Antibiotic Drug Discovery

New Targets and Molecular Entities

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Preface

The introduction of penicillin 75 years ago ushered in, arguably, the greatest advancement in the history of medicine. Its discovery by Fleming and subsequent demonstration of efficacy and mass production by Florey and others contributed significantly to the Allied war effort saving many thousands of lives. The broad application of penicillin during and after World War II demonstrated the great benefit antibiotics provided the medical community in treating surgical-, wound-, skin- and systemic-based infections. The continued discovery and development of antibiotics throughout the 1950's to the 1970's bolstered the number of new therapeutics available to doctors to treat a wide variety of infections. This golden age of antibiotic discovery resulted in generations of humans that never feared acquiring a life-threatening infection. Indeed, antibiotics performed so well through the later part of the 20th century that many people in the industrialized world have forgotten the significant threat that bacterial infections pose to humans. Infectious disease was the second leading cause of death in the United States prior to World War II and remains the leading cause of death worldwide today (primarily driven by neglected tropical infections in the developing world). Thus, despite the tremendous discovery and innovation in the field of infectious disease medicine over the past seven decades, bacterial infections remain a significant worldwide scourge.

Even with the successes achieved from 1950–2000, the turn of the century has seen a significant increase in antibiotic-resistance and a heightened awareness of the emergent threat. Antibiotic resistance has always existed. Indeed, resistance to penicillin was detected only a few years after its introduction into clinical practice. Yet, this problem is now more severe because of the rise of resistance in pathogenic bacteria and because we are beginning to identify bacteria that are resistant to all currently available classes of

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antibiotics. This is particularly troubling because historically, resistance was dealt with by simply switching to another antibiotic. The rise of multi-drug-resistant organisms renders this method of treatment challenging and risky for clinicians.

How did we get here? There are a multitude of factors that played a role. The previously mentioned success in identifying new antibiotics cultivated hubris in thinking that the infectious microbial world had or could be conquered. Economics also played a major role. Many large pharmaceutical companies exited infectious disease drug discovery as research and development became increasingly expensive, protracted clinical trials slowed development and the expectation by payers and the public that antibiotics should be low cost hindered a return on investment. The scientific community too grew weary of a growing list of failed drug discovery and development campaigns, the lack of novel targets and the feeling that nothing innovative remained to be uncovered in antibiotic drug discovery. Lastly, governments worldwide were slow in appreciating the threat posed by antimicrobial resistance and historically have done little to facilitate the advancement of therapeutics. These contributing factors have stymied investment in and discovery of new therapeutics to meet the emerging unmet need of treating antibiotic-resistant infections.

As a result, in 2017, we have arrived at a point where there are few treatment options for many Gram-negative infections, where methicillin-resistant *Staphylococcus aureus* is more common than susceptible strains and where infections due to *Clostridium difficile* are increasingly drug resistant and mortal. Subsequently, clinicians are being forced to resort to older, less well-tolerated drugs to treat resistant microbes. The global community is rapidly approaching the prospect of drug-resistant bacterial epidemics that will have the potential to claim millions of lives and produce an enormous financial burden on health-care systems worldwide. A second golden age of antibiotic drug discovery is desperately needed.

There have been many recommendations for addressing antibiotic resistance including new stewardship control measures, better hygiene, and new methods to identify at-risk patients. Indeed, several valuable, recent initiatives have been started by the U.S. and European governments and regulators to dramatically speed up and reduce the cost antibiotic drug development and many incentives are now available for these pursuits. However, almost everyone that has sought to address this problem agrees that the long-term solution is discovery and introduction of new antibiotic targets and new chemical matter that leads to novel therapeutics. This book presents the latest advancements to this end. The eight chapters in this book provide an exciting discussion of novel targets in purine and isoprenoid biosynthesis, lipopolysaccharide transport, and biofilm production. Also included are reviews of unique targets in tuberculosis and *Clostridium difficile* infections, narrow spectrum antibiotics, as well as a discussion of a new antibiotic isolated from soil bacteria. The chapters focus on targets

and inhibitors that are not clinically used, but represent new approaches towards the treatment of resistant infections. It is our hope that the reader will draw inspiration from this collection of scientific advancements and join the critical effort to discover and develop the next era of antibiotics. We are certain that without these new innovations, the next 75 years will not be as healthy as the last.

Steven M. Firestine and Troy Lister
Editors

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CHAPTER 1

Treatment of Clostridium difficile *Infections*

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1.1 Background

Clostridium difficile infection (CDI) is a nosocomial disease mainly correlated with antibiotic-associated diarrhea. These infections are caused by *Clostridium difficile*, an anaerobic, rod shaped, gram-positive bacterium that is normally found in the gastrointestinal tract (Figure 1.1).[1]

Approximately 5% of healthy adults, and 50% of newborns are asymptomatic carriers of *C. difficile*.[2] *C. difficile* was originally thought to be a commensal bacterium, but due to the recent boom of antibiotic therapies and advancements, it was quickly recognized that *C. difficile* is the leading cause of hospital-acquired diarrhea worldwide.[3] In the United States alone, there are roughly 500 000 cases of CDI annually, with associated costs estimated to be approximately $4.8 billion.[4]

C. difficile has a unique lifecycle such that it can form metabolically dormant, non-reproductive spores when stressed (Figure 1.2).[5]

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