Antisense beginnings

Liz Fletcher

Antisense Drug Technology: Principles, Strategies and Applications
Edited by Stanley T. Crooke
Marcel Dekker; $225, 916 pp, hardcover
ISBN 0-8247-0566-1, 2001

Over the past decade, antisense technology has weathered many of the trials and tribulations facing any new branch of pharmacology, but it is now coming of age. One antisense drug, Isis Pharmaceuticals' (Carlsbad, CA) Vitravene (used topically to treat cytomegalovirus infections in AIDS patients), is already on the market, and that company's recent multimillion-dollar deal with Eli Lilly heralds renewed interest—indeed, restored confidence—in this new technology.

For those keen to get a bird's eye view of the world of antisense, *Antisense Drug Technology* provide one vantage point. Edited by Stanley Crooke, founder and chief executive officer of Isis Pharmaceuticals and arguably the "father of antisense", the book covers the basics of the science of antisense, its chemistry, and looks at its potential as a source of new medicines and tools for validating disease targets.

Part I of the book eases the reader in with reviews of the technology of antisense, its chemistry, and its role in target validation. One of the earliest problems for antisense was the need to create molecules that were not degraded in the gut, because DNAs survive only for short periods. Consequently, researchers developed phosphorothioate oligonucleotides incorporating changes to the phosphate backbone.

Part II of the book looks at how these modified oligos have behaved as drugs—their pharmacokinetics and pharmacodynamics—and, as it turned out, also their toxicity. Partly, as a result of the less-than-ideal properties of these molecules, chemists sought to create oligonucleotides with varying chemistries, some of which have profiles more suitable for use as human medicines.

In Part III, authors explain the development and application of further chemical modifications such as peptide nucleic acids (PNAs), locked nucleic acid (LNA), and phosporodiamidate morpholino oligomers. A number of chapters in Part III also examine clinical data in support of a role for antisense in the treatment of diseases—from cancers to cardiovascular disease—and their value as experimental tools for the study of other conditions such as inflammation and cardiovascular disease.

As with any attempt to cover a fast-moving area of science, the book will be rather outdated before it reaches the bookshelf, but it should serve as a valuable resource for those interested in how antisense developed to its state today and where it ended up (mostly at Isis Pharmaceuticals, given that around half of the chapters are from Crooke's own staff). Given Isis's domination of the field, perhaps this was unavoidable.

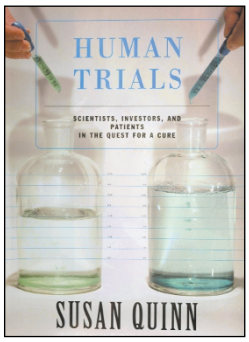
In any case, antisense, it seems, is well on its way to market. In the words of the editor: "Arguably, we are at the end of the beginning of this technology."

Patient waiting

Michael Francisco

Human Trials: Scientists, Investors, and Patients in the Quest for a Cure
By Susan Quinn
Perseus Publishing; $26, 295 pp, hardcover
ISBN 0-7382-0182-0, 2001

Occasionally in the drug-making business, economics and the bottom line overshadow the ultimate aim—patient care and welfare. It is not difficult to imagine how companies that have struggled many years to convert a promising biological discovery into a product, a research project into a commercial venture, and a start-up into an established public firm lose sight of their original altruistic aims, especially when lucrative drug markets finally seem within their grasp.



Human Trials follows the birth of a scientific idea—the application of oral tolerance to the autoimmune diseases multiple sclerosis and rheumatoid arthritis—through the eyes of its primary proponent, Howard Weiner of Brigham and Women's Hospital at Harvard Medical School. From the struggles of his early career, to a small measure of celebrity (a *New York Times* story in 1983) and the resulting backlash from scientific peers, to the decision to start up what would become AutoImmune (Lexington, MA), Weiner and his research are front-and-center throughout. Indeed, quotes from his journals provide running commentary on his endeavors, both personal and professional, and are an illuminating portrait of his motivation and determination.

The story of AutoImmune's formation is eminently readable. Writer Susan Quinn displays obvious affection for the personalities involved in the growth and funding of the company. And similar to a good CEO, she knows how to sell the science. The theory of oral tolerance is explained clearly (repeated administration of a disease-associated antigen eventually ameliorates disease) from its use in ancient times to Chase's advances in the 1940s, and finally to the work for AutoImmune. No doubt, its very elegance was a major factor for investors: AutoImmune at one point had over $40 million in cash to run clinical trials for its leads, Myloral and Colloral. Whether these drugs were high-tech biotechnology drugs is debateable—Myloral was a form of cow myelin purified from brain white matter, Colloral a type II collagen purified from the cartilage of chicken sternums. Not exactly high tech.

In any case, the book best serves in its portrayal of the patients whose hopes rise and fall with the results of the trials. Their interactions with their doctors—and those of the doctors and AutoImmune—tell a story of bravery and optimism, but also of differing goals. What happens to the interests of individual patients in clinical trials? What is the company's responsibility in the design and timing of the trial?

AutoImmune was criticized for moving too quickly into phase III trials of Myloral, their MS drug. Financial considerations certainly played a part in the decision. As one trial director states, "The minute a patient enters a clinical trial they become part of something that's more important than they are." But, one might counter, the minute a company embarks on a clinical trial, the same also applies.