Bugs as Drugs

THERAPEUTIC MICROBES FOR THE PREVENTION AND TREATMENT OF DISEASE

EDITED BY
Robert A. Britton
Baylor College of Medicine, Molecular Virology and Microbiology, Houston, Texas

Patrice D. Cani
Université catholique de Louvain, Louvain Drug Research Institute, WELBIO—Walloon Excellence in Life Sciences, Brussels, Belgium

ASM PRESS
Washington, DC
Contents

Contributors vii
About the Editors xii
Preface xiii

A. TRADITIONAL PROBIOTIC APPROACHES
1 Biochemical Features of Beneficial Microbes: Foundations for Therapeutic Microbiology 3
   Melinda A. Engevik and James Versalovic

2 The Genomic Basis of Lactobacilli as Health-Promoting Organisms 49
   Elisa Salvetti and Paul W. O'Toole

3 Bifidobacteria and Their Health-Promoting Effects 73
   Claudio Hidalgo-Cantabrana, Susana Delgado, Lorena Ruiz, Patricia Ruas-Madiedo, Borja Sánchez, and Abelardo Margolles

B. NEXT-GENERATION BACTERIOTHERAPY: OPPORTUNITIES IN CHRONIC DISEASES
4 Microbial Interactions and Interventions in Colorectal Cancer 101
   Terence Van Raay and Emma Allen-Vercoe

5 Microbial Impact on Host Metabolism: Opportunities for Novel Treatments of Nutritional Disorders? 131
   Hubert Plovier and Patrice D. Cani

6 Therapeutic Opportunities in the Vaginal Microbiome 149
   Gregor Reid

7 Lung Microbiota and Its Impact on the Mucosal Immune Phenotype 161
   Benjamin G. Wu and Leopoldo N. Segal

8 Microbiota, Liver Diseases, and Alcohol 187
   Anne-Marie Cassard, Philippe Gérard, and Gabriel Perlemuter

9 The Potential of Probiotics as a Therapy for Osteoporosis 213
   Fraser L. Collins, Naiomy D. Rios-Arce, Jonathan D. Schepper, Narayanan Parameswaran, and Laura R. McCabe

10 Ecological Therapeutic Opportunities for Oral Diseases 235
   Anilei Hoare, Philip D. Marsh, and Patricia I. Diaz
C. CONTROL OF INFECTIOUS DISEASE BY MICROBES

11 Control of *Clostridium difficile* Infection by Defined Microbial Communities  269
James Collins and Jennifer M. Auchtung

12 Fecal Microbiota Transplantation: Therapeutic Potential for a Multitude of Diseases beyond *Clostridium difficile*  291
Guido J. Bakker and Max Nieuwdorp

13 Enterococci and Their Interactions with the Intestinal Microbiome  309
Krista Dubin and Eric G. Pamer

D. NEXT-GENERATION MICROBIAL THERAPEUTICS: TOOLS AND REGULATION

14 Engineering Diagnostic and Therapeutic Gut Bacteria  333
Brian P. Landry and Jeffrey J. Tabor

15 Use of Traditional and Genetically Modified Probiotics in Human Health: What Does the Future Hold?  363
Luis G. Bermúdez-Humarán and Philippe Langella

16 Genetic Tools for the Enhancement of Probiotic Properties  371
Laura Ortiz-Velez and Robert Britton

17 Genome Editing of Food-Grade Lactobacilli To Develop Therapeutic Probiotics  389
Jan-Peter van Pijkeren and Rodolphe Barrangou

18 United States Regulatory Considerations for Development of Live Biotherapeutic Products as Drugs  409
Sheila M. Dreher-Resnick, Scott Stibitz, and Paul E. Carlson, Jr.

E. INDIRECT STRATEGIES TO TARGET MICROBIOME FUNCTION FOR HEALTH

19 Bacteriophage Clinical Use as Antibacterial “Drugs”: Utility and Precedent  419
Stephen T. Abedon

20 Modulation of the Gastrointestinal Microbiome with Nondigestible Fermentable Carbohydrates To Improve Human Health  453
Edward C. Deehan, Rebbecca M. Duar, Anissa M. Armet, Maria Elisa Perez-Muñoz, Mingliang Jin, and Jens Walter

Index  485
Contributors

Stephen T. Abedon
Department of Microbiology, The Ohio State University, Mansfield, Ohio

Emma Allen-Vercoe
Molecular and Cellular Biology, University of Guelph, 50 Stone Road East, Guelph, Ontario, Canada

Anissa M. Armet
Department of Agricultural, Nutritional and Food Science, University of Alberta, Edmonton, Alberta, Canada

Jennifer M. Auchtung
Alkek Center for Metagenomics and Microbiome Research and Department of Molecular Virology and Microbiology, Baylor College of Medicine, Houston, Texas

Guido J. Bakker
Department of Internal and Vascular Medicine, Academic Medical Center, Amsterdam, The Netherlands

Rodolphe Barrangou
Department of Food, Bioprocessing and Nutrition Sciences, North Carolina State University, Raleigh, North Carolina

Luis G. Bermúdez-Humarán
Micalis Institute, INRA, AgroParisTech, Université Paris-Saclay, Jouy-en-Josas, France

Robert A. Britton
Baylor College of Medicine, Molecular Virology and Microbiology, Houston, Texas

Patrice D. Cani
Université catholique de Louvain, Louvain Drug Research Institute, WELBIO – Walloon Excellence in Life Sciences, Brussels, Belgium

Paul E. Carlson, Jr.
Division of Bacterial, Parasitic, and Allergenic Products, Office of Vaccines Research and Review, Center for Biologics Evaluations and Research, Food and Drug Administration, Silver Spring, Maryland
Anne-Marie Cassard
INSERM U996 Inflammation, Chemokines and Immunopathology,
DHU Hepatinov, Univ Paris-Sud, Université Paris-Saclay,
Clamart, France

Fraser L. Collins
Department of Physiology, Michigan State University, East Lansing, Michigan

James Collins
Alkek Center for Metagenomics and Microbiome Research and Department
of Molecular Virology and Microbiology, Baylor College of Medicine,
Houston, Texas

Edward C. Deehan
Department of Agricultural, Nutritional and Food Science, University of
Alberta, Edmonton, Alberta, Canada

Susana Delgado
Department of Microbiology and Biochemistry of Dairy Products,
Dairy Research Institute of Asturias, Spanish National Research
Council (IPLA-CSIC), Villaviciosa, Asturias, Spain

Patricia I. Diaz
Division of Periodontology, Department of Oral Health and Diagnostic Sciences,
University of Connecticut Health, Farmington, Connecticut

Sheila M. Dreher-Resnick
Division of Bacterial, Parasitic, and Allergenic Products, Office of Vaccines
Research and Review, Center for Biologics Evaluations and Research,
Food and Drug Administration, Silver Spring, Maryland

Rebecca M. Duar
Department of Agricultural, Nutritional and Food Science,
University of Alberta, Edmonton, Alberta, Canada

Krista Dubin
Immunology Program and Infectious Disease Service, Memorial
Sloan-Kettering Cancer Center, and Immunology and Microbial
Pathogenesis Program, Weill Cornell Graduate School of Medical
Sciences, New York, New York

Melinda A. Engevik
Department of Pathology and Immunology, Baylor College of Medicine, and
Department of Pathology, Texas Children’s Hospital, Houston, Texas

Philippe Gérard
Micalis Institute, INRA, AgroParisTech, Université Paris-Saclay,
Jouy-en-Josas, France

Claudio Hidalgo-Cantabrana
Department of Microbiology and Biochemistry of Dairy Products,
Dairy Research Institute of Asturias, Spanish National Research
Council (IPLA-CSIC), Villaviciosa, Asturias, Spain
Anilei Hoare  
Division of Periodontology, Department of Oral Health and Diagnostic Sciences, University of Connecticut Health, Farmington, Connecticut

Mingliang Jin  
Department of Microbiology and Immunology, Northwestern Polytechnical University, Xi’an, Shaanxi, China

Brian P. Landry  
Department of Bioengineering, Rice University, Houston, Texas

Philippe Langella  
Micalis Institute, INRA, AgroParisTech, Université Paris-Saclay, 78350 Jouy-en-Josas, France

Abelardo Margolles  
Department of Microbiology and Biochemistry of Dairy Products, Dairy Research Institute of Asturias, Spanish National Research Council (IPLA-CSIC), Villaviciosa, Asturias, Spain

Philip D. Marsh  
Division of Oral Biology, School of Dentistry, University of Leeds, Leeds, United Kingdom

Laura R. McCabe  
Department of Physiology, Department of Radiology, and Biomedical Imaging Research Center, Michigan State University, East Lansing, Michigan

Max Nieuwdorp  
Dept. of Internal & Vascular Medicine, Academic Medical Center, and Dept. of Internal Medicine, VU Univ. Medical Center, Amsterdam, The Netherlands; Wallenberg Laboratory, Dept. of Molecular and Clinical Medicine, Univ. of Gothenburg, Gothenburg, Sweden

Laura Ortiz-Velez  
Baylor College of Medicine, Molecular Virology and Microbiology, Houston, Texas

Paul W. O’Toole  
School of Microbiology and APC Microbiome Institute, University College Cork, Ireland

Eric G. Pamer  
Memorial Sloan-Kettering Cancer Center and Weill Cornell Graduate School of Medical Sciences, New York, New York

Narayanan Parameswaran  
Department of Physiology, Michigan State University, East Lansing, Michigan

Maria Elisa Perez-Muñoz  
Department of Agricultural, Nutritional and Food Science, University of Alberta, Edmonton, Alberta, Canada
Contributors

Gabriel Perlemuter
INSERM U996 Inflammation, Chemokines and Immunopathology, DHU Hepatino, Univ Paris-Sud, Université Paris-Saclay, and AP-HP, Hepatogastroenterology and Nutrition, Hôpital Antoine-Béclère, Clamart, France

Hubert Plovier
WELBIO-Walloon Excellence in Life Sciences and Biotechnology, and Metabolism and Nutrition Research Group, Louvain Drug Research Institute, Université Catholique de Louvain, Brussels, Belgium

