Reverse Logic

Smart drugs target HIV and a herpesvirus

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Soon after Lewis Carroll's Alice stepped through the looking glass, she stumbled upon a poem called "Jabberwocky," written in a seemingly obscure language. After puzzling over it, she declared, "Why, it's a Looking-glass book, of course! And, if I hold it up to a glass, the words will all go the right way again."

Today's molecular chemists are tinkering with a similar kind of reverse logic to build a more rational drug. Instead of letters of the alphabet, these chemists string together nucleotides, the building blocks of nucleic acids. And instead of stacking these blocks in their "sensible" order, they build a sequence of nucleotides that is the mirror image of a target nucleic acid — in this case, messenger RNA.

The resulting antisense compounds shut down the cellular factory churning out a disease-causing protein.

"This is a whole new class of chemicals," declares David J. Ecker, vice president of biology for Isis Pharmaceuticals in Carlsbad, Calif.

The promise of antisense drugs lies in the theory that they work on a specific target disease without causing significant side effects. For all their potential and the enthusiasm they have generated, however, neither the mechanism nor the safety of such drugs has been proved.

Although researchers have been conducting laboratory and animal tests of antisense compounds for about a decade, clinical data are just starting to roll in at scientific meetings.

At the Teratology Society's annual meeting held in June at Las Croabas, Puerto Rico, Ecker reported preliminary results from a human test of an antisense drug aimed at cytomegalovirus (CMV), a type of herpesvirus that can cause a vision-threatening eye infection for AIDS patients. Next week, Ecker's colleague, Alan G. Palestine of Georgetown University in Washington, D.C., will update those promising results at the Tenth International Conference on AIDS in Yokohama, Japan.

Also at the AIDS meeting, Sudhir Agrawal, chief scientific officer of Hybridon, a biotechnology company in Worcester, Mass., will describe his team's early data on human trials with another antisense drug — one that attacks HIV, the virus that causes AIDS.

So do these compounds represent the next generation of wonder drugs? "There just isn't enough information one way or another," says C.A. Stein, an antisense researcher at Columbia University College of Physicians and Surgeons in New York City. But some researchers and drug companies have bet heavily on the future of antisense therapies.

Traditionally, medications have worked by binding to a naturally produced substance, such as a protein, that causes or results in human illness. By tying up that protein, the drug can ameliorate symptoms of disease, says Thomas B. Knudsen of Jefferson Medical College in Philadelphia, who chaired the antisense symposium at the teratology meeting.

Antisense compounds intervene before a disease-associated protein is ever produced (SN: 2/16/91, p.108; 6/10/89, p.360). Despite their name, these compounds make perfect sense. Here's how they work.

Chemists start by synthesizing a short segment of nucleic acid called an oligonucleotide. The sequence of nucleotides in that synthetic molecule complements the sequence in the messenger RNA that is the intended target. Cells use messenger RNA to transmit the genetic code from a gene to a ribosome, a workbench where the cell assembles proteins using RNA as a "blueprint."

What happens when an antisense compound meets its natural opposite? The nucleotides of the messenger RNA and the antisense molecule stick together, much as two pieces of Velcro do. The result: no protein. If the drug engineer has identified the correct illness-producing protein, that genetic knockout punch should lead to a reprieve from symptoms.

HIV infects nearly 1 million people in the United States alone. For them, the drugs of choice remain antiviral agents such as AZT. This drug works by blocking the action of an enzyme required by HIV to replicate, or copy, itself. Such drugs can prolong the lives of people with AIDS, but they don't kill the virus and they often cause serious side effects. What's worse, many people develop resistance to these agents.

Molecular biologists believe that antisense compounds may improve these grim realities of AIDS treatment. They hope such drugs will shut down HIV's ability to spread by silencing the virus at the messenger RNA level.

Hybridon, the first company to test that theory in humans, has developed an antisense AIDS drug called Gem 91. The experimental compound is an oligonucleotide that's been altered to make it resist degradation — which would kill its effectiveness — once it gets inside an HIV-infected cell.

