute of Influenza (St. Petersburg, Russia), 202
Respiration, M. tuberculosis, 295
Restriction fragment length polymorphism (RFLP) method, 454–455, 583
Retroviral family, 239
Rhesus macaques, 163; see also Macaque models
comparing TB in humans to, 164
“Golden Age” of TB research using, 163, 166
Macaca mulatta, 163, 173
TB studies, 166, 167, 168
21st century TB research, 166
Rhizobium leguminosarum, 613
Rifampin, 86, 527–528
animal models, 279–280
drug candidate, 272, 274, 278, 331
drug resistance, 503, 504, 674
guinea pigs, 282
latent TB infection, 285–286
line probe assays for detecting resistance, 367–368
non-human primates, 283
proof-of-concept molecule, 333
tolerance of infected cells, 639–641
Xpert MTB/RIF for resistance to, 368
Rifapentine
drug candidate, 272
guinea pigs, 282
latent TB infection (LTBI), 285–286
Salmonella
Salmonella enterica
Salmonella enterica serovar Typhi, 462
Salmonella typhimurium, 146, 321, 674, 676
Salmonella typhimurium, 197, 536
Scavenger receptors (SRs), 8
ScienFinder, 329
Screening
acidic pH, 341, 342
biofilms, 341, 343
hypoxia, 341, 342
multiple physiological stresses, 341, 342
Screening assays
compound transformation during, 330
designing high-throughput screens for phenotypically tolerant mycobacteria, 322–323, 325
post-, 327, 328
potential compound transformation during, 325, 329
Screenation (SecA1) pathway
cell wall synthesis and remodeling factors, 609
conserved, 607–608
conserved SecA1 exportome, 608–611
entering dormancy, 610
exported virulence factors, 610
lipoproteins, 609–610
models of SecA1 export, 608
reactivation/resuscitation from dormancy, 611
Screenation (SecA2) pathway
dormancy, 619
features of SecA2-dependent substrates, 613
identification, 611–612
immunomodulation and, 618–619
inhibition of apoptosis, 618
KatB (catalase-peroxidase), 616
Mce transporters, 614–615
mechanism, 612–613
models of SecA2 export, 608
multiple components of Mce transporters, 615
phagosome maturation arrest, 617
PknG (eukaryotic-like serine-threonine kinase), 616
protein export pathway, 611–613
reactive radicals and, 619
SBPs (solute binding proteins), 613–614
secA2 mutant as vaccine candidate, 619–620
SecA2 and DosR regulon, 616–617
SecA2 exportosome, 613–616
SodA (Fe-superoxide dismutase), 615–616
virulence and, 617–619
Secretion system, see also ESX-1 (ESAT-6 secretion system-1)
ESAT-6 (ESX-1), 627, 631–632
Shuman, Stewart, 591
Simian immunodeficiency virus (SIV), M. tuberculosis and, coinfection macaque models, 171–172
Smear microscopy, diagnostics for active TB, 363–364
Solute carrier, 615
Solute carrier, 146
South Africa
challenges and opportunities of implementation, 394, 396
GeneXpert implementation, 397
GeneXpert placement, 394
national implementation of Xpert NTB/RIF assay, 393–394
tuberculosis in, 391, 393
South African Tuberculosis Vaccine Initiative (SATVI), 104, 105
Spectroscopy, 683–684, 701
Spoligotyping, 455, 457, 461
Staphylococcus aureus, 609, 611
Streptococcus pneumoniae, 197, 536
Streptomyces coelicolor, 591
Streptomyces griseus, 502, 503
Sucinate:quinone oxidoreductase, 300–301
Swedish Institute of Infectious Disease Control, 167
Systems biology, tuberculosis, 429
T
TB-associated immune reconstitution inflammatory syndrome (TB-IRIS), 76
T cells, see also Memory T cells cytotoxic, in TB-immune reconstitution inflammatory syndrome (TB-IRIS), 255–256
M. tuberculosis infection, 217–219, 548–549
responses to tuberculosis (TB), 225
Technical Expert Group, 365
Thioalkalivibrio, 458
Thiorhodovibrio, 458
Thioridazine, 297, 299
Threonine auxotroph, 704
Time-lapse microscopy, 684–685
Tissue remodeling, tuberculosis (TB), 225
Toll-like receptor 9 (TLR9), 4
Toll-like receptors (TLRs), 7–8, 39, 145
Trained immunity, 13, 17, 107
Transcriptional profiling, M. tuberculosis in macrophages, 636–638
Transcriptome studies, 674, 683–684
Transcriptomic profiling, biomarkers, 226–227
Transforming growth factor (β TGFβ), 48
Transgenic mice, 145
TrSAH screening method, 704
Treatment outcomes, impact of GeneXpert
MTB/RIF, 401, 402–404
Trifluoperazine, 299, 300
Trudeau, E. L., 131
Tryptophan auxotroph, 704–705
Tuberculin skin testing (TST), 213, 214, 215, 220, 221, 225
administering and reading TST, 381
latent TB infection, 380
purified protein derivative (PPD)-based
TST, 381
Tuberculosis (TB), see also Animal models;
HIV-TB coinfection; Human tuberculosis (TB); Vaccine candidates