Gregor Reid
Lawson Health Research Institute, Human Microbiome and Probiotics, F3-106, 268 Grosvenor Street, London, Ontario, Canada

Naiomy D. Rios-Arce
Department of Physiology, Michigan State University, East Lansing, Michigan

Patricia Ruas-Madiedo
Department of Microbiology and Biochemistry of Dairy Products, Dairy Research Institute of Asturias, Spanish National Research Council (IPLA-CSIC), Villaviciosa, Asturias, Spain

Lorena Ruiz
Department of Microbiology and Biochemistry of Dairy Products, Dairy Research Institute of Asturias, Spanish National Research Council (IPLA-CSIC), Villaviciosa, Asturias, Spain

Elisa Salvetti
School of Microbiology and APC Microbiome Institute, University College Cork, Ireland

Borja Sánchez
Department of Microbiology and Biochemistry of Dairy Products, Dairy Research Institute of Asturias, Spanish National Research Council (IPLA-CSIC), Villaviciosa, Asturias, Spain

Jonathan D. Schepper
Department of Physiology, Michigan State University, East Lansing, Michigan

Leopoldo N. Segal
Department of Medicine, NYU Division of Pulmonary, Critical Care, & Sleep Medicine, New York, New York

Scott Stibitz
Division of Bacterial, Parasitic, and Allergenic Products, Office of Vaccines Research and Review, Center for Biologics Evaluations and Research, Food and Drug Administration, Silver Spring, Maryland

Jeffrey J. Tabor
Department of Bioengineering and Department of Biosciences, Rice University, Houston, Texas
Jan-Peter van Pijkeren
Department of Food Science, University of Wisconsin-Madison,
Madison, Wisconsin

Terence Van Raay
Molecular and Cellular Biology, University of Guelph, 50 Stone Road East,
Guelph, Ontario, Canada

James Versalovic
Department of Pathology and Immunology, Baylor College of Medicine,
and Department of Pathology, Texas Children’s Hospital, Houston, Texas

Jens Walter
Department of Agricultural, Nutritional and Food Science and Department of
Biological Sciences, University of Alberta, Edmonton, Alberta, Canada

Benjamin G. Wu
Department of Medicine, NYU Division of Pulmonary, Critical Care,
& Sleep Medicine, New York, New York
About the Editors

Dr. Robert Britton is a Professor in the Department of Molecular Virology and Microbiology and is a Member of the Alkek Center for Metagenomics and Microbiome Research at Baylor College of Medicine. He presently directs a Therapeutic Microbiology laboratory that is focused on the use of microbes to prevent and treat human disease. Currently funded research projects in the laboratory range from the study of how traditional probiotic strains can ameliorate osteoporosis to how intestinal microbial communities resist invasion by the diarrheal pathogen *Clostridium difficile*. His laboratory has made several advances in the development of genetic and microbial growth platforms to aid in the understanding of how microbes promote health and disease. These include the development of precision genome engineering technologies for lactic acid bacteria and the development of human fecal minibioreactor arrays to study the function of microbial communities in a high-throughput manner.

Dr. Patrice D. Cani is a Professor at the Université catholique de Louvain (UCL) and investigator for WELBIO (Walloon Excellence in Lifesciences Biotechnology) and the Fund for Scientific Research (FRS-FNRS). He is a member of the Royal Academy of Medicine of Belgium and the recipient of prestigious grants and prizes. He has published more than 200 papers, reviews, and chapter books in the field of gut microbiota, prebiotics/probiotics, and metabolism. In the early 2000s, he started to investigate the interactions between gut microbes and complex biological systems (endocannabinoids, immunity) by using prebiotics. In 2007, he discovered the concept of metabolic endotoxemia and more recently the role of specific bacteria (e.g., *Akkermansia*). Twitter: @MicrObesity.
Preface

The reinvigoration of research into the human microbiome—the collection of microbes that reside within and on our body—has resulted in novel insights into the role of these microorganisms in health and disease. Associations between the composition of the intestinal microbiome and many human diseases, including inflammatory bowel disease, cardiovascular disease, metabolic disorders, and cancer, have been elegantly described in the past decade. Because of these seminal discoveries and the increased public interest in the use of probiotics and prebiotics to impact health, many researchers and entrepreneurs are working toward translating the human microbiome into novel diagnostics and therapeutics. Thus, one of the main objectives of this volume is to provide insights into how one may capitalize on the enormous amount of knowledge being generated in microbe-human interactions for the translation into products that will benefit humankind.

We note that microbiome research, and the use of microbes as therapeutics, is not of recent origin. Elie Metchnikoff posited over 100 years ago that lactic acid bacteria found in fermented milk were beneficial to health and prevented intestinal “putrefaction.” Ben Eiseman and colleagues began using fecal enema as an adjunct therapy in the treatment of pseudomembranous enterocolitis in 1958, a full 20 years prior to Clostridium difficile being identified as one of the main causative agents of this disease. Indeed, fecal transplantation for the treatment of disease dates back centuries to the 4th century, when Ge Hong, a well-known traditional Chinese medicine doctor, described the use of human fecal material by mouth to treat his patients with severe diarrhea.

Why, then, the increase in developing novel therapeutics and diagnostics using microbes now? Significant improvements in genetic engineering of non-model organisms, next-generation sequencing technology, and metabolic profiling have certainly stimulated much confidence in being able to harness microbes to improve health. In addition, systems biology approaches and synthetic engineering of microbes are now high-throughput and cost-effective enough to explore a much wider range of therapeutic possibilities to be vetted.

Finally, we note there is much hype and enthusiasm over the use of microbes—not only classical probiotics but also future next-generation beneficial microbes and engineered bacteria—to make significant impacts on many human diseases and to restore healthy microbial communities. However, our understanding of how microbial communities function to influence health is still quite shallow, and translation to therapeutics will require patience and basic research. For example, the linking of many diseases to altered microbial communities is only
by association, and in many cases these correlations have only been uncovered in mouse models. We must acknowledge that despite the explosion of science in the gut microbiome in the past decade, much of the work has described associations between the microbiome and disease with few instances of causation. Until microbiome shifts that are associated with disease are shown to be truly driving disease manifestation, it will be difficult to know which diseases can be tackled via microbiome manipulation. It is important to remind the scientific community that just because one or several bacteria are increased or decreased in a specific pathological situation, this does not necessarily mean they play a role in disease. Therefore, a deeper understanding of the mechanisms and functions of microbiome-human interaction will be required to fully realize the potential of developing drugs for the treatment of acute and chronic diseases. Another objective of this book is for readers to identify key gaps that exist in their respective fields that need to be closed in order to assist in moving therapeutic microbes from the bench to the bedside.

We are indebted to the authors for their contributions to this book, which we know took a considerable amount of time to produce. We hope you find the chapters informative and useful in your endeavors.

Robert A. Britton
Patrice D. Cani
Acetate, short-chain fatty acids (SCFAs), 13
Achromobacter, 172
Achromobacter liquefaciens, 10
Acinetobacter, airway microbiome, 162, 166
Actinobacteria, 3, 49, 73
  alcohol liver disease, 199
  gut microbiota, 291
Actinomyces
  cystic fibrosis, 172
  oral cavity, 236
  periodontitis, 240
Actinomycetaceae, 169
Actuator, definition, 353–354
Acylhomoserine lactones (AHL), quorum-sensing systems, 10–11
Aerococcus, 19
Aeromonadales, 192
Aeromonas hydrophila, 21
Agency for Healthcare Research and Quality, 410
Aggregatibacter actinomycetemcomitans, periodontitis, 240, 246–248
Akkermansia spp.
  commensals, 4
  GI microbes, 456
  intestinal microbiota, 191
Akkermansia muciniphila, 52
  beneficial microorganisms, 137
  gene diversity, 136
  nonalcoholic fatty liver disease (nonalcoholic fatty liver disease), 199
  polyamines, 9
  propionate, 14
Alanine racemase, food-grade selection marker, 374
Alcaligenaceae, cirrhosis, 203
Alcohol consumption, WHO safety threshold, 189
Alcoholic liver disease (ALD), 187. See also Liver diseases
  clinical aspects and diagnosis, 189–190
  current treatments, 191–192
  fecal microbiota transfer for, 201
  microbiota as key player in, 199–201
  pathogenesis of, 187–189
  prebiotics, 201
  probiotics for, 201
Alistipes, gut microbiota, 192
Allergic disease, bifidobacteria, 81, 87–88
Allisonella, NASH patients, 192
Alpha-bug hypothesis
  colorectal cancer (CRC) development, 113, 114
  schematic, 113
Alzheimer’s disease, 16
American College of Gastroenterology (ACG), 297
Amino acid neurotransmitters
  GABA, 8
  polyamines, 8–9
Amoxicillin, 138
Amoxicillin, antibiotic resistance, 312–313
Anaerobacter, 192
Anaerococcus, 150
Anaerobacter, 192
Anaerostipes spp., 14
Antagonistic pleiotropy, 429
Antibiotic-associated diarrhea, bifidobacteria, 84
Antibiotics, treatment of colorectal cancer, 120–121
Antimicrobial compounds
  bacteriocins, 21–26
  enhancing native activity in, 396–397
  hydrogen peroxide, 20–21
  lactic acid, 19–20
  reutericyclin, 27
  reuterin, 26–27
Archaea, vaginal microbiome, 150
Asthma, microbiome studies of, 173
Autoinducer signaling peptide (AIP), 11
Bacillaceae, asthma, 176
Bacillus
  AI-2 quorum-sensing, 11
  polimeric immunoglobulin receptor (pIgR), 169
  probiotics, 4, 220
Bacillus acidophilus, intestines of infants, 79
Bacillus anthracis, 21
Bacillus bifidus, 79
Bacillus cereus, 20, 21, 27
Bacillus licheniformis, 226
Bacillus megaterium, 20
Bacillus mesentericus, 318
Bacillus subtilis
  bone health, 226
  probiotics for colorectal cancer treatment, 119
Bacillus subtilis (continued)
reutericyclin, 27
riboflavin (vitamin B2), 15
Bäckhed, Fredrik, 469
Bacteria-host signaling compounds
amino acid neurotransmitters, 8–10
biogenic amino neuromodulators, 5
GABA (gamma-aminobutyric acid), 5, 8
histamine, 6–8
polyamines, 8–9
tryptophan and indole, 9–10
Bacterial metabolites, 4
Bacterial replacement therapies, 242–243
Bacteriocins, 21–26
class I: lantibiotics, 21–23
class II, 23
class III, 23
class IV, 23–24
colicins, 24–25
diversity and classification, 21–26
functional diversity of, 396
Gram-negative, 24–25
Gram-positive, 21–24
in vivo, 25
microcins, 24
as quorum-sensing molecules, 25–26
Bacteriophages, 243–244. See also Phage therapy
treatment of foods, 419–420
Bacteroides, undernutrition, 140
Bacteroides spp., 456
carbohydrate metabolism, 52
colic microbe, 111
fibrosis, 201
vitamin K, 17
tryptophan and indole, 10
Bacteroides forsythus, 21
Bacteroides fragilis
alpha-bug in CRC, 112
microbiota, 77
outer membrane vesicles, 18
Bacteroides-Prevotella, polyamines, 9
Bacteroides thetaiotaomicron
acetate, 13
G1 microbe, 461
intestinal physiology, 382
polyamines, 9
as treatment for vancomycin-resistant
enterococci (VRE), 320
Bacteroides uniformis, nonalcoholic fatty liver
disease (nonalcoholic fatty liver disease), 198
Bacteroidetes
alcohol liver disease, 199
cirrhosis, 202
colic microbe, 296
colonization resistance, 279–280
gastrointestinal tract, 279
gut microbiota, 12, 291
irritable bowel syndrome (IBS), 301
lung microbiome, 171, 172
nonalcoholic fatty liver disease, 192
steatosis, 192
Bacteroidetes/Firmicutes ratio, gut microbiota, 134
Bakken, Johan, 280–281
Bdellovibrio bacteriovorus, 243
Beneficial microbes, 4, 5
Bifidobacteria
acetate, 13
acquisition and development in infancy, 75–76
allergic disease, 87–88
antibiotic-associated diarrhea, 84
Bifidobacterium genus, 73–74
chemotherapy treatments, 86
Clostridium difficile-associated diarrhea, 84
colorectal cancer, 85–86
correlations with microbiota, 76–78
Helicobacter pylori infection, 84–85
inflammatory bowel disease, 86–87
intestinal disorders, 81, 84
irritable bowel syndrome, 86–87
liver disease, 86
as members of human intestinal microbiota,
74–78
necrotizing enterocolitis, 87
for prevention and treatment of disease, 80–81,
84–88
as probiotics, 78–80
strains as probiotics, 82–83
visualization of B. animalis subsp. lactis growth,
81
Bifidobacteriaceae, family, 73
Bifidobacteriales order, 73
Bifidobacterium
colic microbiota, 111
distribution in bowel, 74–75
fibrosis, 202
genetically modified probiotics, 366–367
GI microbes, 456
interindividual variability, 74–75
lactocepin, 19
natural probiotics, 334
polyamines, 9
positive effects of strains on gastrointestinal
functions, 79
prebiotics, 469
prebiotics for colorectal cancer treatment, 119
probiotics, 4, 220, 364
probiotics for colorectal cancer treatment,
118–119
species evolution with age, 74–75
Bifidobacterium genus, 73–74