Test-tube studies with this drug showed that dousing cultures of HIV-infected human cells with Gem 91 shut down replication of the virus for more than 80 days. Hybridon's Agrawal and his colleagues reported that advance in the May 1, 1993 PROCEEDINGS of the NATIONAL ACADEMY of SCIENCES.

Such results raise the possibility that antisense compounds will keep HIV at bay, perhaps long enough to be considered a virtual cure. Although antisense drugs don't destroy HIV itself, their ability to cripple viral duplication may give the body's immune system a chance to contain the disease.

Of course, Hybridon has a long way to go to prove the drug works in people. Along with the French governmental agency that studies AIDS, Hybridon has launched clinical trials, giving the experimental drug to 24 people infected with HIV. In addition, Hybridon researchers are working with a team at the University of Alabama at Birmingham, where they're giving the compound to six people with HIV infection.

So far, the drug hasn't triggered any ill effects in people, Agrawal says. Yet when researchers injected a high dose of Gem 91 into the bloodstream of monkeys, some of the animals died. Agrawal says those deaths were due to the high dose of

Gem 91. He points out that people would receive a far lower dose of the drug. Still, the report has some scientists concerned, especially in light of the unbridled enthusiasm surrounding these antisense drugs.

Stein says that complications are sure to surface as the human trials continue. "You can be certain there will be side effects," he says.

HIV isn't the only virus that plagues people with AIDS. Isis Pharmaceuticals has developed another oligonucleotide, this one targeted at CMV. Most healthy people carry this virus, but it's kept in check by the immune system and thus doesn't cause illness. In people with AIDS and other immune-compromising illness, CMV can lead to an inflammation of the lungs or liver. In up to 40 percent of AIDS patients, CMV can cause a blinding infection of the retina, the part of the eye that converts images to electrical impulses before sending them to the brain for processing.

During the early stages of HIV infection, CMV remains latent. However, once HIV has decimated the immune system, CMV starts to spread like wildfire. "CMV just rips up the retina," Ecker says. "When it gets to the key centers of the eye, it destroys vision."

Two federally approved drugs, ganciclovir and foscarnet, fight CMV infection in people with AIDS. However, both drugs produce serious side effects, as does AZT. Thus, some people with AIDS must choose between their HIV-fighting antiviral agent and a drug to prevent blindness.

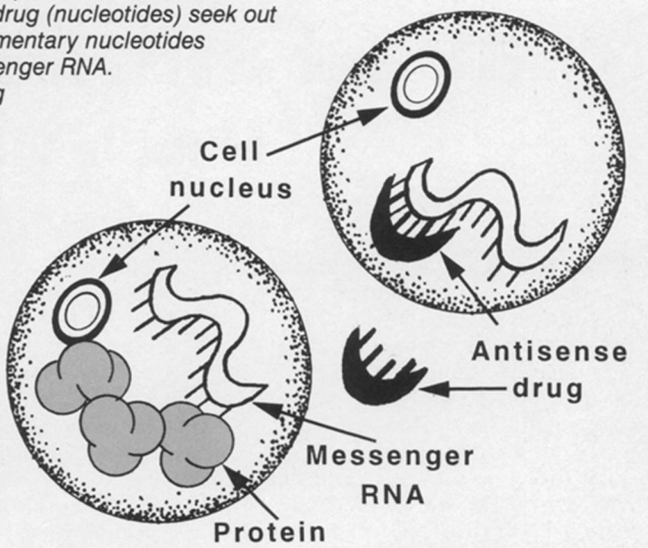
Isis thought it had a better way.

Early research by Isis indicated that an antisense compound would prove effective against CMV if it homed in on one of the messenger RNAs that help produce the series of proteins CMV needs for replication. Isis devised such a compound and gave it to about 12 patients with CMV retinitis. All had AIDS and about a year left to live.

