Assessing antisense

An NDA withdrawal signals another setback, but hope remains for next-generation drugs.

BY DAVID FILMORE

Genasense, an antisense compound developed by Genta with its partner Aventis, recently went from "priority" to off-the-table. In May, following a negative assessment from an FDA advisory committee of outside experts, Genta informed the agency that it was withdrawing its New Drug Application (NDA) for the advanced melanoma candidate.

If approved, Genasense would have been the first new drug for this disease in several decades. It also would have been the first ever systemically delivered antisense therapy. But for the time being, as the two companies meet with the FDA to determine next steps for the program, Genasense represents another in a string of setbacks for antisense therapeutics.

Antisense, a strategy for inhibiting target messenger RNA with modified reverse-sense oligonucleotides, has been on a roller-coaster ride for the past 20 years. Its promise as a highly specific and simple therapeutic approach has received little public validation, along with several high-profile disappointments, since the technology's discovery in the late 1970s. So the progress of Genasense has attracted significant attention.

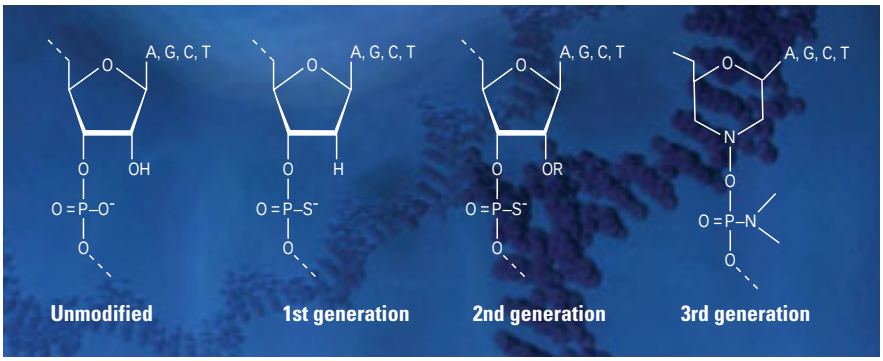
"Because antisense, as a drug class, has had some notable failures in the recent and not so recent past, an approval of Genasense brings the tide in for all antisense," says Alan Timmins, president and COO of AVI BioPharma, a company involved in antisense drug development.

The recent failures include Phase III trial results announced by ISIS Pharmaceuticals in March 2003 for one of its lead candidates, Affinitak, an anticancer therepy co-developed with Eli Lilly.

Another ISIS antisense candidate, alicaforsen, exhibited disappointing Phase III efficacy results in 1999 for treating Crohn's disease. But two restructured Phase III trials are under way for this indication, as are two Phase II trials for alicaforsen treatment of ulcerative colitis.

Currently, one antisense drug is on the market. However, Vitravene, marketed for AIDS-related cytomegalovirus-induced retinitis by Novartis under an ISIS license, is delivered locally (by eye injection) and has rare application and almost negligible sales.

Genasense, on the other hand, offers the possibility of a larger market that could put to rest a major concern regarding antisense—namely a lack of in vivo stability.



Antisense family tree. Genasense contains first-generation ribonucleotide modifications, but other compounds in development have gone through further chemical alterations. R = alkyl or alkoxy group.

The compound, delivered intravenously, inhibits expression of BCL-2, a protein thought to block chemotherapy-induced apoptosis. Genta and Aventis submitted an application in December 2003 for the use of Genasense in combination with a marketed chemotherapy agent (dacarbazine) for treating advanced melanoma.

The submission was largely based on an open-label 771-patient trial that didn't achieve statistical significance for overall survival, its primary end point, but claims statistically significant improvements in the secondary end points: progression-free survival, time to progression, and overall response in patients taking Genasense.

In February, the FDA granted priority review status to the application, which targeted an agency action by June 8. In April, the investigational drug was made available to advanced melanoma patients with no treatment alternatives.

However, at a May 3 meeting of the FDA's Oncologic Drugs Advisory Committee, both the agency and the committee members expressed some serious concerns with how the pivotal trial was run.

"Any claims of improved efficacy based on secondary end points—progression-free survival and antitumor response rate—are questionable because of the open-label nature of the study, missing data, and differences in assessment interval between the two treatment groups," wrote an agency reviewer in briefing material for that meeting.

The committee, which recommends actions to the agency but does not make final rulings, voted that the data submitted by the two companies could not be considered substantial evidence of effectiveness. "There might be something here, but it just isn't clear," noted committee member Professor Stephen George of the Duke University Medical Center.

Timmins and others in the antisense business community were hoping for positive Genasense results to attract greater public—and investor—attention to antisense programs in general. There are now almost 20 other antisense candidates in various stages of clinical development,

almost all accounted for by the four companies AVI BioPharma, Genta, ISIS, and Hybridon, and more in preclinical studies.