Bacteroidetes
alcohol liver disease, 199
cirrhosis, 202
colic microbe, 296
colonization resistance, 279–280
gastrointestinal tract, 279
gut microbiota, 12, 291
irritable bowel syndrome (IBS), 301
lung microbiome, 171, 172
nonalcoholic fatty liver disease, 192
steatosis, 192
Bacteroidetes/Firmicutes ratio, gut microbiota, 134
Bakken, Johan, 280–281
Bdellovibrio bacteriovorus, 243
Beneficial microbes, 4, 5
Bifidobacteria
acetate, 13
acquisition and development in infancy, 75–76
allergic disease, 87–88
antibiotic-associated diarrhea, 84
Bifidobacterium genus, 73–74
chemotherapy treatments, 86
Clostridium difficile-associated diarrhea, 84
colorectal cancer, 85–86
correlations with microbiota, 76–78
Helicobacter pylori infection, 84–85
inflammatory bowel disease, 86–87
intestinal disorders, 81, 84
irritable bowel syndrome, 86–87
liver disease, 86
as members of human intestinal microbiota,
74–78
necrotizing enterocolitis, 87
for prevention and treatment of disease, 80–81,
84–88
as probiotics, 78–80
strains as probiotics, 82–83
visualization of B. animalis subsp. lactis growth,
81
Bifidobacteriaceae, family, 73
Bifidobacteriales order, 73
Bifidobacterium
colic microbiota, 111
distribution in bowel, 74–75
fibrosis, 202
genetically modified probiotics, 366–367
GI microbes, 456
interindividual variability, 74–75
lactocepin, 19
natural probiotics, 334
polyamines, 9
positive effects of strains on gastrointestinal
functions, 79
prebiotics, 469
prebiotics for colorectal cancer treatment, 119
probiotics, 4, 220, 364
probiotics for colorectal cancer treatment,
118–119
species evolution with age, 74–75
Bifidobacterium genus, 73–74

Bacteroidetes
alcohol liver disease, 199
cirrhosis, 202
colic microbe, 296
colonization resistance, 279–280
gastrointestinal tract, 279
gut microbiota, 12, 291
irritable bowel syndrome (IBS), 301
lung microbiome, 171, 172
nonalcoholic fatty liver disease, 192
steatosis, 192
Bacteroidetes/Firmicutes ratio, gut microbiota, 134
Bakken, Johan, 280–281
Bdellovibrio bacteriovorus, 243
Beneficial microbes, 4, 5
Bifidobacteria
acetate, 13
acquisition and development in infancy, 75–76
allergic disease, 87–88
antibiotic-associated diarrhea, 84
Bifidobacterium genus, 73–74
chemotherapy treatments, 86
Clostridium difficile-associated diarrhea, 84
colorectal cancer, 85–86
correlations with microbiota, 76–78
Helicobacter pylori infection, 84–85
inflammatory bowel disease, 86–87
intestinal disorders, 81, 84
irritable bowel syndrome, 86–87
liver disease, 86
as members of human intestinal microbiota,
74–78
necrotizing enterocolitis, 87
for prevention and treatment of disease, 80–81,
84–88
as probiotics, 78–80
strains as probiotics, 82–83
visualization of B. animalis subsp. lactis growth,
81
Bifidobacteriaceae, family, 73
Bifidobacteriales order, 73
Bifidobacterium
colic microbiota, 111
distribution in bowel, 74–75
fibrosis, 202
genetically modified probiotics, 366–367
GI microbes, 456
interindividual variability, 74–75
lactocepin, 19
natural probiotics, 334
polyamines, 9
positive effects of strains on gastrointestinal
functions, 79
prebiotics, 469
prebiotics for colorectal cancer treatment, 119
probiotics, 4, 220, 364
probiotics for colorectal cancer treatment,
118–119
species evolution with age, 74–75
Bifidobacterium genus, 73–74
Bifidobacterium spp., 3, 10, 137
Bifidobacterium adolescentis, 16, 460
Bifidobacterium animalis, 16, 81
Bifidobacterium animalis subsp. lactis, 9, 365
Bifidobacterium bifidum, 23
Bifidobacterium breve, 15, 18
Bifidobacterium dentium, 8, 18
Bifidobacterium longum, 8, 16, 18
bone health, 221, 223
nonalcoholic fatty liver disease, 199
oral candidiasis, 249
osteoporosis, 225
probiotics for colorectal cancer treatment, 119
Bifidobacterium pseudocatenulatum, nonalcoholic fatty liver disease, 198
Biocontrol, 421, 424. See also Phage therapy
Biofilm effect hypothesis
development of colorectal cancer, 116
schematic, 113
Biogenic amines, neuromodulators, 5
Biological output, definition, 354
Bioreactors, testing engineered gut bacteria, 352
Blaser, Martin, 134
Blautia hydrogenatrophica, 461
Blautia producta, antagonizing Clostridium difficile, 279
Bone health. See also Osteoporosis
disease, 214, 216–219
effect of probiotics (animal studies), 222–223
osteoclasts and osteoblasts, 214, 216, 217, 218
probiotics and, 224–225
probiotics and, in livestock, 225–226
role of intestinal microbiota, 220
Broad-spectrum antibiotics, 430
Burkholderiaceae, 172
Burkholderia cepacia, 172
Burkitt, Denis, 454
Butyrate, short-chain fatty acids (SCFAs), 14
Bystander effect hypothesis
development of colorectal cancer, 117
schematic, 113
Campylobacter, undernourished children, 138
Campylobacter jejuni, 243
Candida spp.
oral candidiasis, 240–241, 249, 252
oral community, 237, 252
Candida albicans, 20
Candida parapsilosis, growth of, 151
Cani, Patrice, 468
Capnocytophaga, oral cavity, 236
Capnocytophaga spuitgena, 21
Carbohydrate metabolism, lactobacilli, 52
Caries
dysbiotic changes associated with, 239
etiology of, 238
limitations of current microbial therapies, 250, 251
microbial therapeutics for, 244–246
potential benefits of microbial therapies, 251
Carnobacterium, 19
Carnobacterium maltaromaticum, 53
Carnobacterium piscicola, bacteriocins, 23
Catonella, cystic fibrosis, 172
Cellular memory, definition, 354
Center for Biologics Evaluation and Research, 410, 414
Chassis, definition, 354
Chassis selection, engineering smart probiotics, 341, 344–345
Chemical or physical inputs, definition, 354
Chemistry, manufacturing and controls data, 411
current good manufacturing practice (CGMP), 414
product release testing, 413–414
purity, 413
strain characterization, 412–413
Chemotherapy treatments, bifidobacteria, 86
Chlamydia, 150
Chromosomal integration strategies, 372–373
Chronic noncommunicable diseases
associated with GI microbiome, 454
diets low in nondigestible carbohydrates, 454
gastrointestinal microbiome and, 453–455
glucose and lipid metabolism, 465–466
human diet, 454–455, 471–472
systemic inflammation and, 466–467
Chronic obstructive pulmonary disease (COPD), 162–163, 167, 170–171
Chryseobacterium, 176
Cirrhosis, microbiotas associated with, 203
Citrobacter rodentium, 10
Clastogens, 117
Clinical Guide to Probiotic Products, 27
Clostridia, 192, 456
Clostridiales, 192, 203
Clostridium spp.
fibrosis, 202
gut microbiota, 192
hepatocellular carcinoma, 204
lung microbiome, 171
polyamines, 9
short-chain fatty acids, 12
tryptophan and indole, 10
Clostridium bifermentans, antagonizing C. difficile, 279
Clostridium boltaea, 318
Clostridium botulinum, 21
Clostridium butyricum, 119, 318
Clostridium difficile. See also Fecal microbiota transplantation (FMT)
asymptomatic carriage in adults, 272
Clostridium difficile (continued)

asymptomatic carriage in infants, 272
bacterial replacement therapy, 242–243

bifidobacteria and *C. difficile*-associated diarrhea, 84
carriage and disease, 271–273
colitis, 161
cumulative number of articles in PubMed, 271
enzymiotics for infections, 398
fecal microbiota transplantation (FMT), 275, 277–281, 292, 296–297
gastrointestinal track resisting infection by, 275, 276
history of infection, 270–271
life cycle, 273–274
metabolic syndrome, 136
microbiota transplantation, 155
potential mechanisms of colonization resistance, 274–275
potential mechanisms underlying asymptomatic carriage, 272–273
prevalence and cost of infection, 269
stratification of disease severity, 270

