Contents

List of Contributors xvi
Foreword xviii
Series Preface xxi
Preface xxiii

1 Introduction: A Guide to Treatment and Prevention of Tuberculosis Based on Principles of Dosage Form Design and Delivery 1
A.J. Hickey
1.1 Background 1
1.2 Dosage Form Classification 3
   1.2.1 Dosage Forms 3
1.3 Controlled and Targeted Delivery 5
1.4 Physiological and Disease Considerations 6
1.5 Therapeutic Considerations 7
1.6 Conclusion 8
References 8

Section 1 Pathogen and Host 11

2 Host Pathogen Biology for Airborne Mycobacterium tuberculosis: Cellular and Molecular Events in the Lung 13
Eusondia Arnett, Nitya Krishnan, Brian D. Robertson and Larry S. Schlesinger
2.1 Introduction 13
2.2 Lung 14
   2.2.1 Alveoli 16
   2.2.2 The Different Lung Macrophages 17
   2.2.3 Other Immune Cells in the Lung 17
vi Contents

2.3 General Aspects of Mucus and Surfactant 17
2.4 General M. tuberculosis 18
2.5 M. tuberculosis Interaction with the Lung Macrophage 19
  2.5.1 Initial Interactions Following Inhalation 19
  2.5.2 Interactions with the Macrophage 19
2.6 M. tuberculosis Interaction with other Respiratory Immune Cells 23
  2.6.1 Neutrophils 23
  2.6.2 Dendritic Cells 24
  2.6.3 NK Cells 25
  2.6.4 B Cells 26
  2.6.5 T Cells 27
2.7 TB Granuloma 29
2.8 Conclusion 30
References 30

3 Animal Models of Tuberculosis 48
David N. McMurray

3.1 Introduction 48
3.2 What is an Animal Model of TB? 49
3.3 How are Animal Models of TB Used? 50
3.4 TB Animal Models Currently Used for TB Drug and Vaccine Evaluation 51
  3.4.1 Guinea Pig 53
  3.4.2 Mouse 54
  3.4.3 Non-human Primate 55
  3.4.4 Rabbit 56
  3.4.5 Zebrafish 57
  3.4.6 Rat 57
  3.4.7 Domestic Animals and Wildlife Reservoirs 58
3.5 Summary 58
References 59

Section 2 Immunological Intervention 67

4 Vaccine Preparation: Past, Present, and Future 69
Dominique N. Price, Nitesh K. Kunda, Amber A. McBride and Pavan Muttil

4.1 Introduction 69
4.2 Early Efforts in TB Vaccine Development 71
  4.2.1 Early BCG Formulation and Manufacturing 71
  4.2.2 History of the BCG Vaccine and Routes of Administration 72
  4.2.3 Quality Control Issues 72
4.3 Current BCG Vaccine Formulation 73
  4.3.1 BCG Vaccine Strain Variability 73
  4.3.2 BCG Lyophilization for Stability 73
  4.3.3 Manufacturing Process 74
  4.3.4 Packing and Storage 75
  4.3.5 Transportation 75
  4.3.6 Needle-stick Issues 76
4.4 Novel TB Vaccination Strategies 76
  4.4.1 Formulation and Stabilization Techniques 78
  4.4.2 Manufacturing of TB Vaccines 81
  4.4.3 Whole-Cell Vaccine 82
  4.4.4 Subunit Vaccines 83
  4.4.5 Regulatory Approval Process 83
  4.4.6 Vaccine Packaging 84
4.5 Future Perspective 84
4.6 Conclusions 85
References 85

5 TB Vaccine Assessment 91
André G. Loxton, Mary K. Hondalus and Samantha L. Sampson
5.1 Introduction 91
5.2 Preclinical Vaccine Assessment 92
  5.2.1 Murine Model 93
  5.2.2 Guinea Pig Model 94
  5.2.3 Cattle Model 94
  5.2.4 Non-human Primate Model 95
5.3 Clinical Assessment of Vaccines 97
  5.3.1 Human Clinical Trials and Phases of Testing 97
  5.3.2 Live Attenuated Vaccine Candidates 97
  5.3.3 Viral Vectored Subunit Vaccines 99
  5.3.4 Adjuvanted Subunit Vaccines 100
  5.3.5 Therapeutic Vaccines 101
  5.3.6 Route of Immunization 101
5.4 Laboratory Immunological Analysis and Assessment of Vaccine Trials 102
  5.4.1 Decision on Population of Interest 102
  5.4.2 Detection of Infection 102
  5.4.3 Detection of Protective Immunity 102
5.5 How well do the Available Preclinical Models Predict Vaccine Success in Humans? 103
References 105