At the Roth Capital Partners Growth Stock Conference in February, Hybridon CEO Stephen Seiler told investors that a Genasense approval would "reawaken interest in antisense as a science."

But antisense developers are quick to highlight that the technology has progressed significantly since molecules such as Genasense, Affinitak, and alicaforsen came to the stage.

These candidates are among the most successful of the so-called first-generation antisense compounds, which contain a sulfur modification to the oligonucleotide's phosphate backbone. The phosphorothioate backbone enhances resistance to enzymatic breakdown, but it also causes slightly reduced affinity toward complementary RNA compared with conventional oligonucleotides. In addition, it can lead to non-antisense protein binding.

These compounds, Timmins says, are "potentially good drugs in some very important areas like cancer, where toxicity isn't a huge concern." But, he asserts, they are not a broadly applicable therapeutic strategy.

This attitude is driving much of the current antisense therapy development toward second- and third-generation compounds.

ISIS, for example, while still eager for positive progress from its first-generation candidates, sees its future elsewhere. "We are in the process of converting our pipeline to second-generation antisense drugs," ISIS CEO Stanley Crooke said at the Biotechnology Industry Organization CEO and Investor Conference in February. "This is a fundamental shift."

The company is clinically testing compounds with alkyl modifications to the phosphorothioate structures for arthritis, psoriasis, diabetes, and other conditions.

The second-generation compounds "are at least 10-fold more potent," Crooke said at the conference, "because they are more stable to enzymes. They are also less prone to side effects." Furthermore, he said, the cost of therapy is reduced "nearly 100-fold" because of the lower necessary dosages.

Hybridon previously had first-generation compounds in its pipeline, but it replaced them all with second-generation candidates.

AVI BioPharma, on the other hand, is working on the "third generation." Its candidates contain synthetic backbones with a ring structure completely different from that of natural oligonucleotides. The molecules, unlike other antisense compounds, are uncharged, which, AVI BioPharma believes, further hinders toxic binding interactions and adds extra stability.

AVI's clinical results in March for its candidate AVI-4557 highlighted another important potential advantage of newer antisense drugs: oral delivery. A drug given prior to five daily oral doses of AVI-4557, which targets the expression of a gene involved in drug metabolism, showed a reduced metabolism rate and longer persistence in the body compared with the drug being given alone.

"We believe that is the first demonstration of oral bioefficacy by an antisense drug," Timmins says.

ISIS and Hybridon are also pursuing this mode of delivery. All three companies are investigating other routes as well, such as subcutaneous delivery.

How the Genasense disappointment will affect the long-term momentum of antisense is hard to say. Interested companies, however, hope that second- and third-generation compounds will eventually move it into the mainstream of drug discovery.

"We think RNA will be a site for drug discovery and development equal to proteins in the 21st century," Crooke believes. ■

Clinical antisense studies

Product (generation)	Company	Indication	Phase
Genasense (1st)	Aventis/Genta	15 different cancers	I–III
MG98 (2nd)	Methylgene	Renal cell carcinoma	II
GTI 2040 (1st)	Lorus Therapeutics	Cancer	II
GTI 2051 (1st)	Lorus Therapeutics	Prostate cancer	II
Affinitak (1st)	ISIS	Non-small-cell lung cancer	III
Alicaforsen, parenteral delivery (1st)	ISIS	Crohn's disease	III
Alicaforsen, enema	ISIS	Ulcerative colitis	II
ISIS 14803 (1st)	ISIS	Hepatitis C	II
ISIS 104838 (2nd)	ISIS	Rheumatoid arthritis, psoriasis	II
ISIS 113715 (2nd)	ISIS	Diabetes	II
ISIS 301012 (2nd)	ISIS	Cardiovascular	I
ISIS 112989 (2nd)	ISIS/OncoGenex Technologies	Cancer	II
ISIS 107248 (2nd)	ISIS/Antisense Therapeutics	Multiple sclerosis	II
GEM 231 (2nd)	Hybridon	Cancer	I/II
GEM 92 (2nd)	Hybridon	HIV	I
GEM 640/ AEG35156 (2nd)	Hybridon/Aegera	Cancer	I
Resten-NG (3rd)	AVI BioPharma	Restenosis	II
Oncomyc-NG (3rd)	AVI BioPharma	Lymphoma, prostate cancer	I/II
AVI-4020 (3rd)	AVI BioPharma	West Nile virus	I
AVI-4557 (3rd)	AVI BioPharma	Drug metabolism	I/II
AVI-4126 (3rd)	AVI BioPharma	Polycystic kidney disease	I/II