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Bench to Bedside

Cells' Sugar Coating Zaps Cancer

Heparin is an inexpensive "blood-thinning" drug that doctors use to stop blood from clotting. The medicine is widely prescribed to treat dozens of health conditions in which blood clotting can be especially dangerous, such as stroke and many heart disorders. Now, NIGMS grantee **Ram Sasisekharan** of the Massachusetts Institute of Technology in Cambridge has unearthed a brand-new potential use for heparin: treating cancer. Sasisekharan is a biochemist who studies the sugar molecules, or carbohydrates, that coat the surfaces of cells. To investigate the potential importance of a cell's sugar "coat" in the development of cancer, he and his coworkers injected an enzyme called heparinase into mice with tumors. Heparinase is an enzyme that cuts up complex sugars, generating molecules of heparin. The researchers found that one particular heparinase treatment slowed the growth of skin, lung, and prostate tumors in the mice. Surprisingly, however, a chemical cousin of heparinase actually accelerated tumor growth in mice, indicating that slightly different forms of this family of molecules can have very different effects on cell growth and cancer. Heparin and molecules like it cloak the surfaces of nearly all the cells in our bodies, and Sasisekharan suspects that these sugary molecules interact with cancer-controlling proteins circulating in the blood and on the surfaces of other cells. If the findings can be repeated in people, heparin could be put to use quickly, since it is already an FDA-approved medicine and as such has been demonstrated to be safe for human use.

Do the Math

Few would argue that the ability to accurately predict the course of disease outbreaks and other serious health problems affecting millions of people would be worthwhile. Two NIGMS grantees — **Simon Levin** and his group at Princeton University in New Jersey and **Martin Blaser** of New York University in New York City — have used entirely different approaches to mathematically model the behavior of infectious microorganisms that impact large populations of people. In the first case, Joshua Plotkin and Jonathan Dushoff, working with Levin, analyzed the gene sequences of flu strains from the last 16 years and discovered patterns that researchers may be able to use to predict which particular strain of flu will emerge in the coming season. If accurate, such a prediction would be a helpful tool to avoid misery and save many lives by permitting the makers of the following year's flu vaccine to better target the precise variants of flu likely to be the most prevalent. Levin and his coworkers delved into a computer database containing DNA sequences representing 560 samples of different flu viruses. The researchers discovered that the many strains separated naturally into a small number of distinct clusters, and they showed that clustering could be useful in predicting how the flu virus evolves over time. In the second case, infectious disease specialist Blaser teamed up with mathematician Glenn Webb of Vanderbilt University in Nashville to pursue a different line of research addressing another issue of widespread health concern. Blaser, who models the infectious behavior of the ulcer-causing bacterium *Helicobacter pylori*, applied his knowledge to produce a model of how the deadly bacterium *Bacillus*



anthracis could be spread through the U. S. postal system. The researchers simulated the outbreak of mail-borne anthrax in the fall of 2001 and concluded that all the known cases of infection could be traced back to contamination through the mail from only six original envelopes. The researchers also concluded from their mathematical model that the rapid and widespread use of antibiotics probably averted many additional potentially deadly infections from this outbreak.

The Side Effects of a Misspelling

Many people are surprised to learn that medicines may only work properly in a percentage of those who take them. What's more, whether or not people develop side effects — and if they do, which ones they'll get — varies widely. While many factors such as diet, environment, and the amount of exercise a person gets can help account for this variability in drug response, a key determinant is genes. So-called pharmacogenetics research aims to unravel some of the biological reasons why people react so differently to medicines. In recent years, pharmacogenetics scientists have found many examples where a change in one or a few of the DNA "letters" that spell out genes can cause people to have different responses to medicines. For example, NIGMS grantee **Mark Ratain** of the University of Chicago has identified a group of cancer patients who have a bad reaction to a chemotherapy drug called irinotecan, which is used to treat a variety of solid tumors. Ratain and his research team have found that some patients have two extra letters in the gene that instructs the body to make a protein that metabolizes irinotecan and other drugs. Because of this genetic difference, these people have much higher levels of irinotecan than most patients given the same dose. When administered this medicine, patients with extra letters in the gene experienced dramatic drops in their white blood cell counts, making these patients more likely to develop a potentially life-threatening infection. The same patients also experienced severe diarrhea, which can cause dangerous fluid loss in people who are already very sick. Ratain predicts that future genetic screening of patients may help avoid toxic side effects and help determine the precise dose of chemotherapy needed to treat their cancer.

