References and Notes

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Antisense Research

As a participant in the *Nature Medicine* conference "The Art of Antisense" (held on 21 and 22 September 1995 in New Orleans, Louisiana), I was disappointed by the Research News article, "Antisense has growing pains" (27 Oct., p. 575) by Trisha Gura. The meeting was intended to be a forum for discussion of the successes and the challenges in antisense research. Gura emphasized some of the early difficulties and negative results discussed in some of the talks and discussions, yet did not include many of the positive results presented at the conference.

There have been several papers demonstrating specific inhibition of gene expression and corresponding biological activity by oligonucleotides in vitro and in vivo using multiple criteria (*1*). These publications strongly support the idea that oligonucleotides can, in fact, work by an antisense mechanism of action.

Another focus of the conference was the tremendous advances which have been made in the medicinal chemistry of oligonucleotides. Second and third generation oligonucleotide analogs were described which exhibit greater potency, enhanced nuclease stability, altered pharmacokinetic parameters, and potentially decreased toxicity.

What Gura did emphasize was that the proper use of antisense oligonucleotides is a highly demanding and rigorous scientific challenge, as are most scientific endeavors. This view is in contrast to some of the initial approaches taken, when it was thought that simply designing a single oligonucleotide to hybridize to a target gene, ordering the oligonucleotide from the DNA synthesis lab, and adding it to cells or animals would result in the selective inhibition of expression of the targeted gene product. Today, we know that carefully controlled studies with multiple oligonucleotides, both control and antisense compounds, are required to demonstrate that they are producing a biological effect as a result of the antisense mechanism of action. Identification of active antisense oligonucleotides requires screening multiple oligonucleotides designed to hybridize to different regions on the target mRNA to identify optimal target sites on the mRNA. Furthermore, it was strongly recommended that the initial screens should directly examine the expression of the targeted gene product, rather than test oligonucleotides by an indirect biological process such as cell proliferation.

It has been demonstrated that oligonucleotides, like any other pharmacological agent, exhibit both expected pharmacological activity and unanticipated activity. To expect otherwise would be naïve. However, because an oligonucleotide produces an unexpected effect, such as polyclonal activation of B lymphocytes or binding to extracellular matrix proteins, it does not mean that all observed biological activities are the result of nonantisense effects of the oligonucleotide. Similarly, it is unlikely that all biological effects of antisense oligonucleotides can be ascribed to an antisense mechanism of action. As with any other pharmacological agent, it is important to perform careful dose response curves as well as structure activity relationships, to correlate in vitro effects with in vivo effects, and to use caution when interpreting data obtained with such agents.

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