*Clostridium perfringens*, colorectal cancer treatment, 118

*Clostridium scindens*, 140, 274

*Clostridium sporogenes*, 21

Codex Alimentarius Commission, 457

Colicins, Gram-negative bacteriocins, 24–25

Collinsella, irritable bowel syndrome (IBS), 301

Colon

anatomy of human, 103
characteristics across regions of, 106
chronic inflammation in, 394–395

colon crypt, 104
colonic crypt signaling pathways, 102, 105
crypt architecture, 105
development of proximal and distal, 107
goblet cells and mucin, 105, 107

makeup of colon epithelium, 102
model of Wnt signaling, 104

normal microbiota, 109–111
proximal and distal, 105

Wnt signaling, 105

Colonization, definition, 354

Colorectal cancer (CRC), 16. See also Colon

alpha-bug hypothesis, 112, 113, 114

antibiotics and, 120–121

bifidobacteria, 85–86

biofilm effect hypothesis, 113, 116

bystander effect hypothesis, 113, 117

conjecture for, 109
driver-passenger hypothesis, 113, 114–115

gut microbiota associated with, 111–117

initiating event for, 107–108

intestinal microbiota adaptations hypothesis, 113, 115–116

most common gastrointestinal tract cancer, 101

physiology and development in, 101–102

potential treatment with microbial modulation therapies, 117–121

prebiotics and, 119–120

probiotics and, 118–119

proximal vs. distal CRCs, 108–109

schematic of microbiome changes leading to, 113
treatment for the future, 121

Wnt signaling in proximal vs. distal, 109

*Commamonadaceae*, in proximal colon, 111

Commensal bacteria, 4, 5, 7

Commensal-driven bystander effect hypothesis, colorectal cancer, 113, 117

Commensal microbes, 19–20

Comparative genomics, strains of *L. delbrueckii*, 58

Confocal scanner laser microscopy, visualization of *Bifidobacterium animalis*, 81

*Caproccoccus*, prebiotics for colorectal cancer treatment, 120

Coronary heart disease, 16

Corticosteroids, use in lung microbiome, 169–170

*Corynebacterium*, airway microbiome, 162, 166

cre-lox-based system for double-crossover integration, 373–374

CRISPR-Cas system, 378–380

antimicrobials, 398, 400

genome editing in lactobacilli, 394

primary classes of, 393

probiotic dual-delivery system of, as bacteriophages, 401

protecting against invasive elements, 392–393

repurposing, as antimicrobials, 399

tool in engineering probiotics, 390

Crohn’s disease

adherent-invasive *E. coli*, 114

bifidobacteria, 86

fecal microbiota transplantation (FMT) in, 297–299

*Fusobacterium nucleatum* and, 114

IL-10-secreting *L. lactis*, 337, 366, 367

Crude lysate, definition, 420

Cystic fibrosis, 172

disordered airway clearance, 172

microbiome studies of, 173

Daptomycin, antibiotic resistance, 313

Delzenne, Nathalie, 468

Device, definition, 354

d’Hérelle, Félix, 432, 433

Diagnostic gut bacteria, definition, 354

Diarrhea

bifidobacteria for antibiotic-associated, 84

*Clostridium difficile*-associated, 84

Dietary fiber, gastrointestinal microbiome and, 457–458
DNA damage and repair, colorectal cancer development, 117
Dong Jin dynasty, 292
Driver-passenger hypothesis
development of colorectal cancer, 114–115
schematic, 113
Drug factory probiotic
definition, 354
design, 335, 340
Lactococcus lactis, 335, 336
Dysbiosis
COPD exacerbations, 171
malnutrition, 131–132
nonalcoholic steatohepatitis and, 192–193
vaginal microbiome, 156
Economics, phage therapy, 441–442
Eikenella, 236
Eikenella corrodens, 21
Eiseman, Ben, 292
Eliava Phage Therapy Center, 438
Endotoxin definition, 420
Energy metabolism. See also Nutrition
studying germfree mice, 132–133
Engineered gut bacteria, 333–334
bioreactors, 352
classes of, 334
comparison of development process, 335
components to construct, 347
diagnostic gut bacteria, 336
drug factory probiotic, 336
effects of, 336, 342–343
experimental validation, 352–353
genetically encoded sensors, 338–339
ngenetically encoded therapeutic actuators, 340–341
genetic circuits, 339–340
mouse models, 352–353
natural probiotics, 334, 335
smart probiotics, 334, 337
synthetic biology, 337–338
types of sense, compute and respond behavior, 338
Engineering smart probiotics. See also Probiotics
bioreactors, 352
chassis selection, 341, 344–345
colonization, 341, 344
computation speed, 349
defined media, 352
experimental validation, 352–353
genetic actuators, 351–352
logic circuits, 346–350
memory circuits, 344–345
implementing logic, 346–349
logic circuit outlook, 350
long-term functionality, 350
memory circuits, 350–351
memory circuits outlook, 351
mouse models for, 352–353
outlook for, 353
recombinases, 351
robustness to environmental variability, 349–350
sensor design, 345–346
sensor outlook, 346
sensor performance characteristics, 345–346
sensor portability, 345
toggle switches, 350–351
Enterobacteriaceae
AI-2 quorum-sensing, 11
airway microbiome, 166
alcohol liver disease, 199
asthma, 176
cirrhosis, 202–203
fibrosis, 202
gut microbiota, 192
irritable bowel syndrome (IBS), 301
lung microbiome, 171, 172
microbiota, 77
microcins, 24
nonalcoholic fatty liver disease, 196
short-chain fatty acids, 12
in sigmoid colon and rectum, 111
Enterococcus
antibiotic resistance: ampicillin, 312–313
antibiotic resistance: daptomycin, 313
antibiotic resistance: genetics, 313–314
antibiotic resistance: vancomycin, 313
clinical importance of, 310–312
development of antibiotic resistance, 312–314
direct inhibition by anaerobic commensals, 317–318
direct inhibition by commensal enterococci, 318
diversity in genomic composition and habitats, 314–316
fecal microbiota transplantation and probiotics as treatment, 319–320
habitats, 315–316
indirect inhibition through innate immune defense, 317
indirect inhibition through intestinal barrier maintenance, 317
infections, 310–311
interactions with intestinal microbiome, 316–320
lactic acid, 19
occurrence in diverse environments, 309–310
population genetics, 314–315
probiotics, 220, 318, 319
transmission and sources of infectious, 311
treatment of, 311–312
vitamin K, 17
Enterococcus faecalis, 309–310
bacteriocins, 23, 24
growth of, 151
gut colonization by, 117
Enterococcus faecalis (continued)
hydrogen peroxide, 20
lactic acid, 20
phage against, 426
reutericyclin, 27