The AIDS virus selectively destroys CD4 T lymphocytes, a type of white blood cell. Healthy people have a CD4 T lymphocyte count of about 600 to 800 cells per cubic millimeter of blood. The average CD4 T lymphocyte count for these patients was 4 per cubic millimeter of blood, a sign of just how debilitated their immune systems had become.

The Isis recruits could no longer benefit from treatment with ganciclovir, foscarnet, or both. Without the experimental treatment, they faced blindness. Although the toxicity study was not designed to prove efficacy, it showed that the drug halted CMV progression in 10 of the 12 people, Ecker says. In some cases, the antisense compound kept the virus at bay for as long as 26 weeks.

"I think this is historic," Ecker says.



An antisense drug (black) is a short piece of nucleic acid that is the mirror image of its target, a segment of messenger RNA (white). The individual units that make up the antisense drug (nucleotides) seek out and stick to the complementary nucleotides that comprise the messenger RNA. Once the antisense drug has reached its target, messenger RNA can't provide the instructions for protein synthesis. As a result, the cell doesn't manufacture the disease-causing protein.

"This is the first time clinical efficacy was shown in patients with an antisense compound," he adds.

So far, the side effects include an inflammation of the eye that researchers can treat with a steroid drug.

Of course, Isis must prove the antisense compound safe and effective in a clinical trial. Right now, its researchers are titrating the dose to see if they can achieve antiviral activity without triggering the inflammation. Once they get the dosage of the drug, they plan to launch a larger trial, this one designed to evaluate efficacy more completely.

"Because [antisense] compounds act through an entirely novel mechanism, we believe they will allow treatment of many conditions for which there are currently no satisfactory therapies," says a 1994 letter from Isis Chief Executive Officer Stanley T. Crooke to stockholders.

There's no shortage of enthusiasm for antisense compounds, because they seem to offer biotechnology firms a cash cow of sorts. Medicinal chemists can, in theory, create a whole batch of antisense molecules. Chemists can add to and subtract from a basic nucleic acid until they hit upon a compound that acts against human disease. Thus, without changing their core chemistry group, companies like Isis can switch from an antisense compound that battles CMV to one that attacks the wart-causing strains of human papillomavirus.

Antisense targets aren't limited to the microbial world. Companies and academic laboratories are rushing to design antisense drugs that may help slow the growth of cancer, ameliorate inflammation, and even slow the symptoms of Alzheimer's disease.

According to proponents, antisense molecules appear much more specific than conventional drugs, which can be thwarted by a wily variant of a disease-causing protein.

"The advantage with antisense is that you're targeting the RNA that codes for a specific protein," Knudsen says. "What we're hoping is to look at a situation where you can pretty much knock out the protein's presence rather than using a drug that simply interacts with that protein."

Other scientists are more skeptical. "The problem with these compounds — it's almost impossible to prove that you have an antisense effect," Stein says. While Isis has shown that some patients with CMV have stabilized, the company lacks solid data that the drug is working via an antisense mechanism, he adds.

That same criticism goes for Hybridon's Gem 91. Indeed, Stein points out, this drug can bind directly to the CD4 receptor, the portal through which HIV enters the T lymphocytes. Gem 91 may work simply by preventing HIV's entry and thus its ability to replicate.

That mechanism probably holds less appeal for scientists and investors, who are looking for a smart drug that does one thing and one thing only. It may be that many different oligonucleotides act in the same way. Thus, a company that patented the latest oligonucleotide would find the field flooded with new products, all of which block the CD4 receptor and thus slow HIV's progress, Stein adds.

That may have little meaning to an AIDS patient who just wants a drug that works. Yet drugs that act in a variety of ways are more likely to trigger unintended side effects. Stein and his colleagues have shown that antisense compounds can bind to certain growth factors in cells. So far, nobody knows the clinical significance of that finding.

For the near future, such adventures with antisense just make the field more challenging, Stein says. Adds Knudsen: "There are still a lot of questions about how these compounds work." □