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Contents

Contributors ix
Preface xiii

SECTION I
TOWARDS EDWARD JENNER’S REVENGE: DEVELOPING AN EFFECTIVE TUBERCULOSIS VACCINE / 1

A. BASIC IMMUNOLOGY

1 Innate Immune Responses to Tuberculosis / 3
   Jeffrey S. Schorey and Larry S. Schlesinger

2 Cytokines and Chemokines in Mycobacterium tuberculosis Infection / 33
   Racquel Domingo-Gonzalez, Oliver Prince, Andrea Cooper, and Shabaana Khader

3 Regulation of Immunity to Tuberculosis / 73
   Susanna Brighenti and Diane J. Ordway

4 The Memory Immune Response to Tuberculosis / 95
   Joanna R. Kirman, Marcela I. Henao-Tamayo, and Else Marie Agger

5 Pathology of Tuberculosis: How the Pathology of Human Tuberculosis Informs and Directs Animal Models / 117
   Randall J. Basaraba and Robert L. Hunter

B. ANIMAL MODELS

6 Animal Models of Tuberculosis: An Overview / 131
   Ann Williams and Ian M. Orme

7 Mouse and Guinea Pig Models of Tuberculosis / 143
   Ian M. Orme and Diane J. Ordway

8 Non-Human Primate Models of Tuberculosis / 163
   Juliet C. Peña and Wen-Zhe Ho

9 Experimental Infection Models of Tuberculosis in Domestic Livestock / 177
   Bryce M. Buddle, H. Martin Vordermeier, and R. Glynn Hewinson

C. VACCINES

10 Clinical Testing of Tuberculosis Vaccine Candidates / 193
   Mark Hatherill, Dereck Tait, and Helen McShane

D. HUMAN IMMUNOLOGY

11 Human Immunology of Tuberculosis / 213
   Thomas J. Scriba, Anna K. Coussens, and Helen A. Fletcher
30 The Minimal Unit of Infection: *Mycobacterium tuberculosis* in the Macrophage / 635
Brian C. VanderVen, Lu Huang, Kyle H. Rohde, and David G. Russell

31 Metabolic Perspectives on Persistence / 653
Travis E. Hartman, Zhe Wang, Robert S. Jansen, Susana Gardete, and Kyu Y. Rhee

32 Phenotypic Heterogeneity in *Mycobacterium tuberculosis* / 671
Neeraj Dhar, John McKinney, and Giulia Manina

33 *Mycobacterium tuberculosis* in the Face of Host-Imposed Nutrient Limitation / 699
Michael Berney and Linda Berney-Meyer

Index / 717
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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.

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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
Adjuvantive therapeutic vaccination, TB disease, 196–197
Animal models, 131, 139; see also
Experimental infection models;
Guinea pigs; Mouse models
assessment of new drugs, 136–137
assessment of vaccines, 135
cattle, 134
common experimental designs, 280
efficacy testing, 277–284
ethical and husbandry issues, 138–139
guinea pigs, 132
host response and pathogenesis, 134–135
limitations of, 137–139
mechanism of protection, 136
mice, 132, 278–280
mini pigs, 134
non-human primates (NHP), 132–133
primary host response to M. tuberculosis infection, 122–123
process and capacity, 135–136
rabbits, 133
rats, 133–134
Treg cell responses in experimental, 80–87
Treg cell responses 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, 683, 686
Antibiotics, 535
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
HIV, 239
HIV-TB coinfection, 250
HIV-TB immune constitution inflammatory syndrome (IRIS), 252–253, 253–256
influence on T cell responses in coinfection, 251
Apoptosis, 563
Archaebacteria, 455
Archivel Farma SL, 202
Arginine auxotrophs, 702
Arginine auxotrophs, 702
Arginine auxotrophs, 702
Asparagine auxotrophs, 702
Aspartic acid auxotrophs, 702
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
asparagines, 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
isoleucine, 704
leucine, 704
lysine, 703–704
methionine, 702–703
nicotinamide, 706
panthothenate (vitamin B3), 706
proline, 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

Biology
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 genomics, 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
Callithrix jacchus (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
CCR3, 50–51
CCR5, 51–52
CCR6, 51
CCR7, 51–52
CXC receptors and ligands, 52–53
CXCR1, 52
CXCR2, 52
CXCR3, 52–53
CXCR5, 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
Clotrimazole
animal models, 270–278
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
n-Cycloserine, drug resistance, 505
Cynomolgus macaques
comparing TB in humans to, 164
Golden Age of research, 163, 166
Macaca fascicularis, 163, 172
TB studies, 166–167, 168
21st century TB research, 166
Cysteine auxotrophs, 702
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, 42–45
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