Enterococcus faecium, 23, 309–310
Enzybiotics, bacteriophage-derived endolysins, 395, 397–398
Epithelial cells, 7
Erysipelotrichaeae, undernutrition, 140
Erysipelotrichia, steatosis, 192
Escherichia
gut microbiota, 192
nonalcoholic fatty liver disease, 196
probiotics, 220
undernourished children, 138
Escherichia coli
alpha-bug model, 112
antagonizing Clostridium difficile, 279
bacteriocins, 25, 396
colibactin-producing, 85
diarrhea, 166
fecal microbiota transplantation, 302
growth of, 151
hydrogen peroxide, 20–21
lactic acid, 20
osteoporosis, 224
phage therapy, 428
riboflavin (vitamin B2), 15
strain selection, 390
Escherichia coli Nissle 1917 strain, 390, 409
Escherichia coli O157
acetate, 13
polyamines, 8
probiotics, 4
propionate, 14
tryptophan and indole, 9–10
Eubacterium, 4, 456
Eubacterium hallii, 14
Eubacterium lentum, 17
Eubacterium rectale, 14, 460
European Food Safety Authority (EFSA), 49, 79, 364
European Society for Microbiology and Infectious Disease (ESCMID), 297
Exopolysaccharide
bifidobacterial molecules, 77
production in Lactobacillus, 52–53
Exponential Biotherapies, Inc., 427
Faecalibacterium spp., 3, 456
commensals, 4
NASH patients, 192
Faecalibacterium prausnitzii
gene diversity, 136
microbiota, 77, 111
prebiotics, 120, 469
propionate, 14
Fecal microbiota transfer, alcohol liver disease, 201
Fecal microbiota transplantation (FMT). See also Clostridium difficile
administration of solution, 294–295
alternatives to, 279–281
Clostridium difficile infection treatment, 275, 277–281, 296–297
donors, 277–278, 292–294
history of, 292
in inflammatory bowel disease (IBD), 297–299
in intestinal colonization by multidrug-resistant pathogens, 301–302
in irritable bowel syndrome (IBS), 301
in metabolic disease, 299–301
practical guidelines, 292–296
preparation of sample, 294
recipients, 278
recolonization of gastrointestinal tract after, 279
results in severely ill patients, 278
route of administration, 278–279
safety, 295–296
treatment for vancomycin-resistant enterococci (VRE), 319–320
as treatment for VRE colonization, 319–320
variables influencing success of, 277–279
Fermentable dietary fiber, gastrointestinal microbiome and, 457–458
Fibrosis
advanced liver disease, 187, 201–202
histology of liver, 188
Fidaxomicin, 273, 275, 296
Firmicutes, 49
alcohol liver disease, 199
colonic microbiota, 296
gastrointestinal tract, 279
gut microbiota, 12, 192, 291
lung microbiome, 168, 171, 172
nonalcoholic fatty liver disease, 192
propionate, 13, 14
undernourished children, 138
Western-style diet, 110
Flavonifractor, gut microbiota, 192
Folates, 16
Food, Drug and Cosmetic Act, 411
Food and Agriculture Organization (FAO), 78, 220, 241
Food and Drug Administration (FDA), 410, 411–412, 428, 458
Food-grade lactobacilli
altering probiotic immune-modulatory profile, 394–395
as antimicrobial production factories to alter microbiota, 395
as chassis for tailored probiotics, 394–400
CRISPR-based antimicrobials, 398, 400
enhancing native antimicrobial activity, 396–397
enzyliotics, 395, 397–398
future perspectives, 400
genetic diversity for strain selection, 391
probiotic features of Lactobacillus, 391–392
repurposing CRISPR-Cas systems as antimicrobials, 399
selection of strains, 390–392
Fractobacillus, 51, 64
Fructooligosaccharides, colorectal cancer treatment, 119
Fusobacteria, lung microbiome, 171
Fusobacterium
  airway microbiome, 162
  periodontitis, 240
Fusobacterium nucleatum
  colorectal cancer tissues, 114–115
  Crohn’s disease, 114
  genotoxic bacteria, 85
  hydrogen peroxide, 21
  plaque in mouth, 116
Fusobacterium varium, polyamines, 9
Galactooligosaccharides (GOS), colorectal cancer treatment, 119
Gammaproteobacteria
  gut microbiome, 173
  steatosis, 192
Gardnerella vaginalis
  hydrogen peroxide, 21
  vaginal pathogen, 57, 150, 153
Gastroesophageal reflux disease (GERD), 166–167
Gastrointestinal microbiome
  assessing efficacy of nondigestible fermented carbohydrates (NDFCs) in, 469–471
  categories of nondigestible carbohydrates (NDCs), 459
  and chronic noncommunicable diseases, 453–455
  elucidating exact mechanisms of NDFCs in, 471
  fermentable dietary fiber and, 457–458
  future directions for NDFCs, 469–471
  glucose and lipid metabolism, 465–466
  health effects of NDFCs, 468–469
  healthy and diseased, 164
  human diet, 454–455, 471–472
  immunoregulation, 466
  impact of NDFCs on function of, 462–463
  mechanisms for NDFC metabolism, 464, 465
  microbiota-accessible carbohydrates (MACs), 458–460
  modulation of, 455–460
  modulation of microbiota composition and diversity, 460–462
  physiological effects of NDFCs on host, 463–467
  prebiotics and, 455–457
  regulation of satiety, 465
  systemic inflammation, 466–467
Gastrointestinal tract, 3–4
  AI-2 quorum-sensing, 11–12
bifidobacteria, 74, 81
genomic diversity of enterococcal strains, 315–316
genus Enterococcus in, 309–310
normal colonic microbiota, 109–111
  resisting Clostridium difficile infection, 276
Ge Dong, 292
Gemella
  colorectal cancer, 115
  lung microbiome, 170
Genetic actuators, 340–341
  colorimetric reporters, 351
  engineered gut bacterium, 347
  fluorescent reporters, 351–352
  luminescent reporters, 351
  nucleic acid reporters, 352
  reporters, 351–352
Genetically encoded sensors, 338–339
Genetically modified organisms (GMOs), 381
Genetically modified probiotics (GMPs)
  perspectives about, 367–368
  preventing and treating human diseases, 365–367
  recombinant technology, 363–364
  use in humans, 367
Genetic circuit, definition, 354
Genetic circuits, 339–340
Genetic engineering. See also Genetically modified probiotics (GMPs)
  probiotic strains, 27–28
Genetic logic circuits
  computation speed, 349
  engineered gut bacterium, 347
  engineering smart probiotics, 346–349
  parts to implement logic, 346–349
  robustness to environmental variability, 349–350
Genetics, antibiotic resistance of enterococcal strains, 313–314
Genetic tools for manipulating lactobacilli
  alanine racemase as food-grade selection marker, 374
  combining Cas9 genome editing with ssDNA recombineering, 378–380
  cre-lox system for double-crossover integration, 373–374
dsDNA recombineering in L. plantarum, 376
  genome manipulation of lactic acid bacteria (LAB), 375
  impact on safety and efficacy of probiotics, 381
  inducible gene expression, 380–381
  oligonucleotide-mediated recombineering for genome editing, 375–378
  recombineering for genome engineering in LAB, 375, 376
  traditional chromosomal integration strategies, 372–373
  uracil-phosphoribosyltransferase (upp)-based counterselection gene replacement, 374
Genome editing, *Lactobacillus*, 392–394

Genome sequences, *L. gasseri* strains, 59

George Eliava Institute of Bacteriophages, Microbiology and Virology, 433, 439

Goblet cells, 7

*Granulicatella adiacens*, 115

GRAS (Generally Recognized as Safe), 49, 79, 81, 341, 389, 430, 442

Guidelines for Allergic Disease Prevention (GLAD-P), 88

Gut microbes

childhood undernutrition, 138–140

intestinal barrier function and, 135

Gut microbiome, 3–4

Gut microbiota. See also Nutrition
balanced composition, 291–292

causality in diseases, 298

causative role for, in nonalcoholic fatty liver disease, 193

diet influencing, 134, 139, 140

harnessing fitness of healthy, 136

in liver disease, 197

malnutrition-associated metabolic disorders, 133–138

mechanisms linking, to nonalcoholic fatty liver disease, 193, 196–198

milk oligosaccharides for priming, 138–139

nonalcoholic fatty liver disease, 192–199

regulating host energy metabolism, 132–133

stages of nonalcoholic fatty liver disease, 194–195

in undernourished children, 138

Habitats, genomic diversity of enterococcal strains, 315–316

*Haemophilus*

AI-2 quorum-sensing, 11

lung microbiome, 171

oral cavity, 236

*Haemophilus influenzae*

airway microbiome, 166

hydrogen peroxide, 21

lung microbiome, 172

macrophages, 170

rhinovirus, 169

*Helicobacter*, undernourished children, 138

*Helicobacter pylori*, 243

bifidobacteria, 84–85

fucose-containing lipopolysaccharide, 53

gut microbiome, 167

lactic acid, 20

Hepatocellular carcinoma (HCC), 187, 204

Hillman, Jeffrey D., 244

Hipsley, Eben, 457

Histamine, signaling compound, 6–8

HPV infection, 156

Human health, probiotics and, 364–365

Human intestinal microbiota, bifidobacteria as members of, 74–78

Human Microbiome Project, 161, 410

Human microbiota, 409–410

Human skeleton
bone health, 213–214

bone remodeling, 214, 215

osteoclasts and osteoblasts, 214, 216

osteoinmunology, 214

Hydrogen peroxide, 20–21

Immune cells, 7

Immune systems, phages and, 431–432

Immunoregulation, chronic noncommunicable diseases (CNCDs), 467

Inflammatory bowel disease (IBD)

adherent-invasive *E. coli*, 114

bifidobacteria, 81, 86–87

International Scientific Association for Probiotics and Prebiotics (ISAPP), 78, 455–456

Intestinal disorders, bifidobacteria, 81, 84

Intestinal microbiome

colonization resistance mediated by, 316

direct inhibition by anaerobic commensals, 317–318

direct inhibition by commensal enterococci, 318

enterococcal interactions with, 316–320

enterococci as probiotics, 318

indirect inhibition through barrier maintenance, 317

indirect inhibition through innate immune defense, 317

Intestinal microbiota adaptations hypothesis
development of colorectal cancer, 115–116

schematic, 113

Investigational New Drug (IND), 411–412

Irritable bowel syndrome (IBS)
bifidobacteria, 81, 86–87

fecal microbiota transplantation in, 301

*Klebsiella sp.*, 20
growth of, 151

undernourished children, 138

*Klebsiella oxytoca*, 173

*Klebsiella pneumoniae*, 13, 14, 173

Koch, Robert, 132

Kollath, Werner, 364

Kwashiorork, 138, 140

*Lactobacillus*, 3, 111
cirrhosis, 202, 203

lung microbiome, 172

vaginal pathogen, 150

Lactic acid, commensal microbes, 19–20

Lactic acid bacteria (LAB)
food supply and, 389–390

GABA, 8

Hydrogen peroxide, 20–21

Immune cells, 7

Immune systems, phages and, 431–432

Immunoregulation, chronic noncommunicable diseases (CNCDs), 467

Inflammatory bowel disease (IBD)
adherent-invasive *E. coli*, 114

bifidobacteria, 81, 86–87

International Scientific Association for Probiotics and Prebiotics (ISAPP), 78, 455–456

Intestinal disorders, bifidobacteria, 81, 84

Intestinal microbiome
colonization resistance mediated by, 316
direct inhibition by anaerobic commensals, 317–318
direct inhibition by commensal enterococci, 318
enterococcal interactions with, 316–320
enterococci as probiotics, 318
indirect inhibition through barrier maintenance, 317
indirect inhibition through innate immune defense, 317

Intestinal microbiota adaptations hypothesis
development of colorectal cancer, 115–116
schematic, 113
Investigational New Drug (IND), 411–412
Irritable bowel syndrome (IBS)
bifidobacteria, 81, 86–87
fecal microbiota transplantation in, 301
*Klebsiella sp.*, 20
growth of, 151
undernourished children, 138
*Klebsiella oxytoca*, 173
*Klebsiella pneumoniae*, 13, 14, 173
Koch, Robert, 132
Kollath, Werner, 364
Kwashiorork, 138, 140
*Lactobacillus*, 3, 111
cirrhosis, 202, 203
lung microbiome, 172
vaginal pathogen, 150
Lactic acid, commensal microbes, 19–20
Lactic acid bacteria (LAB)
food supply and, 389–390
GABA, 8