Section 3 Drug Treatment 111

6 Testing Inhaled Drug Therapies for Treating Tuberculosis 113
Ellen F. Young, Anthony J. Hickey and Miriam Braunstein
6.1 Introduction 113
6.2 The Need for New Drug Treatments for Tuberculosis 114
6.3 Inhaled Drug Therapy for Tuberculosis 114
6.4 Published Studies of Inhalation Therapy for TB 115
6.5 The Guinea Pig Model for Testing Inhaled Therapies for TB 116
6.6 Guinea Pig Study Design 117
6.7 Purchase and Grouping Animals 118
6.8 Infecting Guinea Pigs with Virulent Mycobacterium tuberculosis 118
6.9 Dosing Groups of Guinea Pigs with TB Drugs 119
6.10 Collecting Data 121
6.11 Aerosol Dosing Chambers and Practice 122
   6.11.1 Study Timing with Regard to Scale of Manufacturing 122
   6.11.2 Animal Model Selection 123
   6.11.3 Dose and Dosing Regimen 123
6.12 Nebulizer Aerosol Delivery Systems for Liquids 123
6.13 Dry-Powder Aerosol Delivery Systems for Solids 125
6.14 Summary 127
Acknowledgements 127
References 127

7 Preclinical Pharmacokinetics of Antitubercular Drugs 131
Mariam Ibrahim and Lucila Garcia-Contreras
7.1 Introduction 131
7.2 Factors Influencing the Pharmacokinetic Behavior of Drugs 132
   7.2.1 Physicochemical Properties of the Drug 132
   7.2.2 Formulation and Routes of Administration 137
   7.2.3 Disease State 138
7.3 Pulmonary Delivery of Anti-TB Drugs 138
7.4 Pharmacokinetic Study Design 140
   7.4.1 Animal Models 140
   7.4.2 Biological Samples 141
   7.4.3 Analytical Method 142
   7.4.4 Calculation of PK Parameters 142
7.5 Implications of PK Parameters on Efficacy 144
   7.5.1 Tissue Samples 144
   7.5.2 Pharmacokinetics of Anti-TB Drug in Granulomas 145
   7.5.3 PK/PD Correlations 146
7.6 Case Studies (Drugs Administered by Conventional and Pulmonary Routes) 146
   7.6.1 Rifampicin 146
   7.6.2 Capreomycin 151
References 152

8 Drug Particle Manufacture – Supercritical Fluid, High-Pressure Homogenization 156
Kimiko Makino and Hiroshi Terada
8.1 Introduction 156
8.2 Preparation of Nano- and Micro-particles 157
   8.2.1 Microparticles Prepared by a Supercritical Antisolvent–Drug Excipient Mixing (SAS–DEM) Technique 157
   8.2.2 Nanoparticles Prepared by a Supercritical Fluid (SCF) Technique 157
8.2.3 Nanosuspension 158
8.2.4 Liposomes 159
References 159
9 Spray Drying Strategies to Stop Tuberculosis
Jennifer Wong, Maurizio Ricci and Hak-Kim Chan
9.1 Introduction 161
9.2 Overview of Spray Drying
9.2.1 Advantages of Spray Drying 163
9.2.2 Hardware 163
9.2.3 Spray Dryer Classifications 168
9.2.4 Process Parameters 170
9.2.5 Particle Formation Mechanism 172
9.3 Advances in Spray Drying Technology
9.3.1 The ‘Quality by Design’ Approach 174
9.3.2 The Nano Spray Dryer B-90 175
9.3.3 Novel Multi-Channel Nozzles 177
9.4 Anti-Tuberculosis Therapeutics Produced by Spray Drying
9.4.1 Controlled-Release Microparticles 179
9.4.2 Maximal Drug-loaded Microparticles 184
9.4.3 Vaccines 186
9.5 Conclusion 187
9.6 Acknowledgements 187
References 187