adjuvantive therapeutic vaccination, 196–197
anti-TB vaccine design, 39
biomarkers in human, 226–227
diabetes mellitus, 222–223
diversity, 680
global epidemic, 389–390
HIV-1 heterogeneity at site of disease, 247
HIV-1 replication at site of disease, 245–247
HIV and, 172, 222
lung, 3–6
malnutrition, 223–224
necrotizing lesions in active pulmonary,
533–534
positive and negative roles of chemokines
in, 36
positive and negative roles of cytokines
in, 35
post-primary, 119–121, 123–127
preventing recurrent TB, 196–197
prevention of disease, 195–196
progression from infection to disease,
222–226
proposed framework for spectrum of
infection, 380
protective memory against, 96–97
risk factors for, 222
states biology of, 429
targeting replisome for new drug
development, 595–596
Treg cell responses in human, 74–80
vaccine, 40, 43, 45, 46, 49
vaccine development strategies, 197–198
vitamin D deficiency, 223
Tuberculosis (TB) vaccination
animal models, 80
guinea pig model, 86
mouse models, 83–84
Tumor necrosis factor alpha (TNFa), 34–37
roles in TB, 35
Type I interferons (IFN-γ), tuberculosis, 224
University of Pittsburgh, 166–167, 171
University of Zaragoza and Biofabri, 202
Urine lipoarabinomannan rapid test, 366
U.S. Food and Drug Administration (FDA), 382
Vaccae, vaccine candidate, 197, 198, 202
Vaccination
adjuvantive therapeutic vaccination, 196–197
BCG and disease protection, 194
clinical trials of TB candidates, 197–203
M. tuberculosis, 95–96
prevention of M. tuberculosis infection,
193–195
prevention of recurrent TB disease,
196–197
prevention of TB disease, 195–196
Vaccine candidates, 198
Ad5Ag85A, 201
Crucell Ad35, 201
DAR-901, 202
development strategies, 197–198
experimental medicine role in
development, 203–206
global clinical pipeline of, 198
H1::I31 and H1::CAF01, 198
H4::I31, 199
H56::I31, 198–199
ID93::GLA-SE, 199
inactivated whole-cell and fragment TB
vaccines, 202
M72/AS01E, 199–200
MTBVAC, 202–203
MVA85A, 200–201
Protein-adjuvant TB vaccines, 198–200
recombinant mycobacterial vaccines,
202–203
RUTI, 202
secA2 mutant as, 619–620
TB/Flu-04L, 202
Vaccae, 201
VAP 1002, 203
Vaccines, see also Vaccine candidates
Ad85A (human adenovirus 5 expressing
Ag85A), 181–182
animal models and testing protocols,
136, 137
animal models for assessment of, 135
antibody-inducing, 220
BCG protection, 40, 43, 45, 46, 49, 220
BCG vaccination in animals, 100
BCG vaccination in guinea pigs, 86
BCG vaccination in humans, 76, 100
BCG vaccination in mice, 83–84
biomarkers correlating disease
severity, 184
biomarkers predicting efficacy, 182
guinea pig model, 153–154
macaque models of evaluating TB vaccine,
167, 170
mechanism of protection, 136
memory immunity by novel TB, 107–108
Mycobacterium bovis bacillus Calmette-
Guérin (BCG), 95, 117, 179–180
new-generation TB, 180–182
novel TB candidate MVA85A, 77–78, 96,
104, 108, 200–201
predictivity of animal models, 137–138
proof of concept for, 194, 196, 203–206
role of experimental medicine in vaccine
development, 203–206
schedules of BCG and virally vectored,
183–184
types of new, tested in cattle, 181
Vacczine Projekt Management GmbH, 203
Valine auxotroph, 704
Valinomycin, 297, 299
Vertex Pharmaceuticals, 643
Vibrio cholerae, 465
Viral-vectored vaccines, 200–202
Vitamin B5 (pantothenate), 706
Vitamin B6 (pyridoxamine), 706–707
Vitamin B8 (biotin), 707
Vitamin B12 (cobaalamin), 707–708
Vitamin D deficiency, 223
Wayne model, 136, 137
Wayne model, hypoxia, 318, 323, 325
Whole-genome sequencing (WGS)
emergence of, 495
M. tuberculosis L2 Beijing sublineage,
500
resistant strains, 502, 506–507
World Health Organization (WHO), 193,
226, 239
global TB epidemic, 389–390
line probe assay recommendations,
368–369
TB disease control, 379, 533
TB screening, 363, 364
X
XLAAD (X-linked autoimmunity allergic
dysregulation syndrome), 73
Xpert MTB/RIF, see also GeneXpert
MTB/RIF technology
background of, 391
diagnostics for TB, 365, 368
maximizing impact of new diagnostics,
371, 373–374
timeline of availability, 374
Y
Yersinia pseudotuberculosis, 674
Z
Zebrafish
animal models, 133, 685, 686
granuloma formation, 135
in vitro model, 530
M. marinum, 36, 133, 699
Ziehl, F., 520
ZN (Ziehl-Neelsen) stain, 519; see also AF
(acid-fast) mycobacteria
clinical diagnosis of TB, 522–523
history of acid-fast (AF) staining, 520–522
M. tuberculosis, 521, 528