Hydrogen peroxide, 20–21

Immune cells, 7

Immune systems, phages and, 431–432

Immunoregulation, chronic noncommunicable diseases (CNCDs), 467

Inflammatory bowel disease (IBD)
adherent-invasive *E. coli*, 114

bifidobacteria, 81, 86–87

International Scientific Association for Probiotics and Prebiotics (ISAPP), 78, 455–456

Intestinal disorders, bifidobacteria, 81, 84

Intestinal microbiome
colonization resistance mediated by, 316
direct inhibition by anaerobic commensals, 317–318
direct inhibition by commensal enterococci, 318
enterococcal interactions with, 316–320
enterococci as probiotics, 318
indirect inhibition through barrier maintenance, 317
indirect inhibition through innate immune defense, 317

Intestinal microbiota adaptations hypothesis
development of colorectal cancer, 115–116
schematic, 113
Investigational New Drug (IND), 411–412
Irritable bowel syndrome (IBS)
bifidobacteria, 81, 86–87
fecal microbiota transplantation in, 301
*Klebsiella sp.*, 20
growth of, 151
undernourished children, 138
*Klebsiella oxytoca*, 173
*Klebsiella pneumoniae*, 13, 14, 173
Koch, Robert, 132
Kollath, Werner, 364
Kwashiorork, 138, 140
*Lactobacillus*, 3, 111
cirrhosis, 202, 203
lung microbiome, 172
vaginal pathogen, 150
Lactic acid, commensal microbes, 19–20
Lactic acid bacteria (LAB)
food supply and, 389–390
GABA, 8
inducible gene expression, 380–381
recombineering for genome engineering, 375, 376
technologies for genome manipulation, 375
therapeutic delivery of, 371–372

Lactobacilli. See also Food-grade lactobacilli
beneficial effects of, 49–51
carbohydrate metabolism, 52
distribution of probiotic-related traits in, 52–53
genetic tools for manipulation of, 372–380
genomic diversity of, 51–52
genomics of surface carbohydrate decoration, 52–53
influencing vaginal health, 152–153
Lactobacillus acidophilus
bacteriocins, 23
description of, 54–55
distribution of probiotic-related traits in, 52–53
engineered, for therapeutic protein expression, 381–383
folates, 16
GABA, 8
probiotic properties, 54
Lactobacillus brevis
description of, 55–56
probiotic properties, 54
Lactobacillus bulgaricus
oral candidiasis, 249
Lactobacillus casei, 318
bacteriocins, 23
description of, 54–55
distribution of probiotic-related traits in, 52–53
genomes, 372
probiotic properties, 54
Lactobacillus coryniformis, vitamin B12, 17
Lactobacillus crispatus
bacteriocins, 23
description of, 54–55
distribution of probiotic-related traits in, 52–53
probiotic properties, 54
Lactobacillus delbrueckii
biofilms, 10
chromosome integration, 372
GABA, 8
lactocepin, 18–19
probiotic properties, 54
Lactobacillus delbrueckii subsp. bulgaricus
description of, 57–59
probiotic properties, 54
Lactobacillus helveticus
bacteriocins, 23
description of, 54–55
distribution of probiotic-related traits in, 52–53
probiotic properties, 54
Lactobacillus iners, 150
Lactobacillus johnsonii
asthma, 173
bacteriocins, 23
description of, 60
folates, 16
probiotic properties, 54
Lactobacillus lactis, engineered probiotics, 381–383
Lactobacillus paracasei

description of, 55–56
GABA, 8
nonalcoholic fatty liver disease, 198
osteoporosis, 224
probiotic properties, 54
smart probiotic chassis, 341
vaginal health, 154

Lactobacillus pentosus, 151

Lactobacillus plantarum

description of, 60–61
dsDNA recombineering in, 375, 376
folates, 16
GABA, 8
genome editing, 392
germfree mice, 133
osteoporosis, 224
probiotic properties, 54
riboflavin (vitamin B2), 15
smart probiotic chassis, 341

Lactobacillus reuteri

bone health, 221, 222
cobalamin, 52
description of, 61–62
osteoporosis, 224, 225
probiotic features, 54, 391–392
recombineering/CRISPR-Cas9 genome engineering in, 379
reuterin, 396
ssDNA recombineering, 375–378
vaginal health, 151, 155

Lactobacillus rhamnosus

bone health, 221, 222
colorectal cancer, 85
description of, 62–63
GABA, 8
histamine, 7
nonalcoholic fatty liver disease, 198
probiotics, 54, 365
secreted proteins p40 and p75, 19
as treatment for vancomycin-resistant enterococci (VRE), 319
vaginal health, 153

Lactobacillus saerimneri, 7

Lactobacillus sake, 22

Lactobacillus sakei

bacteriocins, 23
description of, 63
probiotic properties, 54

Lactobacillus salivarius

bacteriocins, 23, 26, 396
description of, 63–64
folates, 16
probiotic features, 54, 391–392

Lactocepin, 18–19

Lactococcus

airway microbiome, 162, 166
alcohol liver disease, 199
lactic acid, 19
vitamin K, 17

Lactococcus lactis

folates, 16
GABA, 8
genetically modified probiotics (GMPs), 365–367
lantibiotics, 21–22
murine interleukin-10 (IL-10), 390
natural probiotic, 335

Lactococcus reuteri

bacteriocins, 26
folates, 16
reutericyclin, 27
vitamin B12, 17

Lactococcus rhamnosus

Leptotrichia, airway microbiome, 162

Leuconostoc, 19, 51
alcohol liver disease, 199
vitamin K, 17

Leuconostocaceae, 64

Leuconostoc mesenteroides, bacteriocins, 23
Li Shizhen, 292
Listeria innocua, reutericyclin, 27
Listeria ivanovii, hydrogen peroxide, 21
Listeria monocytogenes, 20, 21
bacteriocins, 25, 26
phage treatment of, 419

Live biotherapeutic products (LBPs), 410

chemistry, manufacturing and controls data, 411, 412–414
clinical investigations with, 410–412
current good manufacturing practice (CGMP), 414
genetically modified LBPs, 414
Investigational New Drug (IND) application, 411
product release testing, 413–414
purity, 413
strain characterization, 412–413

Liver diseases. See also Alcoholic liver disease (ALD); Nonalcoholic fatty liver disease (NAFLD)

advanced, 201–204
bifidobacteria, 86
cirrhosis, 189, 202–204
differences between ALD and NAFLD, 189
fibrosis, 188, 189, 201–202
hepatocellular carcinoma (HCC), 204
histology of liver, 188
intestinal microbiota in, 197
metabolic, 187–192
steatosis, 187–188
treatments of ALD, 191–192
treatments of NAFLD, 190–191

Long-chain fatty acids (LCFAs), benefiting host, 14–15
Ludwik Hirszfeld Institute of Immunology and Experimental Therapy, 433
Lung-gut axis, role in disease, 172–173, 175
Lung microbiome
  challenges in evaluating, 163, 165–166
  corticosteroids in, 169–170
  in disease states, 170–172
  future directions in study of, 178–179
  healthy and diseased, 164
  lung-gut axis and its role in disease, 172–173, 175
  selection pressures of lower airway, 167–170
Lung microbiota, 161–162
  host-microbiota interaction in lung, 174
  lower airway, 162, 175–178
  sources of microbial challenge to lower airways, 166–167
  upper respiratory tract, 162–163
LuxI/LuxR-type, quorum-sensing systems, 10–11
Lysate, definition, 420
Lysogen, definition, 420
Lysogeny, definition, 420
Magnetic resonance imaging (MRI), 190
Malnutrition, 131–132. See also Nutrition
  kwashiorkor, 138, 140
Mechnikov, Ilya, 132
Memory circuits
  engineered gut bacterium, 347
  engineering smart probiotics, 350–351
  outlook, 351
  recombinases, 351
  toggle switches, 350–351
Metabolic diseases, fecal microbiota transplantation in, 299–301
Metabolic endotoxemia, concept of, 134–135
Metabolic syndrome, 131, 132
  dysbiosis during, 132
  impact of gut microbiota on malnutrition-associated, 133–138
Metabolites
  bacterial, 4
  benefiting host, 12–19
  lactocepin, 18–19
  long-chain fatty acids (LCFAs), 14–15
  outer membrane vesicles (OMVs), 17–18
  secreted proteins p40 and p75, 19
  serpin, 18
  short-chain fatty acids (SCFAs), 12–14
  vitamins, 15–17
Metchnikoff, Elie, 364, 389–390
Metronidazole, Clostridium difficile infection, 273, 275
Micr Obesity, 133
Microbiota
  gut, associated with colorectal cancer, 111–117
  lactobacilli as antimicrobial factories altering, 395
  milk oligosaccharides and priming, 138–139
  normal colonic, 109–111
  phage impact on nontarget, 426–427
  role in influencing bone, 220
  Microbiota-accessible carbohydrates, 455
  gastrointestinal microbiome and, 458–460, 462
  Microcins, Gram-negative bacteriocins, 24
  Milk oligosaccharides, priming the microbiota, 138–139
  Moraxella catarrhalis, hydrogen peroxide, 21
  Mucosa-associated invariant T (MAIT) cells, 169–170
  Multidrug-resistant pathogens, fecal microbiota transplantation in intestinal colonization by, 301–302
  Multilocus sequence analysis, 61
  Mycobacterium avium, cystic fibrosis, 172
  Mycobacterium tuberculosis, 25, 169
  Mycoplasmataceae, 172
National Institutes of Health, Roadmap for Medical Research, 161
Necrotizing enterocolitis, bifidobacteria, 87
Neisseria
  airway microbiome, 162
  cystic fibrosis, 172
  lung microbiome, 170
Neisseriaceae
  lung microbiome, 172
  polymeric immunoglobulin receptor (pIgR), 169
Neisseria gonorrhoeae, 21
Neisseria meningitidis, 21
Nicolle, Charles, 432
Nonalcoholic fatty liver disease (NAFLD), 187, 454
  causative role for gut microbiota in, 193
  clinical aspects and diagnosis, 189–190
  current treatments, 190–191
  mechanisms linking gut microbiota to, 193, 196–198
  microbiotas associated with stages of, 194–195
  pathogenesis of, 187–189
  prebiotics, 198–199
  probiotics, 198
  symbiotics, 199
  therapeutic approaches, 198–199
Nonalcoholic steatohepatitis (NASH), 187–189
  dysbiosis and, 192–193
  fecal microbiota transplantation (FMT) in, 299–300
  microbiotas associated with, 194–195
Nondigestible carbohydrates (NDCs)
  categories of, 459
  disease associated with diet low in, 454
Nondigestible fermented carbohydrates (NDFCs)
  assessing clinical efficacy of, 469–471
  elucidating exact mechanisms, 471
  gastrointestinal microbiome and, 460–462
Nondigestible fermented carbohydrates (NDFCs) (continued)

glucose and lipid metabolism, 465–466
impact on GI microbiome function, 462–463
metabolism mechanisms, 464
microbiota-mediated health effects of, 468–469
physiological effects on host, 463–467