10 Formulation Strategies for Antitubercular Drugs by Inhalation
Francesca Buttini and Gaia Colombo
10.1 Introduction 197
10.2 Lung Delivery of TB Drugs 198
10.3 Powders for Inhalation and Liquids for Nebulization 200
10.4 Antibacterial Powders for Inhalation: Manufacturing
of Respirable Microparticles 202
10.5 Antibacterial Powders for Inhalation: Devices
and Delivery Strategies 208
10.6 Conclusions and Perspectives 211
References 211

11 Inhaled Drug Combinations
Sanketkumar Pandya, Anuradha Gupta, Rajeev Ranjan, Madhur Sachan,
Atul Kumar Agrawal and Amit Misra
11.1 Introduction 213
11.2 Standard Combinations in Oral and Parenteral Regimens 214
11.2.1 Combinations for the Directly Observed Treatment
Short-Course (DOTS) Regimen 214
11.3 The Rationale for Inhaled Therapies of TB
11.3.1 Single Drug, Supplementing Other Orally Administered Drugs 218
11.3.2 Single Drug Replacing Injectable First- or Second-Line Agents 219
11.3.3 Multiple Inhaled Drugs, Adjunct or Stand-alone Therapy 220
11.3.4 “Stimulate the Phagocyte” 220
References 211
Contents

11.4 Combinations of Anti-TB Drugs with Other Agents 222
11.4.1 Drugs that Primarily Affect the Pathogen 222
11.4.2 Drugs that Affect Host Responses 223
11.4.3 Drugs that Affect both Host and Pathogen 224
11.5 Formulation of Inhaled Drug Combinations 224
11.5.1 Excipient-free Formulations 224
11.5.2 Applications of Excipients 225
11.5.3 Preparing Multi-Component Particles and Vesicles 227
11.5.4 Shelf Stability 227
11.5.5 Drug Release and Pharmacokinetics 228
11.5.6 Inhalation Dosimetry 229
11.6 Conclusions 230
References 230

12 Ion Pairing for Controlling Drug Delivery 239
Stefano Giovagnoli, Aurélie Schoubben and Carlo Rossi
12.1 Introduction 239
12.2 Ion Pairing Definitions and Concepts 240
12.2.1 Ion Pairing as Physicochemical Tuning Tool 241
12.2.2 Metal Ion Complexation 242
12.2.3 Some Considerations on Ion Pair and Metal Complex Stability 244
12.3 Ion Pairs, Complexes and Drug Delivery 245
12.3.1 Oral Route 245
12.3.2 Transdermal/Dermal and Mucosal Route 246
12.3.3 Parenteral Route 247
12.3.4 The Pulmonary Route and Infectious Diseases 247
12.3.5 Toxicity Considerations 248
12.4 Remarks 252
References 254

13 Understanding the Respiratory Delivery of High Dose Anti-Tubercular Drugs 258
Shyamal C. Das and Peter J. Stewart
13.1 Introduction 258
13.2 Tuberculosis 259
13.3 Drugs Used to Treat Tuberculosis, Doses, Challenges and Requirements for Therapy in Lungs 260
13.3.1 Current TB Treatment Regimen 260
13.3.2 Challenges of Conventional Oral and Parenteral Therapy 261
13.3.3 Rationale for Respiratory Delivery 261
13.4 Approaches for Respiratory Delivery of Drugs 262
13.5 Current DPI Formulations and Their Mechanisms of Aerosolization 262
13.6 DPI Formulations for Tuberculosis and Requirements 264
13.7 Issues to Consider in Respiratory Delivery of Powders for Tuberculosis 264
13.8 Relationship between De-agglomeration and Tensile Strength 266
13.9 Strategies to Improve De-agglomeration 268
Contents

13.10 DPI Formulations having High Aerosolization 269
13.11 Devices for High Dose Delivery 270
13.12 Future Considerations 271
References 272

Section 4 Alternative Approaches 275

14 Respirable Bacteriophage Aerosols for the Prevention and Treatment of Tuberculosis 277
Graham F. Hatfull and Reinhard Vehring
14.1 Introduction 277
14.1.1 Bacteriophages 277
14.1.2 Mycobacteriophages 280
14.1.3 Mycobacterium tuberculosis as a Host for Phage Infection in vivo 282
14.1.4 Mycobacteriophages and TB Diagnosis 282
14.2 Treatment or Prevention of Tuberculosis Using Phage-based Agents 282
14.2.1 Bacteriophages as Therapeutic Agents 282
14.2.2 Prospects for Using Mycobacteriophages for Therapy or TB Prevention 283
14.3 Selection of Mycobacteriophages 284
14.4 Respiratory Drug Delivery of Phages 285
14.5 Summary and Outlook 288
Acknowledgements 288
References 288

