p1269 Safety first: The FDA gets more power to monitor drug safety.

p1272 Genetic 'blue'-print: How we respond to depression may be all in our genes.

p1274 "Parasi-what?": Victoria Hale's OneWorld Health revives interest in tropical diseases.

Researchers look for 'sweet' method to diagnose cancer

Scientists looking for the earliest signs of cancer are tracking changes in the sugary coatings on proteins, which may signal malignancy long before conventional methods can.

The surfaces of many proteins are studded with complex carbohydrates, dubbed glycans. These sugar chains, attached soon after proteins are made, help proteins fold and bind to other molecules. The combination of glycans on a protein, the 'signature', can also tell researchers something about the cell in which the protein originated—for example, whether it is part of a tumor.

"The same protein can be made in a cancer cell and a noncancer cell," says Michael Pierce, director of the University of Georgia's Cancer Center, "but the glyco-signature can be completely different."

Every year, more than half a million people die of cancer in the US alone, making it the second leading cause of death in the country. Better diagnostic tests could go a long way toward improving those numbers.

Some diagnostic tests, such as the prostate-specific antigen test for prostate cancer, rely on detecting proteins siphoned from the blood. These aren't always accurate, however. Doctors routinely find high levels of the antigen even in someone who doesn't have cancer and occasionally miss its presence in someone who does. "It's really a horrible test," Pierce says. Tests that scan for multiple protein markers are more accurate, but none have yet made it to the clinic.

In August, the US National Cancer Institute (NCI) launched a $15.5 million five-year initiative that aims to assess whether these glycan signatures can make diagnostic tests more specific and accurate. The scheme funds seven labs that aim to find and validate glycan markers for melanoma and for breast, ovarian, lung, prostate, colon and pancreatic cancers.

"The time is right," says Margaret Huflejt, who heads one of the labs at the La Jolla–based biotech company Cellexicon. "We have no time to waste, because the earlier the detection, the better the prevention."

Glycans have already proven to be effective markers for liver cancer, a disease so deadly that only about ten percent of affected individuals survive longer than five years. Standard screening relies on imaging techniques such as magnetic resonance imaging or ultrasound. Doctors also test high-risk individuals for a protein marker called alpha-fetoprotein, or AFP, high levels of which can indicate the presence of liver cancer. But the marker lacks specificity: hepatitis, testicular cancer and pregnancy can all boost AFP levels in the blood.

Joseph Nettis / Photo Researchers, Inc

A glycan-based diagnostic test may be around the corner.

In the mid-1990s, Japanese researchers found that they could significantly increase the test's accuracy by looking for AFP-L3, a variant of the protein with an attached sugar called fucose (*N. Engl. J. Med.* **328**, 1802–1806; 1993). Based on this work, Virginia-based Wako Diagnostics developed an assay for people with chronic liver disease—a risk factor for liver cancer—that measures blood levels of AFP-L3. Studies have shown that the test can detect cancer 9–12 months sooner than imaging techniques can. In 2005, the US Food and Drug Administration approved the test for clinical use.

An even better test may be just around the corner. In 2004 Timothy M. Block, professor of immunology at Drexel University, and his colleagues isolated a protein called GP73 from woodchucks with liver cancer. As with AFP-L3, the protein's surface was covered with fucose (*Proc. Natl. Acad. Sci.* **102**, 779–784; 2005).

Both GP73 and fucose-studded GP73 have proven to be reliable markers for liver cancer in people. In a study of more than 350 people, GP73 was about two to three times more sensitive than AFP in detecting cancer, says Anand Mehta, a researcher on the Drexel study (*J. Hepatol.* **43**, 1007–1012; 2005). In a smaller study of 80 people, testing for fucose-studded GP73 boosted the test's sensitivity in detecting liver cancer from 65% to more than 90% (*Mol. Cell Proteomics* **5**, 1957–1967; 2006).

The researchers are testing GP73, with and without fucose, in another 1,000 people, comparing its predictive value with that of AFP and AFP-L3. Scientists have also found potential markers for breast, colon and prostate cancers.

When scientists had to track glycans with radioactive labels, characterizing a single molecule used to be tedious work that took many months. "Now it can be done in a week," notes Sudhir Srivastava, head of the NCI's Cancer Biomarkers Research Group. Mass spectrometers that can quickly sort hundreds of compounds have made it easier to identify glycans in tumor tissue. And new arrays that are printed with synthetic glycans can identify glycan-specific antibodies, a noninvasive test for cancer. "Those have been some huge advances over the past five years," says Pierce.

Despite the field's promise, experts are careful to note that most of the evidence is preliminary. "It's a field that needs to be evaluated," says Laura Beretta, a liver cancer expert at the Fred Hutchinson Cancer Research Center in Seattle. "There's always a lot of excitement at the beginning, but it takes a while to evaluate whether the excitement is based on fact."

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