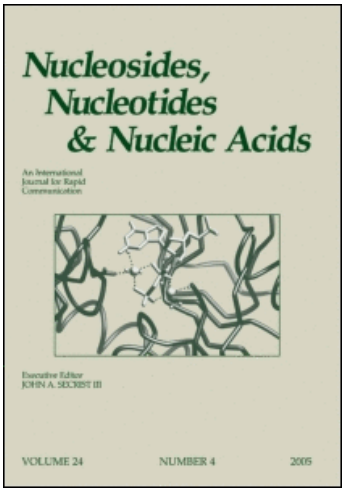
This article was downloaded by:
On: *26 January 2011*
Access details: *Access Details: Free Access*
Publisher *Taylor & Francis*
Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

THE ROLE OF ANTISENSE OLIGONUCLEOTIDES IN THE WAVE OF GENOMIC INFORMATION

Brenda F. Baker[a]
[a] Isis Pharmaceuticals, Inc., Carlsbad, California, U.S.A.

Online publication date: 31 March 2001

To cite this Article Baker, Brenda F.(2001) 'THE ROLE OF ANTISENSE OLIGONUCLEOTIDES IN THE WAVE OF GENOMIC INFORMATION', Nucleosides, Nucleotides and Nucleic Acids, 20: 4, 397 — 399
To link to this Article: DOI: 10.1081/NCN-100002313
URL: http://dx.doi.org/10.1081/NCN-100002313

PLEASE SCROLL DOWN FOR ARTICLE

Full terms and conditions of use: http://www.informaworld.com/terms-and-conditions-of-access.pdf

This article may be used for research, teaching and private study purposes. Any substantial or systematic reproduction, re-distribution, re-selling, loan or sub-licensing, systematic supply or distribution in any form to anyone is expressly forbidden.

The publisher does not give any warranty express or implied or make any representation that the contents will be complete or accurate or up to date. The accuracy of any instructions, formulae and drug doses should be independently verified with primary sources. The publisher shall not be liable for any loss, actions, claims, proceedings, demand or costs or damages whatsoever or howsoever caused arising directly or indirectly in connection with or arising out of the use of this material.

NUCLEOSIDES, NUCLEOTIDES & NUCLEIC ACIDS, 20(4–7), 397–399 (2001)

THE ROLE OF ANTISENSE OLIGONUCLEOTIDES IN THE WAVE OF GENOMIC INFORMATION

Brenda F. Baker

Isis Pharmaceuticals, Inc., 2292 Faraday Avenue,
Carlsbad, California 92008

Downloaded At: 11:58 26 January 2011

ABSTRACT

Technologies which efficiently dissect gene function and validate therapeutic targets are of great value in the post-sequencing era of the human genome project. The antisense oligonucleotide approach can directly use genomic sequence information, in a relatively time and cost effective manner, to define a gene's function and/or validate it as a potential therapeutic target. Antisense oligonucleotide inhibitors of gene expression may be applied to cellular assays (*in vitro*) or animal models of disease (*in vivo*). Information generated by this approach may then direct or supplement traditional drug discovery programs, or support development of the antisense oligonucleotide inhibitor, used to validate the target, as a drug.

Significant progress in the chemical synthesis and biological applications of modified antisense oligonucleotides (ASOs) in the last decade has yielded a technology which has the potential to play a pivotal role in decoding the underlying function of the wave of genetic information now available (1–3). Through direct usage of sequence, this technology maybe used to determine the function of genes in the context of cell processes (4) and pathological conditions (5), as well as identify and validate targets for future therapeutics.

The ASO opportunity is supported by those oligonucleotide modifications which have proven to impart greater nuclease resistance, enhance RNA hybridization, and have suitable bioavailability and pharmacokinetic profiles. These attributes, in conjunction with the development of multiple modes of administration, have allowed broad usage and characterization of this class of compounds *in vitro* (6) and *in vivo* (6–9).

Copyright © 2001 by Marcel Dekker, Inc. www.dekker.com

ORDER REPRINTS

Biological applications are now further facilitated by the ease of synthesis and identification of antisense oligonucleotides that sequence specifically reduce target messenger RNA levels (10). Evolution of automated oligonucleotide synthesis and the process of ASO lead identification has lead to a rapid turn around time (days) from design to application, and consequently the ability to quickly sift through a relatively high volume of sequence space.

The sequence fidelity of the ASO technology allows for regulation of a single gene from a family of genes (11, 12) or a single ribotype (13) from one gene (14, 15). Oligonucleotides which sterically interfere (16) with the processes of mRNA metabolism, *e.g.* splicing (17, 18) and translation (19, 20), provide the opportunity to determine and direct gene function that is regulated at the RNA level.