15 RNA Nanoparticles as Potential Vaccines 293
Robert DeLong
15.1 Introduction 293
15.2 Nanoparticles 293
15.3 RNA Nanoparticle Vaccines 294
15.4 Progression of Nanomedicines into the Clinic 295
15.5 The Stability Problem 295
15.6 The Delivery Problem 298
15.7 RNA as Targeting Agent or Adjuvant? 298
15.8 Challenges for RNA Nanoparticle Vaccine Characterization 300
15.9 On the Horizon 301
References 301

16 Local Pulmonary Host-Directed Therapies for Tuberculosis via Aerosol Delivery 307
Mercedes Gonzalez-Juarrero
16.1 Introduction 307
16.1.1 Tuberculosis Disease and Control 308
16.1.2 Chemotherapy and Host Immunity to Tuberculosis 308
16.1.3 Aerosol Delivery of Host-Directed Therapies for Tuberculosis Treatment 309
16.2 Lung Immunity to Pulmonary *M. tuberculosis* Infection 309
16.2.1 Overview 309
16.2.2 Influence of Lung Alveoli Environment on Bacilli Survival and its Impact on Tuberculosis Chemotherapy 310
16.2.3 Potential Targets for Host-Directed Therapy 311
16.3 Host-Directed Therapies 313
16.3.1 Previous Studies via Systemic Administration of Host-Directed Therapies 313
16.3.2 Previous Studies via Aerosol Delivery of Host-Directed Therapies 315
16.4 Limitations of Preclinical Studies to Develop Inhalational Host-Directed Therapies for Tuberculosis 317
16.5 Preclinical Testing of Inhaled Small Interference RNA as Host-Directed Therapies for Tuberculosis 318
Acknowledgements 319
References 319

Section 5 Future Opportunities 325

17 Treatments for Mycobacterial Persistence and Biofilm Growth 327
David L. Hava and Jean C. Sung
17.1 Introduction 327
17.2 Mycobacterial Persistence and Drug Tolerance 328
17.3 Mycobacterial Multicellular Growth 329
17.4 Mycobacterial Lipids Involved in Biofilm Formation 330
17.5 Therapies to Treat Mycobacterial Biofilms and Persistence 332
17.5.1 Therapies to Treat Mycobacterial Biofilms 332
17.5.2 Therapies to Disrupt Nutrient Acquisition and Persistence 334
17.5.3 Treatments for Biofilm Dispersion 335
17.5.4 Treatments Derived from Host Innate Defenses 336
17.5.5 Treatments with Inhaled Antibiotics 337
17.6 Conclusion 339
References 339

18 Directed Intervention and Immunomodulation against Pulmonary Tuberculosis 346
Dominique N. Price and Pavan Mutil
18.1 Introduction 346
18.2 TB Immunology 347
18.2.1 Early Events of Infection 347
18.2.2 Delayed Adaptive Immunity 348
18.2.3 Humoral Immunity and Innate Lymphocytes 348
18.2.4 Latent Infection 349
18.2.5 Correlates of Protection and Tolerance 350
18.2.6 Natural Immunity against TB Infection 351
Section 6 Clinical Perspective

19 Clinical and Public Health Perspectives

Ruvandhi R. Nathavitharana and Edward A. Nardell

19.1 Introduction 381
19.2 Background 382
19.3 Clinical Considerations
  19.3.1 Pill Burden and Fixed-dose Combinations 382
  19.3.2 Non-adherence and Medication Monitoring 383
  19.3.3 Intermittent Therapy 383
  19.3.4 Drug Toxicity 384
  19.3.5 Drug Absorption and Therapeutic Drug Monitoring 384
19.4 Public Health Considerations
  19.4.1 DOTS 385
  19.4.2 Community-based Therapy 386
  19.4.3 Incentives and Enablers to Promote Adherence 386
19.5 Inhaled Drugs and Other Alternative Delivery Systems 387
  19.5.1 Possible Advantages 387