Nutrition

Akkermansia muciniphila, 137

gut microbes in childhood undernutrition, 138–140
gut microbiota in undernourished children, 138
harnessing fitness of healthy microbiota, 136
Malawian diet, 139–140
malnutrition, 131–132
malnutrition-associated metabolic disorders, 133–138
metabolic endotoxemia, 134–135
microbial gene diversity and host metabolism, 136
next-generation beneficial microorganisms, 137–138
priming microbiota, 138–139
role for gut microbes during obesity, 133–134
role of classical probiotic bacteria, 136–137
Saccharomyces cerevisiae var. boulardii, 137–138

Obesity, role for gut microbes during, 133–134
Odoribacter, gut microbiota, 192

Oenococcus, 51, 64
histamine, 6
lactic acid, 19

OmniLytics, Inc., 419

One-component system (OCS), definition, 354

Oral candidiasis
dysbiotic changes associated with, 239
etiology of, 240–241
limitations of current microbial therapies, 251, 252
microbial therapeutics for, 249
potential benefits of microbial therapies, 251

Oral diseases
applying microbial-based therapies to, 244–249
bacterial replacement therapies, 242–243
caries, 238
dysbiotic changes associated with, 239
ecological aspects of, 238–241
ecological factors mediating oral communities, 236–238
limitations of current microbial therapies, 249–252
oral candidiasis, 240–241
periodontal diseases, 238–240
predatory bacteria and bacteriophages, 243–244
probiotics, 241–242

Oscillibacter, gut microbiota, 192

Osteoporosis, 16. See also Bone health

bone disease, 214, 216–219
established treatments for, 219
primary, 216–217, 224–225
probiotics and bone health in animal models of, 224–225
secondary, 217–218, 225
skeleton, 213–214
treatments, 218–219

Outer membrane vesicles (OMVs), 15–16

Oxygen availability, oral cavity, 237–238

Parabacteroides, 192
Parabacteroides distasonis, 318
Paracolobactrum coliforme, 10
Parvimonas, colorectal cancer, 115
Pasteurella, AI-2 quorum-sensing, 11
Pasteurellaceae, 172, 176
Pediococcus, 51, 64
alcohol liver disease, 199
histamine, 6
lactic acid, 19

Pediococcus acidilactici, 23
Pediococcus pentosaceus, 23
Peptostreptococcus spp., colorectal cancer, 115

Periodontal diseases
dysbiotic changes associated with, 239
etiology of, 238–240
limitations of current microbial therapies, 250–252
microbial therapeutics for, 246–248
potential benefits of microbial therapies, 251

Petrof, Elaine, 280

Phage, definition, 420
Phage therapy, 419, 442–443

100 years of, 432–433
bacterial viruses as therapeutic agents, 421, 424
definition, 420
emergent property pharmacology, 428–430
formulated products, 425–426
further development of, 440–442
glossary of terms, 420–421
immune systems and, 431–432
low phage impact on nontarget microbiota, 426–427
low toxicity in use, 427
low toxicity of well-chosen phages, 425
modern clinical or human experimental, 422–423
modern use of, 437–440
phage-mediated biocontrol, 424
potential caveats, 430–431
preclinical efforts, 440–441
pre-“modern” human use, 433–437
prevalence of phrase in literature, 436
regulation and economics, 441–442
safety trials for, 427–428

