

Sugar Code-Busters

THE SULFATE GROUPS THAT ADORN SUGAR CHAINS ON CELL SURFACES APPEAR TO HAVE FUNCTIONS BOTH WORKADAY AND PROFOUND.

The chains of sugars that dot the surfaces of cells have been linked to vital processes—such as cell motility, blood clotting, and nerve regeneration—but their precise structures and functions have remained elusive, in large part because of their chemical complexity. Now the secret is out: These chains, called glycosaminoglycans, have a structural code analogous to that of DNA and proteins.

HHMI investigator Linda C. Hsieh-Wilson at the California Institute of Technology and colleagues have taken the first steps toward cracking this code by looking at chondroitin sulfate, a carbohydrate found in the brain and joints—and in many over-the-counter arthritis medications. Chondroitin sulfate consists of two alternating sugars (N-acetylgalactosamine and glucuronic acid) that form the chain's "links." Adding to its complexity are sulfate groups that adorn the chain along its length in a seemingly random fashion.

The conventional view was that the sulfate groups attract water and provide much of the shock-absorbing properties of cartilage. But Hsieh-Wilson wondered if their positions along the sugar backbone could direct the three-dimensional structures of the molecules, thus encoding protein-binding sites and other information.

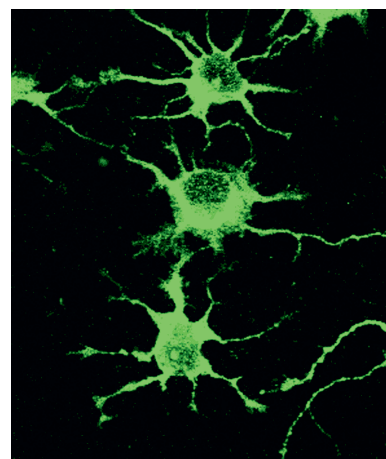
To test this idea, she developed a method to synthesize four molecules of chondroitin sulfate, each with a different pattern of sulfate groups. Hsieh-Wilson then used microarrays to look at the ability of different neuronal growth factors to bind to the synthetic

molecules. She also investigated whether the different forms of chondroitin sulfate would promote neuronal cell growth.

Only one of the four sulfated molecules bound to growth factors and stimulated nerve growth, suggesting that a sequence-specific code on chondroitin sulfate enables protein binding. The work was published in July 2006 in the advance online version of *Nature Chemical Biology*, and appears in the September 2006 print version of the journal.

"This is the first direct evidence that the sulfation patterns of chondroitin sulfate encode specific information," says Hsieh-Wilson. "We're at the early stages of learning the grammar of glycosaminoglycans, but these experiments suggest that they have much to teach us." ■

—JACQUELINE RUTTIMANN



Special arrangements of sulfate groups on certain molecules encourage branching and outgrowth of neurons.

IN BRIEF

Researchers had long assumed that the parasite form that infects red blood cells, called a merozoite, was released from a ruptured liver cell and moved on its own back to the bloodstream. But laboratory studies have shown that the free-moving merozoites are typically destroyed by the liver's resident macrophage immune cells. The movies reveal that the parasites shroud themselves in a liver cell membrane structure called a merozome, allowing them to sneak past macrophages.

The merozomes, which begin as irregular protrusions on the surface of malaria-infected liver cells, were visible in a series of fluorescent images taken at one-second intervals inside living mice. The researchers were able to watch as the protrusions pinched off and carried the parasite into blood vessels. In the studies they also learned that the parasites prevented the dying liver cell from broadcasting a chemical "death signal" that would normally tell a macrophage to ingest it.

SCIENTISTS WATCH HIV TARGET FLIP OUT

Michael F. Summers, an HHMI investigator at the University of Maryland, Baltimore County, and colleagues have identified a new drug target that could defeat HIV's

rapid evolution, the main mechanism of drug resistance. In their July 25, 2006, article in the *Proceedings of the National Academy of Sciences*, the researchers provide evidence for how new HIV particles assemble at the cell membrane before popping out to infect others.

The main HIV protein involved in making viral shells, called Gag, surreptitiously scans the cell's internal signposts and upon finding the right address on the membrane, latches on. Through nuclear magnetic resonance (NMR) studies, the group found that one of the cellular signposts is phosphatidylinositol 4,5-bisphosphate (PIP2). PIP2 binds to a specific end of the Gag protein called the matrix and in a two-step binding process, locks Gag to the cellular membrane.

First, the matrix grabs onto PIP2, which serves as a bridge to the membrane. This binding triggers the matrix to "flip out," exposing a fatty acid tail that drives into the membrane. A tight embrace results: One arm of PIP2 locks deep into the matrix, and the matrix tail juts into the membrane.

Finding a drug that binds PIP2 could block Gag from attaching to the cellular membrane and facilitating assembly of mature HIV virions. Since the segment of the matrix that binds to PIP2 does not rapidly

mutate, the drug might also be immune to new HIV mutations, which have decreased the effectiveness of current anti-viral drugs.

TECHNIQUE YIELDS NEW MOUSE MODEL OF LIVER CANCER

Researchers have greatly shortened the time it takes to create a mouse model of human liver cancer—going from about a year with standard techniques down to about one month with the new approach. Scott W. Lowe, an HHMI investigator at the Cold Spring Harbor Laboratory, and his colleagues described the new model in the June 30, 2006, issue of *Cell*. Unlike traditional mouse models, which involve laboriously creating mutations in the whole mouse and then cross-breeding strains of mice to combine mutations, the new technique begins with the isolation of liver progenitor cells from fetal mice. The researchers can induce precise cancer-causing mutations in the fetal cells and then transplant them into adult mice, where the fetal cells colonize the liver and produce cancers.

The tumors arising in the mice are detected using a genome-wide scanning technique called ROMA (representational oligonucleotide microarray analysis). The researchers say their approach will help