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, 222–233
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
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Index

Dormancy

definition, 654
secretion, 610, 611, 619

Drosophila melanogaster, 17

Drug development
clinical trials, 272–273
macaque models for evaluation, 170–171
targeting replicosome for, 595–596

Drug-resistant M. tuberculosis strains

evolution of, 502–508

evolution of MDR-TB, 503, 506

evolution of resistance to second-line drugs, 506–507

impact of GeneXpert MTB/RIF, 401, 402–404
microevolution during TB infection, 507–508

resistance to first-line drugs, 504

resistance to second-line drugs, 505

suggested model for genetic diversity of subpopulations, 507

Drug susceptibility testing (DST), 363

commercial liquid culture-based DST, 366–367

genotypic tests for, 367

line probe assays for resistance detection, 367–368

noncommercial methods, 367

phenotypic tests for, 366

pipeline of diagnostics, 370

Drug targets, menaquinone biosynthesis, 583–584

Drug susceptibility testing (DST), 363

commercial liquid culture-based DST, 366–367

genotypic tests for, 367

line probe assays for resistance detection, 367–368

noncommercial methods, 367

phenotypic tests for, 366

pipeline of diagnostics, 370

Drug targets, menaquinone biosynthesis, 302–303, 304

Drug tolerance, definition, 654

Drug-tolerant cells
class I persisters, 321–322
class II persisters, 322–325, 329–346

population of nonreplicating, 329–346

Dual-active molecules, 331–332
canonical and noncanonical targets of, 334

E

Ebola virus, 454

Efficacy, see Preclinical efficacy testing

Electron flow, 296

Electron flow, 296

Electron flow, 296

Erdman strain, M. tuberculosis, 166, 167, 168, 170, 171–172

Escherichia coli, 12, 309, 321, 464, 467, 535, 536, 557, 583, 590, 599, 610, 638, 662, 673, 676, 701

ESX-1 (ESAT-6 secretion system-1), 627, 631–632
damage of M. tuberculosis-containing phagosome, 628–630

innate immune mechanisms, 631
interventions by target, 631

phagosome disruption by, 628

regulations of, 630–631

role in TB pathogenesis, 630

Ethambutol
drug resistance, 502, 503, 504
tolerance of infected cells, 640

Ethical issues, animal models, 138–139

Ethionamide, drug resistance, 505

Eubacteria, 455

Evolution of MTBC

animal-related M. tuberculosis complex (MTBC) strains, 461

biogeographical structure of M. tuberculosis Beijing lineage, 463
correspondence table of strains by typing methods, 457
diagram of proposed evolutionary pathway, 456
fingerprint era, 454–455
gene-based phylogeny of MTBC, 459
global phylogeny of MTBC isolates, 465

global picture, 458–461

history and early misconceptions, 453–454

limitations, 466–467

multilocus era, 455–458

pattern for evolving populations, 466

pregenomic era, 454–458

relativity of clock, 464–467

spoligotyping, 453, 457, 461

substitution rate estimates, 464–466

taxonomic nomenclature, 464

whole-genome phylogeny of strains of MTBC, 460

zooming into lineages, 461–464

Evolution of Mycobacterium tuberculosis

drug-resistant strains, 502–508

global spread of M. tuberculosis L2

Beijing and L4 strains, 499–500

L2 Beijing sublineage, 500–501

L4 sublineage, 501–502

lessons from M. canetti, 496–498

molecular key events in evolution, 497

neighbor-joining phylogeny scheme, 499

professional pathogenicity, 498–502

Expanded Program on Immunization (EPI), 193

World Health Organization, 193

Experimental infection models
cattle, 177–178
deer, 179

goats, 178–179

Experimental medicine

controlled human challenge models, 205

examples of, 205

potential outcomes in studies, 204–205

preclinical studies in, 205–206

product development and, 204

role in TB vaccine development, 203–206

scientific community, 206

Extensively drug-resistant (XDR) strains, 533

F

Fatty acids, M. tuberculosis in macrophages, 644–645

Fauci, Anthony, 117

Flow cytometry, 682–684, 685

Fluorescence-activated cell sorting (FACS), 683

Fluorescence recovery after photobleaching (FRAP), 678, 684

Foam cell formation, human post-primary TB, 125

Folate (vitamin B9), 707

Foxp3 (transcription factor forkhead box P3)
coenexpression with CD25, 74, 75–76, 78–79