Natural Bacterial Shield Protects the Body

Your body may be better at protecting you from microbial invaders than you thought. Recently, NIGMS grantee **Charles Serhan** of Brigham and Women's Hospital in Boston, Massachusetts, made the surprising observation that naturally occurring molecules in the body that help fight inflammation also appear to protect tissue linings of the mouth, intestines, and airways from infection. While doing experiments to study the roles white blood cells normally play in controlling inflammation, Serhan and his coworker Sean Colgan unexpectedly discovered something new. In the process of policing epithelial

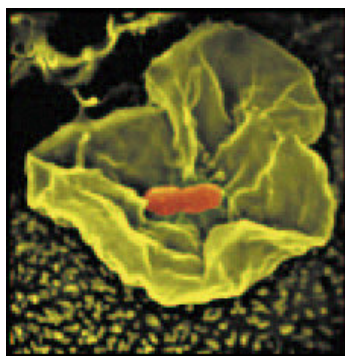


Photo credit: Beth McCormick and James Casanova, Harvard Medical School

cells (the cells that line the organs of the body and skin), white blood cells shoot a chemical signal to the epithelial cells telling them to manufacture a microbe-killing substance, the research team found. This chemical likely protects the cell from a potentially dangerous infection by eliminating bacteria on contact. To verify the observation, the scientists infected epithelial cell cultures growing in plastic lab dishes with the bacterium *Salmonella typhimurium* and then added a chemical that provokes inflammation in the body. In earlier experiments, the researchers showed that in response to the inflammation-prompting substance, epithelial cells boost their production of a "molecular shield" component called BPI. Serhan's research team found

that as BPI levels in the cells increased, more and more *Salmonella* in the culture dishes died, whereas using a "dummy" chemical had no effect. The results are significant in describing a new defense mechanism in the body, but also, as Serhan states, in pointing to new strategies to thwart difficult-to-treat infections of the mouth, intestines, and esophagus.

Stop Cell Death, Help Treat Sepsis?

The body-wide infection called sepsis is the leading cause of death in critically ill patients nationwide, striking 750,000 people every year and killing over 210,000. Sepsis occurs when bacteria leak into the bloodstream, causing widespread damage all over the body. Blood pressure plunges dangerously low, the heart has difficulty pumping enough blood, and body temperature climbs or falls rapidly, in many cases causing multiple organs to fail. In recent years, researchers have come



to realize that the gut, or intestinal tract, plays an important role in sepsis. Scientists have found that after a severe infection or injury, cells in the intestinal lining die off. This form of cell death, called apoptosis, isn't always a bad thing — for example, nerve cells require apoptosis during development to form a healthy brain. However, researchers suspect that blocking apoptosis in the intestines of critically ill patients may help to prevent death from sepsis. NIGMS grantee **Craig Coopersmith** of Washington University in St. Louis, Missouri, reports experiments in mice that suggest this strategy may someday be effective in people. Coopersmith and his coworkers genetically engineered lab mice to produce large amounts in their intestines of a cell-death-blocking protein called bcl-2. The researchers exposed the experimental mice to the bacterium *Pseudomonas aeruginosa*, which can be deadly to people, and discovered that 40 percent of the mice escaped infection and survived, compared to only 4 percent of mice without bcl-2. The results suggest that stopping intestinal cell death may someday be an effective treatment for sepsis.

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