Downloaded from www.asmscience.org by
IP: 54.70.40.11
utility of phages, 424–432
Phage Therapy Unit (Poland), 438, 439
PHAST (Phage Search Tool), 398
*Photobacterium*, AI-2 quorum-sensing, 11
Polyamines (PAs), 8–9
Population genetics, genomic diversity of enterococcal strains, 314–315
*Porphyromonadaceae*, 192
*Porphyromonas*, 116
airway microbiota, 167
cystic fibrosis, 172
lung microbiome, 170
*Porphyromonas gingivalis*
hydrogen peroxide, 21
oral community, 237, 250–251
Prebiotics
alcohol liver disease, 201
colostral cancer treatment, 119–120
gastrointestinal microbiome and, 455–457
nonalcoholic fatty liver disease, 198–199
term, 455
Predatory bacteria, 243–244
*Prevotella*
airway microbiota, 167
cystic fibrosis, 172
fibrosis, 201
lung microbiome, 170
lungs of HIV-infected patients, 169
oral cavity, 236
periodontitis, 240
polymeric immunoglobulin receptor (pIgR), 169
subsistence diet, 110
vaginal microbiome, 150
vaginal microbiota, 155
*Prevotella bivia*, 150
*Prevotellaceae*, 172
*Prevotella copri*, 469
*Prevotella intermedia*, 21
Probiotics. See also Engineering smart probiotics;
Genetically modified probiotics (GMPs)
alcohol liver disease, 201
animal models of osteoporosis, 224–225
*bifidobacteria* as, 78–80
*Bifidobacterium* strains in human trials, 82–83
bone health in livestock, 225–226
and bone in nonpathological animal models, 221–224
colostral cancer treatment, 118–119
community, for vaginal microbiota, 155–156
definition, 4, 364
drug factory, 335, 336
effects on bones (animal studies), 222–223
engineered, for therapeutic protein expression, 381–383
enterococci as, 318
*Helicobacter pylori* infection, 85
human health and, 364–365
*in vitro* studies, 226
*in vivo* studies, 226, 228
mechanism of action, 226–228
nonalcoholic fatty liver disease, 198
natural, 334
oral disease, 241–242
primary osteoporosis, 224–225
role in nutrition, 136–137
secondary osteoporosis, 225
smart, 334, 337
treatment for vancomycin-resistant enterococci, 319–320
Professionally lytic phage, definition, 420
Phage, definition, 420
Propionate, short-chain fatty acids (SCFAs), 13–14
*Propionibacterium* spp.
airway microbiome, 166
cirrhosis, 204
oral cavity, 236
probiotics, 4
*Proteobacteria*, 49–50
alcohol liver disease, 199
asthma, 176
colic microbiota, 296
gastrointestinal tract, 279
gut microbiota, 192, 291
lung microbiome, 168, 171, 172
microcins, 24
nitrosation reactions, 111
rhinovirus, 169
*Proteus mirabilis*, 13
*Proteus vulgaris*, 10
*Pseudomonaceae*, 171
*Pseudomonadaceae*, 172
*Pseudomonas*
airway microbiome, 166
cirrhosis, 204
cystic fibrosis, 172
indole metabolites, 10
lung microbiome, 170, 176
vaginal microbiota, 155
*Pseudomonas aeruginosa*
acetate, 13
biofilms, 168, 244
cystic fibrosis, 172
lactic acid, 20
phage therapy, 426, 428, 439
propionate, 14
vaginal health, 154
*Pseudomonas mirabilis*, 20
*Pseudomonas veronii*, 115
Qualified Presumption of Safety (QPS), 49, 79, 81
Quorum-sensing molecules, 10–12, 25–26
Recombinant technology, 363
Regulation, phage therapy, 441–442
<table>
<thead>
<tr>
<th>Term</th>
<th>Page(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retroactivity, definition</td>
<td>354</td>
</tr>
<tr>
<td>Reutericyclin</td>
<td>27</td>
</tr>
<tr>
<td>Reuterin</td>
<td>26–27, 396</td>
</tr>
<tr>
<td>Rhodotorula sp., lactic acid</td>
<td>20</td>
</tr>
<tr>
<td>Roseburia spp.</td>
<td>4, 14</td>
</tr>
<tr>
<td>Rothia</td>
<td></td>
</tr>
<tr>
<td>- airway microbiota, 167</td>
<td></td>
</tr>
<tr>
<td>- cystic fibrosis, 172</td>
<td></td>
</tr>
<tr>
<td>- periodontitis, 240</td>
<td></td>
</tr>
<tr>
<td>Ruminococaceae, 111</td>
<td></td>
</tr>
<tr>
<td>- alcohol liver disease, 201</td>
<td></td>
</tr>
<tr>
<td>- cirrhosis, 203</td>
<td></td>
</tr>
<tr>
<td>Ruminococcus</td>
<td></td>
</tr>
<tr>
<td>- commensals, 4</td>
<td></td>
</tr>
<tr>
<td>- fibrosis, 201</td>
<td></td>
</tr>
<tr>
<td>- polymeric immunoglobulin receptor (pIgR), 169</td>
<td></td>
</tr>
<tr>
<td>Ruminococcus bromii</td>
<td></td>
</tr>
<tr>
<td>Saccharomyces, 220</td>
<td></td>
</tr>
<tr>
<td>Saccharomyces cerevisiae, 20</td>
<td></td>
</tr>
<tr>
<td>- beneficial microorganisms, 137–138</td>
<td></td>
</tr>
<tr>
<td>- probiotics, 241</td>
<td></td>
</tr>
<tr>
<td>Salmonella, 10</td>
<td></td>
</tr>
<tr>
<td>Salmonella enterica, 25</td>
<td></td>
</tr>
<tr>
<td>Salmonella enterica serovar Enteritidis, 243</td>
<td></td>
</tr>
<tr>
<td>Salmonella enterica serovar Paratyphi, 20</td>
<td></td>
</tr>
<tr>
<td>Salmonella enterica serovar Typhimurium lactic acid, 20 propionate, 14 tetrathionate-sensing, 340</td>
<td></td>
</tr>
<tr>
<td>Salmonella enteritidis, 20</td>
<td></td>
</tr>
<tr>
<td>Secreted proteins, p40 and p75, 19</td>
<td></td>
</tr>
<tr>
<td>Selenomonas, periodontitis, 240</td>
<td></td>
</tr>
<tr>
<td>Sensor, definition, 354</td>
<td></td>
</tr>
<tr>
<td>Sensor design</td>
<td></td>
</tr>
<tr>
<td>- engineered gut bacterium, 347</td>
<td></td>
</tr>
<tr>
<td>- engineering smart probiotics, 345–346</td>
<td></td>
</tr>
<tr>
<td>- outlook, 346</td>
<td></td>
</tr>
<tr>
<td>- performance characteristics, 345–346</td>
<td></td>
</tr>
<tr>
<td>- portability, 345</td>
<td></td>
</tr>
<tr>
<td>Seres Therapeutics, 280</td>
<td></td>
</tr>
<tr>
<td>Serpin, 18</td>
<td></td>
</tr>
<tr>
<td>Severe acute malnutrition, 138</td>
<td></td>
</tr>
<tr>
<td>Shigella, 10</td>
<td></td>
</tr>
<tr>
<td>Short-chain fatty acids (SCFAs)</td>
<td></td>
</tr>
<tr>
<td>- acetate, 13</td>
<td></td>
</tr>
<tr>
<td>- benefiting host, 456, 456–457</td>
<td></td>
</tr>
<tr>
<td>- butyrate, 14</td>
<td></td>
</tr>
<tr>
<td>- chronic noncommunicable diseases, 465–466</td>
<td></td>
</tr>
<tr>
<td>- function of GI microbiome, 462–463</td>
<td></td>
</tr>
<tr>
<td>- GI barrier function, 466–467</td>
<td></td>
</tr>
<tr>
<td>- immunoregulatory effect of, 467</td>
<td></td>
</tr>
<tr>
<td>- mechanism in gastrointestinal microbiota, 463, 464 propionate, 13–14 regulation of satiety, 465</td>
<td></td>
</tr>
<tr>
<td>Sialylated bovine milk oligosaccharides (S-BMOs), 139</td>
<td></td>
</tr>
<tr>
<td>Signaling compounds</td>
<td></td>
</tr>
<tr>
<td>- bacteria-bacteria communication, 10–12</td>
<td></td>
</tr>
<tr>
<td>- bacteria-host, 5–10</td>
<td></td>
</tr>
<tr>
<td>Small intestinal bowel overgrowth (SIBO), 193, 196</td>
<td></td>
</tr>
<tr>
<td>Smart probiotic. See also Engineering smart probiotics; Probiotics definition, 354 genetically engineered, 334, 337</td>
<td></td>
</tr>
<tr>
<td>Sphingomonas, 166</td>
<td></td>
</tr>
<tr>
<td>Spirochaetaceae, 172</td>
<td></td>
</tr>
<tr>
<td>Staphage lysate, definition, 420</td>
<td></td>
</tr>
<tr>
<td>Staphylococcus</td>
<td></td>
</tr>
<tr>
<td>- airway microbiome, 162, 166, 167</td>
<td></td>
</tr>
<tr>
<td>- bacteriocins, 23</td>
<td></td>
</tr>
<tr>
<td>- cirrhosis, 204</td>
<td></td>
</tr>
<tr>
<td>Staphylococcus aureus, 20–21</td>
<td></td>
</tr>
<tr>
<td>- cystic fibrosis, 172</td>
<td></td>
</tr>
<tr>
<td>- growth of, 151</td>
<td></td>
</tr>
<tr>
<td>- methicillin-resistant, 302, 424, 437</td>
<td></td>
</tr>
<tr>
<td>- phage therapy, 426, 428, 434</td>
<td></td>
</tr>
<tr>
<td>- reutericyclin, 27</td>
<td></td>
</tr>
<tr>
<td>Staphylococcus epidermidis, 20, 22</td>
<td></td>
</tr>
<tr>
<td>Staphylococcus gallinarum, 22</td>
<td></td>
</tr>
<tr>
<td>Steatosis, histology of liver, 188</td>
<td></td>
</tr>
<tr>
<td>Stenotrophomonas, 172</td>
<td></td>
</tr>
<tr>
<td>Streptococaceae, 202</td>
<td></td>
</tr>
<tr>
<td>Streptococcus</td>
<td></td>
</tr>
<tr>
<td>- airway microbiome, 162, 166, 167</td>
<td></td>
</tr>
<tr>
<td>- cystic fibrosis, 172</td>
<td></td>
</tr>
<tr>
<td>- GI tract, 111</td>
<td></td>
</tr>
<tr>
<td>- lactic acid, 19</td>
<td></td>
</tr>
<tr>
<td>- lactocepin, 19</td>
<td></td>
</tr>
<tr>
<td>- lung microbiome, 170</td>
<td></td>
</tr>
<tr>
<td>- lungs of HIV-infected patients, 169</td>
<td></td>
</tr>
<tr>
<td>- oral cavity, 236</td>
<td></td>
</tr>
<tr>
<td>- oral community, 237</td>
<td></td>
</tr>
<tr>
<td>- vitamin K, 17</td>
<td></td>
</tr>
<tr>
<td>Streptococcus cremoris, 23</td>
<td></td>
</tr>
<tr>
<td>Streptococcus gordoni, 26</td>
<td></td>
</tr>
<tr>
<td>Streptococcus mitis, 26</td>
<td></td>
</tr>
<tr>
<td>Streptococcus mutans</td>
<td></td>
</tr>
<tr>
<td>- bacteriocins, 26</td>
<td></td>
</tr>
<tr>
<td>- dental caries, 238, 250</td>
<td></td>
</tr>
<tr>
<td>- quorum-sensing systems, 11</td>
<td></td>
</tr>
<tr>
<td>Streptococcus oralis, 12</td>
<td></td>
</tr>
<tr>
<td>Streptococcus pneumoniae, 12</td>
<td></td>
</tr>
<tr>
<td>- gut microbiome, 173</td>
<td></td>
</tr>
<tr>
<td>- hydrogen peroxide, 21</td>
<td></td>
</tr>
<tr>
<td>- lung microbiome, 172</td>
<td></td>
</tr>
<tr>
<td>Streptococcus pyogenes, 20</td>
<td></td>
</tr>
<tr>
<td>Streptococcus salivarius subsp. thermophilus, 364</td>
<td></td>
</tr>
<tr>
<td>Streptococcus sanguinis, 26</td>
<td></td>
</tr>
<tr>
<td>Streptococcus thermophilus</td>
<td></td>
</tr>
<tr>
<td>- antibiotic-associated diarrhea, 84</td>
<td></td>
</tr>
<tr>
<td>- genetically modified probiotics (GMPs), 366</td>
<td></td>
</tr>
</tbody>
</table>
oral candidiasis, 249
riboflavin, 16
Streptomyces cinnamoneus, 22–23
Streptomyces griseoluteus, 23
Succinivibrionaceae, NASH patients, 192
Surface carbohydrate, genomics of, 52–53
Symbiotics, nonalcoholic fatty liver disease, 199
Synthetic biology, engineering discipline, 337–338
Systemic inflammation
barrier function and endotoxemia, 466–467
chronic noncommunicable diseases (CNCDs), 466–467
immunoregulation of CNCDs, 467
Tannerella forsythia, periodontitis, 240
Tanzer, Jason M., 244
Temperate phage, definition, 420
Tetragenococcus, 19
Tissier, Henry, 364
Transduction, definition, 421
Trepheryma whippelii, Whipple’s disease, 169
Two-component system (TCS), definition, 354
Twort, Frederick, 432
Ulcerative colitis
bifidobacteria, 86–87
fecal microbiota transplantation in, 297–299
Undernutrition, 131, 132
alteration of gut microbiota in children, 138
causality and underlying mechanisms, 139
dysbiosis during, 132
gut microbes in childhood, 138–140
gut microbiota and, 140–141
microbial species as prospective therapy against, 139–140
milk oligosaccharides and priming microbiota, 138–139
Uracil-phosphoribosyltransferase (upp)-based
counterselection gene replacement, 374
Ureaplasma, vaginal microbiome, 150
Vaccines, vaginal health, 155
Vaginal microbiome
community probiotics, 155–156
conditions, 149
engineered strains for delivering vaccines, 155
health and cervicovaginal microbiome, 150
lactobacilli protecting host, 150–151, 153–155
mechanisms of beneficial microbes influencing
health, 152–153
metabolome of vaginal bacteria, 154
in reproductive-age women, 153–154
Vagococcus, 19
Vancomycin
antibiotic resistance, 313
Clostridium difficile infection, 273, 275, 302
Vancomycin-resistant enterococci (VRE), 311
development of, 312
fecal microbiota transplantation and probiotics as
treatment, 319–320
Veillonella
airway microbiome, 162
airway microbiota, 167
cystic fibrosis, 172
lung microbiome, 170
lungs of HIV-infected patients, 169
oral cavity, 236
polymeric immunoglobulin receptor (pIgR), 169
vitamin K, 17
Vitamins
benefiting host, 15–17
fat-soluble, 17
folic acid (B9 or M), 16
riboflavin (vitamin B2), 15–16
vitamin B12, 17
vitamin K, 17
water-soluble, 15–17
Weissella, 19, 51, 64
Whipple’s disease, 169
Wolinella recta, 21
World Allergy Organization (WAO), 88
World Health Organization (WHO), 78, 138, 189, 220, 241, 457
Xylooligosaccharides (XOS), colorectal cancer
treatment, 119
Yersinia enterocolitica, 21
Yersinia pseudotuberculosis, 340
Yogurt, probiotic concept, 58
Zinplava (bezlotoxumab), 273