Downloaded At: 11:58 26 January 2011

REFERENCES

1. http://ncbi.nlm.nigh.gov/Genomes/index.html
2. Pennisi, E. HUMAN GENOME: DOE team sequences three chromosomes. Science **2000**, 288 (5465), 417–419.
3. Dunham, I.; Shimizu, N.; Roe, B.A.; Chissoe, S.; Hunt, A.R.; Collins, J.E.; Bruskiewich, R.; Beare, D.M.; Clamp, M.; Smink, L.J.; Ainscough, R.; Almeida, J.P.; Babbage, A.; Bagguley, C.; Bailey, J.; Barlow, K.; Bates, K.N.; Beasley, O.; Bird, C.P.; Blakey, S.; Bridgeman, A.M.; Buck, D.; Burgess, J.; Burrill, W.D.; O'Brien, K.P.; *et al*. The DNA sequence of human chromosome 22. Nature **1999**, 402 (6761), 489–95.
4. Koller, E.; Gaarde, W.A.; and Monia, B.P. Elucidating cell signaling mechanisms using antisense technology. Trends pharmacol. Sci. **2000**, 21 (4), 142–8.
5. Zhang, H.; Cook, J.; Nickel, J.; Yu, R.; Stecker, K.; Myers, K.; and Dean, N.M. Reduction of Liver Fas expression by an antisense olignucleotide protects mice from fulminant hepatitis. Nat. Biotech. **2000**, 18 (8), 862–67.
6. Lebedeva, I.; Benimetskaya, L.; Stein, C.A.; and Vilenchik, M. Cellular delivery of antisense oligonucleotides. Eur. J. Pharm. Biopharm. **2000**, 50 (1), 101–19.
7. Levin, A.A. A review of issues in the pharmacokinetics and toxicology of phosphorothioate antisense oligonucleotides. Biochem. Biophys. Acta **1999**, 1489 (1), 69–84.
8. Bennett, C.F. Antisense oligonucleotide therapeutics. Exp. Opin. Invest. Drugs **1999**, 8 (3), 237–53.
9. Crooke, S.T. Antisense therapeutics. Biotech. Genet. Eng. Rev. **1998**, 15, 121–57.
10. Bennett, C.F.; and Cowsert, L.M. Antisense oligonucleotides as a tool for gene functionalization and target validation. Biochem. Biophys. Acta **1999**, 148 (1), 19–30.
11. Monia, B.P. First and second-generation antisense inhibitors targeted to human c-*raf* kinase: *in vitro* and *in vivo* Studies. Anti-Cancer Drug Design **1997**, 12 (5), 327–39.
12. McKay, R.A.; Miraglia, L.J.; Cummins, L.L.; Owens, S.R.; Sasmor, H.; and Dean, N.M. Characterization of a potent and specific class of antisense oligonucleotide inibitor of human protein kinase C-α expression. J. Biol. Chem. **1999**, 274 (3), 1715–22.
13. Herbert, A.; and Rich, A. RNA processing and the evolution of eukaryotes. Nat. Genet. **1999**, 21, 265–269.

Copyright © Marcel Dekker, Inc. All rights reserved.

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016

ORDER REPRINTS

14. Karras, J.G.; Mckay, R.A.; Dean, N.M.; and Monia, B.P. Deletion of individual exons and induction of soluble murine interleukin-5 receptor-a chain expression through antisense oligonucleotide-mediated redirection of pre-mRNA splicing. Mol. Pharmacol. **2000**, 58 (2), 380–87.
15. Taylor, J.K.; Zhang, Q.Q.; Wyatt, J.R.; and Dean, N.M. Induction of endogenous Bcl-xS through the control of Bcl-x pre-mRNA splicing by antisense oligonucleotides. Nat. Biotech. **1999**, 17, 1097–1100.
16. Baker, B.F.; and Monia, B.P. Novel mechanisms for antisense-mediated regulation of gene expression. Biochim. Biophys. Acta **1999**, 1489 (1), 3–18.
17. Mercatante, D.; and Kole, R. Modification of alternative splicing pathways as a potential approach to chemotherapy. Pharmacol. Ther. **2000**, 85 (3), 237–43.
18. Taylor, J.K.; and Dean, N.M. Regulation of pre-mRNA splicing by antisense oligonucleotides. Curr. Opin. Drug Discov. **1999**, 2 (2), 147–151.
19. Dias, N.; Dheur, S.; Nielsen, P.E.; Gryaznov, S.; Van Aerschot, A.; Herdewijn, P.; Helene, C.; and Saison-Behmoaras, T.E. Antisense PNA tridecamers targeted to the coding region of Ha-ras mRNA arrest polypeptide chain elongation. J. Mol. Biol. **1999**, 294 (2), 403–16.
20. Baker, B.F.; Lot, S.S.; Condon, T.P.; Cheng-Flournoy, S.; Lesnik, E.A.; Sasmor, H.M.; and Bennett, C.F. 2′-O-(2-Methoxyethyl) modified anti-intercellular adhesion molecule 1 (ICAM-1) oligonucleotides selectively increase the ICAM-1 mRNA level and inhibit formation of the ICAM-1 translation initiation complex in human umbilical vein endothelial cells. J. Biol. Chem. **1997**, 272 (18), 11994–12000.

Downloaded At: 11:58 26 January 2011

Copyright © Marcel Dekker, Inc. All rights reserved.

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016

Downloaded At: 11:58 26 January 2011

Request Permission or Order Reprints Instantly!

Interested in copying and sharing this article? In most cases, U.S. Copyright Law requires that you get permission from the article's rightsholder before using copyrighted content.

All information and materials found in this article, including but not limited to text, trademarks, patents, logos, graphics and images (the "Materials"), are the copyrighted works and other forms of intellectual property of Marcel Dekker, Inc., or its licensors. All rights not expressly granted are reserved.

Get permission to lawfully reproduce and distribute the Materials or order reprints quickly and painlessly. Simply click on the "Request Permission/Reprints Here" link below and follow the instructions. Visit the U.S. Copyright Office for information on Fair Use limitations of U.S. copyright law. Please refer to The Association of American Publishers' (AAP) website for guidelines on Fair Use in the Classroom.

The Materials are for your personal use only and cannot be reformatted, reposted, resold or distributed by electronic means or otherwise without permission from Marcel Dekker, Inc. Marcel Dekker, Inc. grants you the limited right to display the Materials only on your personal computer or personal wireless device, and to copy and download single copies of such Materials provided that any copyright, trademark or other notice appearing on such Materials is also retained by, displayed, copied or downloaded as part of the Materials and is not removed or obscured, and provided you do not edit, modify, alter or enhance the Materials. Please refer to our Website User Agreement for more details.

Order now!

Reprints of this article can also be ordered at

http://www.dekker.com/servlet/product/DOI/101081NCN100002313