Preface

Since the advent of microbial genome sequencing and the development of algorithms to compare and annotate genomes, an enormous wealth of information has become available to the scientific community. This information is further extended by technologies such as DNA microarrays that use sequence information to analyze genomic expression patterns, proteomics to analyze the translation of these patterns into protein products, and a variety of methods of functional analysis to determine the ultimate phenotypic manifestation of the genes themselves. The analysis of this treasure trove is far from complete, but initial findings have already revolutionized the field of microbiology. Microbiologists have made strong inroads into utilizing this information for drug discovery, vaccine development, and diagnostics. This information continues to be an integral part of the study of the fundamentals of pathogenesis, how organisms interact with each other and with their host environment, and will undoubtedly point to places where intervention will have a significant positive impact on human health. *Pathogen Genomics: Impact on Human Health* is intended to review recent developments in this unfolding story.

The utility of genomics extends from the smallest viral genomes to larger more complex organisms, including humans. Although significant progress has been made studying diverse collections of microorganisms, including plant pathogens, thermophilic Archaebacteria, and other organisms thriving in extreme environments, the scope of this book has been limited to pathogenic organisms that interact with a human host. Clearly, the genomics of all sequenced human pathogens could not be addressed in a single volume, but rather organisms were chosen to give a balanced presentation of viruses, bacteria, fungi, and protozoa. The goal is to bridge these disciplines and to explore the impact genomics has had on the discovery and choice of drug targets, selection of antigenic determinants for vaccine development, diagnostics, and our understanding of pathogenesis. Common sets of tools, such as genomic comparisons and microarray analysis, are used to explore many of these organisms. The findings from these analyses offer unique insights into the fundamental nature of each pathogen, as well as common strategies adopted by diverse pathogens to be successful in the human host.

Genomic comparisons and computational data mining have been used to identify the metabolic capabilities of specific pathogens and have revealed how

they have adapted to unusual host environments. They have pointed to pathways that are unique to an organism, and have identified pathways that are shared among all prokaryotes, are particular to fungi or protozoa, or are common to all life. The analysis of these data has had a significant impact on the identification and selection of targets for antibacterial, antifungal, and antiparasitic drug discovery, as well as providing candidates for the development of diagnostic tools and vaccines. Some of these findings are reviewed in Chapters 5, 7, 11–14, and 17. Chapter 9 explores the changing nature of epidemiological analysis, from plasmid fingerprinting through sequence-based typing, where advancements in genomic analysis have driven the technological development of new investigative tools for identifying the nature of nosocomial outbreaks.

In silico comparisons of strain-to-strain variations can be used to generate historical genealogies of infectious diseases. In Chapter 6, Behr and Gordon discuss comparisons of genomes of attenuated and virulent strains of organisms such as *Mycobacterium tuberculosis*. These types of analyses are critical to our understanding of the genetic basis of the evolution of virulence, and provide candidate genes whose inactivation may lead to the development of improved live attenuated vaccine strains or may serve as components of subunit vaccines. The use of genomic comparisons for the identification of fungal virulence determinants and vaccine candidates is reviewed in Chapters 15 and 16. Similarly, the identification of proteins involved in the pathogenicity of *Entamoeba histolytica* and *Borrelia burgdorferi*, or with possible utility as vaccine candidates, is explored in Chapters 10 and 18.

Genome analysis using microbial DNA microarrays began with the first eukaryotic genome sequenced, *Saccharomyces cerevisiae (1)*. The yeast arrays have been used extensively for exploring changes in expression profiles resulting from changes in growth conditions, in addition to other microarray applications such as mapping gene cross-over events *(2)*. Microarrays have aided our fundamental understanding of metabolic pathways that are important for antifungal drug discovery, as well as antifungal drug resistance. Chapter 12 reviews microarray analyses of yeast, with particular emphasis on the studies of the effect of inhibitors on ergosterol synthesis in both *Saccharomyces cerevisiae* and *Candida albicans*.

More recently, bacterial arrays have become readily available in the form of hybridization filters (Sigma-Genosys, The Woodlands, TX) for organisms such as *Escherichia coli*, *Helicobacter pylori*, and *Bacillus subtilis*. DNA microarrays containing open reading frames derived by PCR, or oligonucleotides representing these ORFs, continue to be developed and are especially useful in studying pathogenic organisms. One important application of this technology is the examination of the response to a variety of treatments, including antimicrobial drug addition. Chapter 8 reviews the development and utility of bacterial microarray technologies.

Viral microarray technology has taken a two-pronged approach: examination of viral-encoded genes on DNA chips and examination of the host cell

response to viral infection. The goal of both approaches is to determine the full complement of genes that are critical to viral propagation, virulence, or control of latency. Chapters 1, 2, and 3 focus on Herpesviruses, Human Papilloma Virus, and Human Immunodeficiency Virus, exploring the utility of microarrays for the identification of novel antiviral drug targets and analysis of viral/host interactions. An additional chapter in the viral section covers the rational design of gene therapeutics for HIV/AIDS, based upon the sequence of HIV-1 subtypes and identification of useful RNA sites that can be targeted by ribozymes (Chapter 4).

Analysis of microbial genomes has revealed that a significant portion of each genome is of unknown function. Entire operons can be identified that are common to bacterial pathogens, yet the functions of these genes have yet to be elucidated. Through genomics one can identify them and using deletion analysis one can show that they are essential to bacterial survival. Functional genomics can begin to provide clues as to what their role is, thus providing information on how to set up high throughput screens to identify novel classes of inhibitors. Several technologies can be utilized to explore the function of unknown proteins, including the use of protein comparisons to define motifs and domains similar to known proteins and threading algorithms for finding similarities in the 3D structure. Other methods, such as the yeast two-hybrid system, seek to find binding partners that may provide a clue to function. High throughput phenotypic microarrays have also been used to simultaneously test a large number of cellular phenotypes and allow novel functions to be assigned to genes *(3)*. Although it is often important to ascribe a function to a target prior to high throughput screening, several methods have been developed to find ligands that bind to proteins, with the idea that amongst the molecules that bind will be inhibitors of function. These types of screens provide the raw materials for further drug development. Many of these technologies are discussed in Chapters 5, 7, 8, 11, 12, 13, 14, 15, and 16.

As a result of the explosion of pathogen and host genomic information, a new era is at hand. The fundamental nature of target evaluation and drug discovery has been radically changed. The wealth of information available will add significant insights to our knowledge of protein function and pathogen physiology, and the exploitation of these findings for the discovery of novel agents to combat pathogenic organisms will continue in the exciting years ahead.

Karen Joy Shaw, PhD

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