viral hepatitis specialist and director of Thomas Jefferson Medical College's Jefferson Center for Biomedical Research in Doylestown, Pennsylvania. Both drugs are variants of natural sugars, and they work by gumming up two glycoprotein-processing enzymes in the endoplasmic reticulum (ER), the site where cells add carbohydrates to newly synthesized proteins.

When the hepatitis B virus invades liver cells, it depends on the ER's machinery to reproduce. But Dwek and Block found that when they added the compound *N*-nonyl deoxynojirimycin (NN-DNJ) to human liver cells, glycoprocessing was disrupted to a small but crucial extent. The result: The virus couldn't construct its M envelope protein, a critical coat component. These test tube studies show that "inhibition of as little as 6% of cellular glycoprocessing results in a greater than 99% reduction in the secretion of hepatitis B virus," says Dwek. "There seems to be no effect on the host [cells], but it's a lethal change for the virus."

Dwek and Block believe these drugs cause viral replication to go awry by preventing the envelope proteins from folding into the correct three-dimensional shape. "We know that there are proteins called chaperonins in the ER that grab onto a new protein's sugars and help the protein fold correctly," says Dwek. The two scientists suggest that only a small number of misfolded M proteins disrupt the symmetry characteristic of the hepatitis B virus coat and prevent it from escaping the endoplasmic reticulum.

Studies in woodchucks, the preferred animal model for testing potential hepatitis B drugs, confirmed that NN-DNJ stops viral replication cold, with no detrimental effects on the animal's health. "Better yet, we've been unable to find any mutant viruses that can escape this effect," says Block. "That's one big advantage of targeting a host enzyme and doing so at such a low level."

That could come as welcome news to hepatitis B patients, who commonly take a drug called lamivudine. The drug has serious side effects, and in 20% of patients the virus develops at least partial resistance within a year, a figure that rises to 53% after 3 years.

Using the same partial interference approach, Dwek and Block recently developed a second sugar compound, *N*-nonyl deoxygalactojirimycin, that has the same effect on hepatitis C virus in animal tests.

Although this approach has yet to prove itself in humans, a third sugar compound from Dwek's group is well on its way to demonstrating that a subtle adjustment in glycolipid synthesis can benefit at least some patients with Gaucher's disease, one of a class of inherited disorders known as glycolipid storage diseases. Gaucher's disease results from one of many genetic mutations that can either slow or prevent the breakdown of certain glycolipids, which accumulate in storage vesicles and eventually kill cells. Since 1994, Genzyme Therapeutics, headquartered in Cambridge, Massachusetts, has been selling a recombinant form of the enzyme at fault, glucocerebrosidase, under the trade name Cerezyme. The therapy is highly effective, but it requires a 2-hour intravenous infusion as often as three times a week and costs approximately $200,000 a year.

PROFILE

The Best of Both Worlds?

When drug companies search for novel pharmaceuticals, they pay close attention to how well candidate molecules bind to their targets. The tighter the binding, the smaller the amount needed to do the job and, consequently, the cheaper the drug is likely to be. Unfortunately, sugar-based compounds often don't follow this tidy rule of thumb: They typically bind to their targets with numerous weak handholds. They are also poor at crossing cell membranes and are expensive to make. As a result, many drug companies don't bother with them and look instead for more traditional small organic molecules to do the same job. But Ole Hindsgaul thinks sugars have something worth hanging on to.

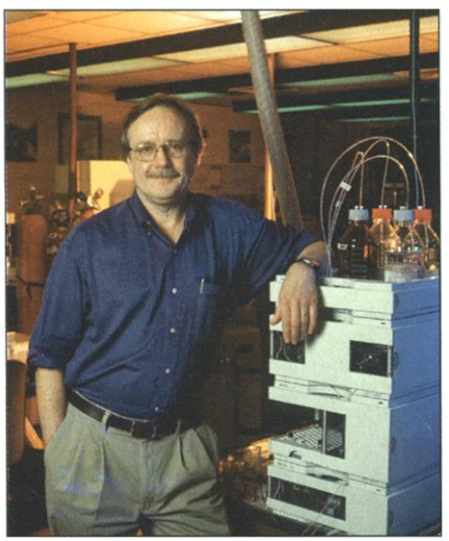
Hindsgaul, a carbohydrate chemist at the University of Alberta in Edmonton, has recently begun making what he calls "carbohybrids," molecules containing a sugar portion linked to other organic groups that are simple to make and typically bind more tightly to protein drug targets. A wide variety of proteins in the body bind oligosaccharides, compounds made up of multiple sugars. And although there are usually many bonds involved, one key sugar group typically embeds itself deeper in the protein than the rest, holding the oligosaccharide in place. "The proteins we're trying to inhibit evolved to bind sugars," says Hindsgaul. "If we give them one of the sugars that fits in the active site, it anchors the compound. As a result, you're more likely to hit only carbohydrate-binding sites."

The strategy is showing early promise. Two years ago, Hindsgaul and his Alberta colleagues devised a high-speed "combinatorial" technique for making hundreds of related carbohybrids. The hybrids were designed to bind to plant proteins that themselves bind oligosaccharides containing the sugar unit galactose. Each hybrid contained a galactose group linked to a different combination of other organic groups, giving it a slightly different shape. Hindsgaul's group tested their compounds against four separate galactose-binding proteins. "Out of the blue, one of these [hybrids] lit up," he says, showing 16-fold better binding ability than a conventional multisugar compound. What's more, the new compound contained groups that make it more lipid friendly, enabling it to cross cell membranes more easily.

The compound's binding ability "is still considered lousy by pharmaceutical standards," says Hindsgaul. "But it's good for sugars." Still, the approach "makes sense," says David Cox, president of Synsorb Biotech, a carbohydrate biotech company in Calgary, Alberta. "By manipulating the organic [groups] to the sugar, you can refine the binding that a sugar has to a protein," he says. If Hindsgaul's group can improve the hybrids' binding still further, says Cox, the molecules could find applications ranging from preventing cancer metastases and tissue rejection to combating viral infections.

Hindsgaul's group is testing further alterations of the hybrids. At a meeting last year, members reported finding a compound that inhibits an enzyme associated with cancer metastasis at a 0.3 micromolar concentration. That's still a lot, about 10-fold higher than the sweet spot for most pharmaceuticals. But the continued improvements mean that carbohybrids are starting to look enticing.

–R.F.S.



Tight grip. Ole Hindsgaul's hybrid molecules bind more strongly to targets than sugars do.

CREDIT: RICHARD SIEMENS