METHODS IN MOLECULAR MEDICINE™

Antisense Therapeutics

Second Edition

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Cover illustration: "The principle of antisense inhibition," Figure 1 from chapter 1, Antisense Therapeutics: *A Promise Waiting to be Fulfilled,* by M. Ian Philips

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Foreword

We are now more than 15 years into a large-scale experiment to determine the viability of antisense technology. The challenges of creating a new pharmacological drug discovery platform are prodigious, requiring sizeable investments, long-term commitment, insight, and perseverance. For antisense technology to progress, advances in understanding the behavior of the receptor, RNA, and the behavior of the drugs, oligonucleotide analogs, were necessary. A new medicinal industry, the medicinal industry of oligonucleotides, had to be invented, and numerous drug development challenges—such as creating efficient manufacturing and analytical processes and formulations—had to be overcome. All of those advances then needed to be focused in drug candidates designed to interact with specific targets and to be effective in patients with specific diseases. This has taken time and a good bit of money and although the progress in the technology has been gratifying, there have, of course, been failures of individual clinical trials and individual drugs along the way.

What have we learned? Antisense technology works. Oligonucleotide analogs with a reasonable drug-dependent property can be synthesized and used to inhibit gene function through a variety of antisense mechanisms. Antisense drugs distribute to a wide range of tissues and reduce the expression of targets in a dose fashion consistent with the pharmaceutics of the drugs. First-generation antisense drugs are sufficient for relatively severe indications and second-generation drugs are performing significantly better. Moreover, these drugs are effective by a wide variety of routes including intravenous, subcutaneous, intradermal, rectal, and aerosol, and progress in oral delivery has been reported. Today numerous clinical trials in a wide range of diseases using a variety of oligonucleotide chemistries and antisense mechanisms are in progress.

In this year alone, positive clinical data in rheumatoid arthritis, diabetes, hyperlipidemia, cancer, and other diseases have been reported.

In this edition of *Antisense Therapeutics*, a number of approaches to antisense and therapeutic areas are discussed, as well as specific diagnostic opportunities. That the breadth of activities presented in this volume is as impressive as it is and yet does not begin to cover all of the work in progress, underscores the range of utility and potential value of antisense technology.

Nevertheless, despite antisense being an accepted tool that has facilitated better understanding of biological systems, much remains to be done before the true potential of the technology for therapeutic purposes can be defined. What this volume emphasizes, however, is that exponential progress in defining the long-term roles and value of antisense-based therapeutics is being made.

We look forward to the continued evolution of the technology.

Stanley T. Crooke, MD, PhD

Preface

This is the second edition of *Antisense Therapeutics*. The first edition was edited by Sudhir Agrawal and published in 1996. At that time there was no therapy based on antisense, but plenty of promise for the highly specific targeting of genes that cause disease. Antisense oligonucleotides were first reported as viral replication inhibitors by Paul Zamecnik and Mary Stephenson in 1978. Although this was excellent work, nothing much happened until new procedures for synthesizing DNA sequences were developed. Once oligonucleotides were easy to make, more and more studies were published in the 1980s, most of which were directed to cells in culture. In the early 1990s antisense oligonucleotides were increasingly tested in vivo. There were many controversies and a great deal of concern about backbone modification of the phosphodiester bridges that link the DNA bases. To protect against breakdown by nucleases in cells or blood, phosphorothioate oligonucleotides were adopted. In 1998 a phosphorothioated antisense agent was the first FDA-approved antisense therapy. Vitravene™, developed by Isis Pharmaceuticals, made antisense therapeutics a reality.

Since then, the complete sequencing of the human genome in April, 2003 has demonstrated the presence of a vast number of targets for antisense oligonucleotides. So we now have thousands of targets, hundreds of preclinical animal studies, and some 20 clinical trials ongoing. Any successful trial with an antisense compound will open a floodgate of new therapies for a panoply of diseases.

This second edition of *Antisense Therapeutics* deals less with the basic science of antisense and more with the actual therapeutic applications. For that reason it is organized into disease states.

I thank the authors for their patience and their strong contributions. Since this book was being edited at a time when I moved from the University of Florida to the University of South Florida, I ended up with two secretaries. I would like to thank Ms. Gayle Butters at the University of Florida and Mr. Eric J. Wheeler at the University of South Florida for their essential help. I am also grateful to Craig Adams at Humana Press for his patience.

M. Ian Phillips, PhD, DSc

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