Book review

Clinical Trials of Genetic Therapy with Antisense DNA and DNA Vectors

edited by Eric Wickstrom, Wiley, 1998. $185.00 (xvii + 427 pages, hardback) ISBN 0-8247-0085-6

Coming soon after the first NDA for an antisense compound, *Clinical Trials of Genetic Therapy with Antisense DNA and DNA Vectors* is a timely and comprehensive review of the potential applications of oligonucleotide- and vector-based gene therapy to treat disease. Wickstrom has assembled contributions from 20 research groups, incorporating late-stage preclinical R&D with results from the first clinical trials of genetic therapies. Development and clinical trial data for these compounds are often not easily accessible in the scientific literature, and this book provides both a readable introduction for newcomers and a useful update for those familiar with the field.

The introductory chapter succeeds in defining the technologies, identifying companies with development programs, and reviewing recent clinical progress. Hawkins draws a clear distinction between the use of gene-targeting methods as applied therapeutics and as research tools. Many of the questions raised about the validity of an antisense approach in basic research (*in vitro* uptake, mechanism of action, specificity, etc.) are less relevant to drug discovery, and so Hawkins focuses his discussion on such development issues as toxicity, pharmacokinetics, and efficacy. This chapter describes the advantage of genetic therapy, 'that drugs can be designed in a rational fashion to address the fundamental mechanisms of disease', but also identifies problems encountered in both antisense and gene therapy.

Antisense and viral vector approaches

Antisense and viral vector approaches to genetic therapy are markedly different in concept and in practice. Wickstrom attempts to merge these broad fields; however, a two-volume work separating oligonucleotide ('antisense') from vector-based ('gene therapy') technologies may have been a better approach. Approximately half of the book focuses on gene therapy for indications including leukemia, glioma, and many other cancers, adenosine deaminase deficiency, restenosis, and tumor targeting by HSV thymidine kinase or allogeneic MHC genes. Of particular interest are chapters describing expression, distribution and toxicity of genes delivered using several different systems, including retrovirus, adenovirus, and vaccinia virus vectors and liposome-encapsulated plasmids.

From a drug development perspective, oligonucleotides are closer to acceptance as pharmaceuticals than are gene therapy protocols. This greater potential of synthetic oligonucleotides as drugs is illustrated in the description by Gonzalez and colleagues of Hybridon's GMP facilities, which can support production of >1000 kg of compound per year. Hybridon is clearly the leader in synthesis of phosphorothioate and advanced backbones, and this chapter successfully refutes arguments that therapeutic oligonucleotides will not be commercially viable. With regard to clinical efficacy, Crooke summarizes Isis' excellent progress in developing the phosphorothioate oligonucleotide fomivirsen for CMV retinitis, making it the first such compound with an NDA filed (April 1998). Isis has several clinical trials in progress for other indications, and it is disappointing that Crooke's review of fomivirsen is the company's only contribution to this book.

Regulatory process

A description of the regulatory process involved in clinical trials of genetic therapy is essential in a book of this kind, especially considering that the field has no established track record for similar compounds. Two chapters address this topic – Epstein documents regulation of gene therapy protocols by the FDA's Center for Biologic Evaluations and Research, and Ahn and DeGeorge review oligonucleotide regulation by the Center for Drug Evaluation and Research. Both chapters highlight the fact that regulation of gene therapy clinical trials has not yet become routine, and provide detailed guidelines for sponsors of proposed INDs. Given that some of the most advanced antisense compounds target viral infections, the CDER's contribution would be more comprehensive if it discussed regulatory issues for oligonucleotide therapy of antiviral as well as anticancer indications.

The book emphasizes the rapid progress of genetic therapy from early scepticism to acceptance of oligonucleotides as drugs effective in animal models and in man. Wickstrom's effort meets the need for a book focusing specifically on drug development and clinical trials of new genetic therapies, and is a valuable reference for all researchers in these fields. Genetic therapy has come a long way from just a few years ago, when there was debate over whether the technology would complement conventional drug development or become the next 'cold fusion'. As the first generation of gene-targeting compounds moves towards the market, it is therefore particularly encouraging and informative to read a book dedicated to the clinical issues facing these new drugs for new targets.

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