Although this approach might not obviate the need for getting structural data for targets, Salemme commented that 'good ligand-binding data is amazingly empowering'.

Final thoughts

In summary, the sense of this meeting was that the discipline of structural genomics, especially as it applies to functional characterization and drug discovery applications, has clearly taken root but is still in its infancy. Structural biology, despite many recent technological improvements that have produced quantum leaps of increased speed and decreased cost, is still a complicated and knowledge-intensive science. Thus, the acceleration of the rate of new structure determination is expected to be slower than the explosive growth rate of sequence-based genomic data. Nevertheless, the information-rich nature of protein structures and their high relevance to drug design presages a coming golden age of structure-based drug discovery in the post-genomic world.

Antisense Drug Technology: Principles, Strategies, and Applications

Edited by Stanley T. Crooke, Marcel Dekker, 2001, Price US$225.00, 929 pages, ISBN 0-8247-0566-1

Making drugs from antisense oligonucleotides (ASOs) is a compellingly simple concept which has been difficult to put into practice. Unlike most other drugs (small molecules or biologics) that target a specific protein, ASOs prevent protein synthesis by eliminating the template mRNA. The appeal of antisense lies in its simple structure–activity relationship; knowing only the nucleotide sequence of a drug target, one can, in theory, design a selective and potent inhibitor using simple base-pairing rules. In the early 1990s (the dawn of antisense drug R&D), it was anticipated that ASOs would find a place in the pharmaceutical armamentarium, and might ultimately transform traditional small-molecule drug discovery.

Many large pharmaceutical companies cultivated alliances to develop antisense therapeutics, including: Roche (Basel, Switzerland) and Searle (Skokie, IL, USA) with Hybridon (Cambridge, MA, USA); Ciba-Geigy (Basel, Switzerland) and Boehringer Ingelheim (Ingelheim, Germany) with Isis Pharmaceuticals (Carlsbad, CA, USA); Glaxo Wellcome (now GlaxoSmithKline, Greenford, UK) with Gilead (Foster City, CA, USA); and Baxter (Deerfield, IL, USA) and Johnson & Johnson (New Brunswick, NJ, USA) with Genta (San Diego, CA, USA).

However, the initial promise of those early days has not yet been fulfilled. Only one oligonucleotide-based drug is currently marketed (Isis' Vitravene™ for CMV retinitis), and controversy remains regarding its true mechanism of action in humans (see *Antisense Wars* by Karl A. Thiel available at http://biotech.about.com/cs/antisense/). In addition, Vitravene is given by intravitreal injection, which circumvents problems with delivery, pharmacokinetics, and the safety of ASO drugs administered by more typical routes.

Although antisense has recently become a popular tool to validate targets for small-molecule drug development, several companies continue to champion the use of ASOs as drugs themselves. The clear leader in this group is Isis Pharmaceuticals, whose CEO, Stanley Crooke, has edited the latest of several recent publications reviewing the antisense field. His effort, *Antisense Drug Technology*, comes close to becoming the definitive reference for the development of ASOs as therapeutics.

What is covered?

Antisense Drug Technology is successful at capturing the key topics involved in developing oligonucleotides into drugs. Part I is an excellent review of ASO basics – mechanism of action, antisense design and synthesis, medicinal chemistry and analytical methods. In Part II, the issues of pharmacokinetics and drug safety in animals and humans, and the steps required for preclinical and clinical drug development, are covered in great detail. Reviews of antisense clinical trials are relatively scarce in the primary literature, and so the extensive data and references are a helpful resource.

Part III, with 22 chapters, is a catch-all for many different aspects of antisense R&D. Topics range from alternative mechanisms (triplex DNA and ribozymes), through novel chemistry (second-generation 2′-modified oligonucleotides, locked nucleic acids, peptide nucleic acids and morpholino oligonucleotides), to delivery in different organs, and finally to ASO potential in various disease areas (respiratory, antiviral, anti-inflammatory, and cardiovascular). This section also includes a comprehensive review by Arthur Krieg (University of Iowa, Iowa City, IA, USA) of immunostimulation by oligonucleotides, a common drug effect that has confounded the interpretation of many antisense studies in animal models.

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What is missing?

An opportunity to provide a comprehensive review of antisense drug development was missed because of the book's emphasis on R&D at Isis Pharmaceuticals (42 of 58 contributors). Of the 33 chapters, 18 are authored or co-authored by Isis, 17 by academia, only three by other biotechs [AVI BioPharma (Corvallis, OR, USA), GeneSoft (South San Francisco, CA. USA) and EpiGenesis (Cranbury, NJ, USA)], with just one contribution by 'big pharma' (Dupont; Wilmington, DE, USA).

As a result, Part II (pharmacokinetics and safety of ASOs) covers primarily Isis methods, compounds and data. P. Dan Cook (Isis Pharmaceuticals, Carlsbad, CA, USA; author of Chapter 2) states that 26 oligonucleotides have reached the clinic, with 16 trials still active; however, Brett P. Monia *et al.* (Isis; Chapter 4) show a table with only nine compounds in the clinic. Although Isis clearly appears to be the leader, with five ASO drugs in clinical development, a state-of-the-art reference should address all current clinical trials, regardless of the company involved. Contributions from Hybridon, Gilead, Genta, Lorus (Markham, Ontario, Canada) and others with antisense development experience would also add a different perspective to Isis' clinical approach.

Another notable omission in a 'drug technology' reference work is the lack of coverage of antisense manufacturing processes. How do Isis and others synthesize and quality control the large quantities of antisense compounds needed for clinical trials? This book could also address unusual regulatory aspects of antisense drugs, with a contribution from a government or industry expert in this area. An overview of antisense drugs from the marketing perspective would also be a useful addition – what are the production costs? What are the projected ASO markets for the currently targeted diseases? What issues might arise regarding formulation and dosing? A manufacturing and marketing case study of Vitravene would provide a valuable example from Isis' own pipeline.

Conclusions

Antisense Drug Technology, with its thorough coverage of antisense efficacy and pharmacology in animals and in the clinic, is an essential reference for those contemplating the development of antisense oligonucleotides as human therapeutics. The book updates and greatly expands on earlier works addressing antisense therapy in the clinic [1,2] and is currently the best single source of ASO drug information. The editor has done a commendable job of bringing together the essential aspects of antisense drug technology in one volume, although additional perspectives from other antisense companies would add value. Researchers interested primarily in antisense as a research tool for functional genomics might be better served by other sources of technical information, such as two recent *Methods in Enzymology* volumes [3,4].

Drug development programs currently average about 14 years from lead generation to approval [5]. Isis, in business since only 1989, has already done better, with approval of its first drug (Vitravene) in 1998. In the next few years, we will have the opportunity to critically assess the results of several other clinical trials discussed in this book; the outcomes will ultimately influence future prospects for the entire field of antisense therapeutics.

References

1 Agrawal, S., ed. (1996) *Antisense Therapeutics* (1st edn), Humana Press

2 Wickstrom, E., ed. (1998) *Clinical Trials of Genetic Therapy with Antisense DNA and DNA Vectors* (1st edn), Marcel Dekker

3 Phillips, M.I., ed. (2000) Antisense technology. Part A. In *Methods in Enzymology* (Vol. 313), Academic Press

4 Phillips, M.I., ed. (2000) Antisense technology. Part B. In *Methods in Enzymology* (Vol. 314), Academic Press

5 DiMasi, J.A. (2001) New drug development in the United States from 1963 to 1999. *Clin. Pharmacol. Ther.* 69, 286–296

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