Heard It From a Fly

Think those tiny, pesky flies circling the fruit bowl in your kitchen are simply a nuisance? Think again! Scientists continue to learn secrets about human health from basic research with simple organisms such as insects, worms, mice, and rats. Fruit flies have been a particular favorite for researchers investigating the role of heredity in the formation of tissues and organs. Both insects and people develop according to a genetically determined body plan, and scientists know that many of the genes involved in this process are very similar among animals.

Using fruit flies as a model system, NIGMS grantee **Grace Boekhoff-Falk** of the University of Wisconsin in Madison recently made a fundamental discovery about hearing. She and her co-workers discovered an insect gene nicknamed *spalt* that profoundly affects flies' ability to hear. The scientists found that experimental flies created to lack the *spalt* gene were deaf, as measured by direct tests of the flies' hearing organs located inside their antennae.

Boekhoff-Falk and her team also discovered that the *spalt* gene is nearly identical in flies and people. That means that what she learns about *spalt* in fruit flies may also apply to humans, and her work may help scientists find new approaches to diagnosing certain inherited hearing disorders.

Botulinum Toxin Vaccine

Botulinum toxin (BT) is the single most poisonous substance known, with very small amounts causing paralysis and death. Botulism, the illness caused by this bacterially produced toxin, typically results from eating contaminated food. Cases of botulism are rare, but concerns about the possible use of BT as a bioterrorism agent have brought a new urgency to research in this area. Of special interest is the effect of inhaling the toxin.

NIGMS grantee **Lance Simpson** of Jefferson Medical College in Philadelphia recently discovered how inhaled BT can cause poisoning by traveling from the airways to the bloodstream, where it does widespread damage to the body. Simpson also found that a piece of the BT protein called the heavy chain served as an effective inhaled vaccine in experimental mice. Simpson's work suggests ways to manufacture a human version of the vaccine against this potential bioterrorism weapon.

Although an antitoxin to neutralize BT circulating in the bloodstream is available, quantities of this remedy are too limited to rapidly treat large numbers of people. More importantly, an antitoxin works only in the bloodstream and it cannot enter poisoned nerve cells, reducing its usefulness. A safe and effective inhalation vaccine could get around these problems.

Tracking a Food-Borne Killer

Listeriosis is a serious infection caused by eating food contaminated with the bacterium *Listeria monocytogenes*. While listeriosis infections are rare, the *Listeria* bacterium is deadlier than other notorious microbes, such as *Salmonella* or *E. coli* O157:H7. Listeriosis infections can be caused by eating contaminated meat and dairy products or unwashed raw vegetables.

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Food scientists had thought that *Listeria* outbreaks were unpredictable, occurring more or less at random across the country. But recent evidence from NIGMS grantee **Martin Wiedmann** of Cornell University in Ithaca, New York, suggests otherwise. This past summer, Wiedmann examined bacterial samples from listeriosis victims obtained throughout New York State over a 4-year period. Wiedmann used DNA fingerprinting techniques to classify the bacterial strains in individual infections.

Contrary to what he expected, Wiedmann discovered a pattern: The bacterial strains occurred in clusters, localized within certain geographic areas. A cluster means that several cases originated from one bacterial source and thus might indicate a disease that is spreading from the original source. The new findings mean that public health officials could potentially stop an outbreak after the first few identified cases by staying on the lookout for listeriosis clusters.

Blasting Cancer

To help diagnose cancer, doctors often use a microscope to examine small tumor samples obtained through procedures called biopsies. Although it is routine, this process isn't foolproof. Some of the subtle molecular changes that predict a tumor's behavior, such as how likely it is to spread or whether it will respond to certain anticancer medicines, are too tiny to be seen with a microscope. NIGMS grantee **Richard Caprioli** of Vanderbilt University in Nashville, Tennessee, has developed an experimental technique called imaging mass spectrometry that may allow more precise diagnosis of cancer and other disorders.

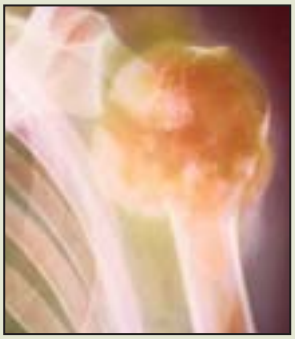
The method takes "molecular photographs" of individual proteins in cells and tissues. Caprioli and his team froze chunks of lung tumors and samples of healthy lung tissue and then cut them into very thin slices. The scientists coated the tissue slices with a chemical solution and slotted the specimens into a lab instrument called a mass spectrometer. A laser beam inside this machine blasted a series of sites on the specimens, shaking loose molecules at each site. These molecules were captured by a detector, analyzed, and displayed as "pixels" in a final, computer-drawn image. Each pixel contained a record of the molecules located in a specific site in the tissue sample.

Caprioli developed a specialized computer program to compare the samples and identified a protein pattern for one particular type of lung cancer that is very difficult to classify by looks alone. Caprioli's mass spectrometry method also successfully predicted whether individual patients would have a good or poor prognosis for surviving the cancer. This information could help doctors decide how aggressively to treat each case of cancer.

Basic Studies Yield Myeloma Drug

A series of lab studies begun in the 1970s by NIGMS grantee **Alfred L. Goldberg** of Harvard Medical School in Boston, Massachusetts, has led to a promising new cancer drug now on pharmacy shelves. The medicine, named Velcade™, was approved by the U.S. Food and Drug Administration in May 2003 to treat a deadly type of bone marrow cancer called multiple myeloma. Velcade is now being tested in more than 30 different clinical trials to determine if it can be helpful in treating many other types of cancer.

Velcade is a brand-new kind of cancer drug that targets a molecular machine found in virtually all cells. Goldberg was a pioneer in the discovery that our cells use this machine, called the proteasome, to continually break down their own protein components in order to remove improperly made or damaged proteins and to control cell growth and other vital processes. He reasoned that small molecules that block proteasome function might be useful in treating different diseases.



Goldberg and other researchers founded a small biotechnology company that went on to design and make Velcade based on detailed chemical knowledge of how the proteasome cuts up proteins. The discovery and development of this drug differs from the traditional approach, which relies on the screening of large numbers of chemicals to find those that that can slow the growth of cancer cells. The findings also show how advances in understanding basic biology can help scientists find new and better ways to treat diseases.