OLIGODEOXYNUCLEOTIDES
Antisense Inhibitors of Gene Expression

TOPICS IN MOLECULAR AND STRUCTURAL BIOLOGY

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A hybrid RNA : DNA duplex in the A-form, with one of the oxygens in each phosphodiester group in the DNA strand substituted with sulphur (yellow). This is an energy-minimized structure generated using the BIOGRAF program on a Silicon Graphics Iris workstation (J. Jaroszewski and J. S. Cohen).

Topics in Molecular and Structural Biology
Volume 12

OLIGODEOXYNUCLEOTIDES

Antisense Inhibitors of Gene Expression

Edited by

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MACMILLAN
PRESS
Scientific & Medical

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Softcover reprint of the hardcover 1st edition 1989 978-0-333-49211-6

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First published 1989

Published by
THE MACMILLAN PRESS LTD
Houndmills, Basingstoke, Hampshire RG21 2XS
and London
Companies and representatives
throughout the world

Typeset by Santype International Limited, Salisbury, Wiltshire

British Library Cataloguing in Publication Data

Oligodeoxynucleotides.

1. Gene expression. Inhibitors. Oligodeoxynucleotides

I. Cohen, Jack S. (Jack Sidney), 1938– II. Series

574.87'322

ISSN 0265-4377

ISBN 978-1-349-10871-8

ISBN 978-1-349-10869-5 (eBook)

DOI 10.1007/978-1-349-10869-5

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Foreword

When Jack Cohen kindly asked me whether I would write a Foreword to the book he was editing on oligonucleotides as antisense inhibitors of gene expression, I was somewhat taken aback. But when he gave me a list of the contributors, I was happy to accept, because I realized that I had been following their work in the literature with interest and to the extent that I had been led to have some ideas of my own in the field.

It is clear to me that the time is ripe for this volume. The marvellous work on the natural occurrence of antisense RNA — so recent after all — and the subsequent use of antisense constructs to manipulate gene expression has been of enormous value to molecular biologists. This work stands, in effect, as a bulwark behind the endeavours discussed in this book. It provides the assurance, if it were necessary, that base pairing provides the ultimate in biological specificity and, hence, in targeting. And it works *in vivo*.

Another strand is of course the development of solid-phase oligonucleotide synthesis, making sequences of virtually any length immediately available. But more important (and this may not yet have become apparent to biologists, as users), the development of appropriate chemistry for the synthesis of novel oligonucleotides has been proceeding apace. The first generation of oligomers — those with normal internucleotide linkages — have given rise to more nuclease-resistant analogues, and to these, in turn, can now be appended virtually any sort of functional group. As I write this, in the New Year period, the Christmas tree analogy springs naturally to mind: the third-generation oligomers are or will be festooned with such groups — groups that clutch and cut; hardly a picture of peace and goodwill, but then it depends on the viewpoint, that of the host or that of the intruder.

There are questions that have hardly been touched yet. Will oligomers of proven activity in tissue culture be effective in whole animals and at what

cost? Will they be immunogenic? Will ribo-oligomer chemistry begin to play a significant part? This publication provides a good point from which to view the state of the field and to look to its future directions, whatever these may turn out to be. I commend it heartily.

Cambridge, 1989

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