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Peptide Nucleic Acids, Morpholinos and Related Antisense Biomolecules

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of the editors (Dr. Janson) during his leave from Yale University;
and to Dr. Stanley Miller, who first proposed the role
of PNA in prebiotic chemical evolution and the ancient history
of life on Earth, thereby raising the question if the recent
discovery of PNA was in fact a fortuitous rediscovery
of our common pre-DNA, pre-RNA origins.

CONTENTS

Part II
Clinical Applications

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PREFACE

When this book project was first contemplated, some of the molecules and applications discussed in this volume (such as mammalian siRNA) did not yet exist, which speaks to the relative progress in the antisense field and the likelihood that further chemical modifications of existing classes of molecules will lead to even more enhanced and greater use of "gene tools" in the future. The original intention of the publisher was to devote an entire book to Peptide Nucleic Acid (PNA), which was an incipient but fast-growing field. Given the diversity of emerging antisense products, we felt that it would be more profitable to compare and contrast PNA with other available oligonucleotide homologues and to consider areas in which these biomolecules could be profitably applied to clinical and diagnostic applications. Because other books and research articles in the primary literature already provided specific protocols for use of PNA and related compounds, we preferred to take a broader review of the existing literature by some of the same innovators who developed the molecules and associated techniques.

There are currently a wide variety of research tools to choose from in the design of experiments utilizing gene knockdown and gene labeling, and the eight chapters in Part I address comparative strengths and weaknesses of various nucleoside homologues: standard modified DNA oligonucleotides, peptide nucleic acid (PNA), locked nucleic acid (LNA), morpholinos, and small interfering RNA (siRNA). In terms of unique properties, PNA is especially useful in situations where DNA binding affinity and resistance to nucleases is important such as gene-based diagnostics, or where another ligand is to be bound to DNA for site-specific mutagenesis, gene-specific drug delivery, or other demanding applications. Other currently popular molecules such as siRNA, LNA, and morpholinos are all efficient and versatile methods of knockdown for in vivo use, but each has distinct advantages and limitations. Some molecules are limited to acting on the RNA level (e.g., siRNA), while others work on the DNA or RNA level (e.g., LNA, PNA, mopholinos). After an overview of the basic characteristics of each "gene tool," the ten chapters in Part II address specific translational or clinical applications for PNA and related antisense biomolecules, such as anti-tumor or anti-AIDS therapies, gene activation, and gene repair.

The editors have aimed to present a balanced view of the methods available for gene targeting and modification, which will have broad appeal for either the research scientist or gene therapist. In the process we have omitted some techniques which originally appeared to have promise but which have subsequently been cast into serious doubt in terms of their specificity and effectiveness, such as DNA-RNA chimeraplasty. The molecules

discussed in this volume are widely considered to be beyond reproach in terms of their potential utility in the research setting, despite the fact that they are still proving themselves in the laboratory and have yet to enter the clinic. Because the same "gene tools" may not be equally effective in research and in the clinic—indeed, it is quite possible that the opposite will be true—we have aimed to strike a balance between the bench and the bedside.

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