function of, 73

host defense against M. tuberculosis, 82

Francisella tularensis, 609, 699, 709
revisiting heritability in post-GWAS era, 416
TB susceptibility, 413, 418–419, 427
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, 684, 687
guinea pig model, 152
in vitro models, 549–550
lung of human with primary tuberculosis, 118, 120–121
morphological features of, 533
M. tuberculosis infection, 217, 636
progressive cavitization, 126
restricting M. tuberculosis movement, 35–36
term, 16
Granulomatous inflammation, 123
Guinea pigs, 150–153; see also Animal models
animal model, 132
anti-TB treatment, 86
BCG vaccination, 86
device for aerosol exposure, 147
gating host cells from lung, 153
granulomas in lungs, 118, 124, 126
human-to-guinea pig transmission, 153
immunopathology of, 152
magnetic resonance imaging of infected lungs, 155
preclinical efficacy models, 282
response to infection, 123, 124, 154
TB disease progression, 122
Treg cells in, 80, 85–86
vaccines, 153–154

H37Rv strain of Mycobacterium tuberculosis, 166, 167, 168, 170, 172, 215
Harvard School of Public Health, 467
Heliobacter 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
heritability 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 infection, 245–247
tuberculosis epidemic and, 389
tuberculosis resurgence, 222
HIV-TB-associated immune reconstitution inflammatory syndrome (IRIS)
acquired immunity and TB-IRIS, 255–256
hypercytokinemia in TB-IRIS, 233, 251
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
cytotoxic lymphocytes in, 251–252
dendritic cells in, 244
dissemination 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
Homeostatic regulation, 73
Homo sapiens
M. tuberculosis, 653
tuberculosis in, 453–454, 458, 460–462, 467
Host genetic studies, tuberculosis, 429
Host-imiquimod platforms, 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, 221
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, 545–546
Human tuberculosis (TB)
balance of Treg activity, 77
cavity formation in lungs, 119, 120
CD3+ Treg cell subsets in, 77–78
granuloma in lung, 118, 120–121
in vitro expansion of mycobacteria-specific Treg cells, 76–77
novel TB vaccine candidate MVA85A, 77–78
post-primary lung reinfection, 124–125
TB disease progression, 122
Treg at site of infection, 79–80
Treg cell responses in, 74–80
Treg cells and anti-TB treatment, 78–79
Treg cells and clinical M. tuberculosis strains, 78
Treg-mediated manipulation of immune cell activation, 75–79
Treg responses in cell and fluid samples, infection, 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
Imidazopyridine amide, TB drug, 300, 305
Immune response, see Memory immune response
Immunodeficiency, 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, 367–368
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 co-infection, 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 primates (NHP), 544–545
zebrafish, 550
IPEX 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,
323, 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 TST, 381
testing methods for, 380
Legionella pneumophila, 699, 709
Leishmania, 146
Lentivirus 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)
 improving 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
mucus and surfactant, 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
hypophase, 5–6
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 (cynomologus 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/saiman 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 co-infection, 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
Macrophages (Continued)
mycobacterial growth and HIV-1 viral replication, 243
non-human primate in vitro models, 344–345
Magnetic resonance imaging (MRI), infected guinea pig lungs, 135
Major histocompatibility complex (MHC), 38, 39, 49, 74, 97
Malnutrition, 223–224
Marmosets (Callithrix jacchus), 172, 284
McMaster (AdSAg85A), 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
CD8 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 

