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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State Key Labs in China

I must compliment *Science* on its effort to let its readers know something about sci-

ence in China through the special section on this topic (17 Nov., pp. 1131–1154). The news article, "Government focuses funds, and hopes, on elite teams," by June Kinoshita (p. 1137) describes the state key, or national, laboratories. As with all national laboratories (*1*), the State Key Laboratory of Molecular Oncology (SKLMO) depends on the Cancer Institute for administrative support, but it is not under the direction of the Cancer Institute. The director of a state key laboratory is appointed by the responsible ministry, the Ministry of Health for the SKLMO. On the other hand, the Cancer Institute is under the Chinese Academy of Medical Sciences, which in turn is under the Ministry of Health.

Generally, national laboratory directors are selected primarily according to scientific achievement rather than administrative experience. The director of the Cancer Institute has no power to select or appoint someone who is on the same level as or above himself in the administrative hierarchy. China has a strict retirement age limit for administrative positions, consequently, the "academician" (*2*) mentioned in your article, Wu Min, whom I have the pleasure of knowing, needed no persuasion to step down. The statement that "It's not easy to convince an academician to step down" is not accurate. Wu was well aware of the age limit and, while still the director of SKLMO, he started looking for a successor and approached Sun Zhong Tan, who was then director, long before Dong Zhiwei was appointed director of the Cancer Institute.

When the state key laboratories were originally initiated, they were commonly called the open laboratories. The original idea was to break up the old stagnancy and encourage personnel exchange among scientific institutions. Each state key laboratory must have a certain proportion of external projects to internal projects. I believe the SKLMO is no exception; even if the director wanted to keep the old stagnancy, the SKLMO wouldn't be able to survive the scrutiny it undergoes by a panel of experts every few years. This system has been instrumental in promoting personnel exchange, much more so than the appointment of a new director to one state key laboratory.

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References and Notes

1. For a brief description of state key laboratories in China, see C.-L. Tsou, *FASEB J.* **3**, 2443 (1989).
2. We have members, but not "academicians" in the Chinese Academy of Sciences.

Corrections and Clarifications

In the News & Comment article "Will NASA's research reforms fly?" (17 Nov., p. 1108), the events surrounding an experiment were incorrectly described on page 1110. The article should have said that a subject wearing an apparatus used to create lower-body negative pressure fainted during a test. (The experiment did not involve injection of a drug.)

Letters to the Editor

Letters may be submitted by e-mail (at science_letters@aaas.org), fax (202-289-7562), or regular mail (*Science*, 1333 H Street, NW, Washington, DC 20005, USA). Letters are not routinely acknowledged. Full addresses, signatures, and daytime phone numbers should be included. Letters should be brief (300 words or less) and may be edited for reasons of clarity or space. Letter writers are not consulted before publication.