Magnetic resonance imaging (MRI), infected guinea pig lungs, 135
Major histocompatibility complex (MHC), 38, 39, 49, 74, 97
Malnutrition, 223–224
Marmosets (Callithrix jacchus), 172, 284
McMaster (AdSAg85A), 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
CD8 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 
MicroRNAs (miRNAs), 10
Microfluidics, 684–685
Microfluidics (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
Moorella, 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
 genetic studies in mice, 145–146
innate immunity, 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
mouse response to infection, 146–150
obstructive alveolar pneumonia, 126
 persistence in M. tuberculosis infection, 654–655, 657–659
 preclinical efficacy models, 278–281
proposed regulation T cell suppression, 84
TB disease progression, 122
Treg cells and TB vaccination, 83–84
Treg cells in, 80–85
Treg cells in chronic TB infection, 82–83
Treg cells in early TB infection, 81–82
Moxifloxacin
animal model, 279
drug candidate, 272, 331
drug resistance, 305
guinea pigs, 282
proof-of-concept molecule, 333
Mucosal associated invariant T (MAIT) cells, 5
M. tuberculosis infection, 216–217, 549
Multidrug-resistant (MDR) strains, 533
Mutagenesis, M. tuberculosis, 595
MVA85A (modified vaccinia Ankara virus expressing antigen 85A)
testing protocols, 136
trial in South Africa, 137–138, 153–154
Mycobacteria
C-family DNA polymerases, 586, 588–591
DNA synthesis, 334–335, 336
evaluating bactericidal action against nonreplicating, 329
fluoroquinolones, 339
folate synthesis, 338
high-throughput screens targeting phenotypically tolerant, 322–323, 325
4-hydroxyquinolines, 338, 339
8-hydroxyquinolines, 338, 339
lipid synthesis, 332–334, 336
membrane depolarizers, 343–346
metabolism and respiration, 309–310
oxidative phosphorylation, 295
peptidoglycan synthesis, 335, 337, 338
 persistence and resistance, 597–599
population heterogeneity as function of applied stress, 598
protein synthesis, 335, 337
protoeolyis/proteostasis pathway, 339–341
quinolines, 338–339
replication machinery, 383, 586
respiration, 309–310
RNA synthesis, 335, 336
screening, 341–343
strategies for evaluating nonreplicating, 323
targeting oxygen reduction in, 303, 305–308
Mycobacterial biofilms, 533, 535, 536
extracellular M. tuberculosis in necrotizing lesions, 535–536
formation, 535, 536, 537
Mycobacterial replisome, working model of, 582
Mycobacteria orygis, 460
Mycobacteria other than tuberculosis (MOTT), 495
Mycobacteriology, 460, 467
Mycobacterium africanum, 453, 455–460, 477
Mycobacterium avium, 13, 52, 679
Mycobacterium bovis, 476, 477
bovine tuberculosis (TB), 177
Raveneil strain, 133
Mycobacterium bovis bacille Calmette-Guérin (BCG), 6, 12, 13, 15, 703
BCG vaccine-induced protection, 43, 46
C3HeB/FeJ mice, 281
cattle model, 134
expressions of Treg cells, 76
responses of innate immune cells to, 12
vaccine, 95, 117, 179–180, 627
Mycobacterium canettii, 456, 458, 460, 476, 477, 479, 481–483, 485
drug resistance, 502
lessons to learn from, 496–498
Mycobacterium caprae, 461, 461, 477, 479, 496
Mycobacterium flavescens, 382
Mycobacterium haemophilum, 495
Mycobacterium kansasi, 382, 495
Mycobacterium leprae, 382, 428, 495, 709
replicase components, 584–586, 587
Mycobacterium lepraeosome, 495
Mycobacterium marinum, 14, 382, 495, 679
mycolic acids, 523
virulence, 610
zebrafish model, 36, 133, 699
Mycobacterium microti, 382, 453–454, 460, 461, 476, 477, 479–481, 485,
496, 498
Mycobacterium mungi, 461, 496
Mycobacterium orygis, 460, 476, 479, 496, 498
Mycobacterium phele, 6, 295
Mycobacterium pinnipedii, 460, 461, 476, 477, 479
Mycobacterium prototuberculosis, 458
Mycobacterium smeaginitis, 10, 308–309, 535, 536, 609, 673, 675, 679, 703
replisome components, 584–586, 587
Mycobacterium suricattae, 496
Mycobacterium szulgai, 382
Mycobacterium tuberculosis, 3;
see also HIV-TB coinfection
ATP synthesis by F1F0 ATP synthase, 308–309
biological differences between animal and human MTBC lineages, 481–482
biological differences between M. canetti and, 482
biological impact of genetic diversity, 480
evidence for potential of biological variation, 480–481
geographical distribution of Beijing isolates, 483
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, 496
cell wall remodeling, 569–570
defense against host-generated reactive oxygen and nitrogen species, 563–564
growth arrest, 567–569
Ser/Thr protein kinases (STPKs) coordinating 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
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
NADH:menaquinone oxidoreductases, 546–547
negative regulatory elements, 637
nonreplicating active, 343, 344
phagosome maturation arrest, 546
phagocytosis, 636
phagosome maturation arrest, 546
response of M. tuberculosis to intracellular environment, 636–638
role of isocitrate lyase (Icl) and methylcitrate 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, 673

Myelic acids chemical structures of, 520
importance of, 523–524
loss of acid-fastness, 519, 529
Myxococcus xanthus, 683

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 (Nrpm1), 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
extracellular M. tuberculosis in, 534–535
Neelsen, F., 520
Neisseria meningitidis, 197
Neutrophils HIV-TB coinfection, 243–244
lung, 5
M. tuberculosis infection, 12, 39, 216, 548
response to M. tuberculosis, 125
Niclosamide, 343–344, 346
Nicotinamide, 706
Nigericin, 297, 298
Nile red stain, 526–527
Nitro-containing compounds, dual- and non-dual-acting, 533
Nitro-containing compounds, dual- and nonreplicating active, 343, 344
3-Nitropropionate, 300, 301
Nocardia farcinica, 13
Nongrowing but metabolically active bacteria (NGMA), 676
identification of, 678, 681, 683
Non-human primate models, see also Animal models
animal model, 132–133
correlation with 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 NRP, 571–572
Nonreplication, diversity in, 319–321
Nontuberculous mycobacteria (NTM), 495
Nucleic acid amplification testing (NAAT), 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
Oxidative phosphorylation
Oxford University, 200
Ofloxacin, drug resistance, 505
Paβo, Svante, 467
Paleomicrobiology, 467
PAMP (pathogen-associated molecular pattern), see also
M. tuberculosis-derived, 246
Pantothenate (vitamin B₅), 706
Paradigm, 121
Parkinson diseases, 630
Pathogenesis
application of animal models, 134–135
macaque models for studying TB, 171
persisting, 672
Pathogens, see Nutrient use of pathogens
Pathology of tuberculosis, 117–121,
125–127
alveolar pneumonia, 126
cavity formation, 119, 120
disease progression in animal models, 122
granuloma within the lung, 118
hypersensitivity of pathogenesis of post-primary TB, 123–125
intrapulmonary spread of mixed inflammatory cells, 121
lipid pneumonia, 121, 125
obstructive lobular pneumonia, 121, 123
post-primary lung reinfecction, 124–125
primary host response to M. tuberculosis infection, 122–123
Pattern recognition, 145
Penicillin, 317–318
Peripheral blood mononuclear cells (PBMCs), 4
Peroxisome proliferator-associated receptor gamma (PPARγ), 4, 10
Persistence definition, 654
drug-induced, 662
gene deletion studies, 659–661
host-induced, 657–662
measurements, 656–662
messages, 662–663
methods, 656
models, 654–656
pathogenicity of M. tuberculosis, 653, 672
physiology of M. tuberculosis, 653
predicted genes for in vivo survival of M. tuberculosis, 661
terms, 653–654
Persisters, 317
class I, 321–322
class II, 322–325, 329–346
diversity in nonreplicating cells, 319–321
killing class II persisters, 329, 331–341
Phagocytosis, 636
Phagosome maturation, 8, 9
Phenotype, 671
Phenotype definitions, 429
Phenotypically tolerant M. tuberculosis, 317–319
class I persisters, 321–322
class II persisters, 322–325, 329–346
compound transformation during screening and secondary assays, 325, 329
conditions for replication rates of, 326
designing high-throughput screens to target, 322–325
diversity in nonreplication, 319–321
evaluating bactericidal action against nonreplicating mycobacteria, 329
fluoroquinolones, 339
future studies, 347–348
high-throughput screening (HTS), 341–343
key observations, 319
key recommendations, 348
killing class II persisters, 329, 331–341
membrane depolarizers, 343–346
modeling hypoxia and metronidazole activity relationship, 318
molecules persisting nonreplicating mycobacteria, 346, 347
nitro-containing compounds, 343
postscreensing assays, 327, 328
proof-of-concept molecules, 331–332
proteolysis/proeostasis pathway, 339–341
quinolones and derivatives, 338–339
screening assays, 325, 329, 330
selecting and designing nonreplicating models, 324
strategies for evaluating viability of nonreplicating, 323
Phenotypic drug resistance, 317
Phenotypic heterogeneity, 671–672
asymmetric cell division and cell aging, 676–679
causes and consequences of, 673
flow cytometry and omics, 682–684
fluorescence 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, 277–284
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
Preto, Cheung, 221
Preto, M., 221
Preto, P., 221
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