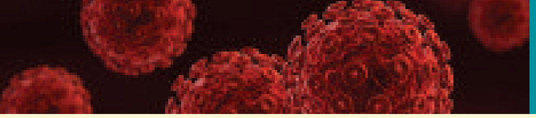

Bench to Bedside

These stories describe NIGMS-funded medical research projects. Although only the lead researchers are named, scientists work together in teams to carry out these studies.

Traumatized T Cells

Automobile accidents, gunshot wounds, and other forms of severe physical trauma make up the leading cause of death for Americans 40 and younger.

New research may improve recovery for people who suffer massive trauma.

Those who survive the initial injury can still suffer serious complications or die later. This is mainly because the human body does not have a reliable strategy for responding to massive trauma.

Most often, the trouble seems to be that the body's own protective immune system works too hard to recover from a serious injury. Researchers know that the resulting disruption of the healthy balance of immune system cells is a trigger for widespread disaster. T cells, in particular, shut down and cannot bolster the body's fight back to health.

Now, immunologist **Carol Miller-Graziano** of the University of Rochester Medical Center in New York has obtained results that help explain the T cells' rapid demise. Miller-Graziano and her team sampled blood from about 20 trauma patients whose organs were failing, as well as from the same number of healthy volunteers.

The scientists then separated T cells from other blood cells in order to identify changes specific to the vulnerable T-cell population. Using an automated approach that could map the activity of all T-cell genes simultaneously, Miller-Graziano found 338 that behaved quite differently in trauma patients.

The findings point to molecular signals after trauma that weaken T cells and send the immune system awry. Finding ways to reverse those signals may offer an opportunity to improve recovery from trauma.
—*Alison Davis*

Resisting AIDS Resistance

Every year during the 1980s and early 1990s, AIDS claimed the lives of roughly half a million people between the ages of 25 and 44. The terrible death toll began to diminish in 1995, when scientists came up with a breakthrough treatment. The critical component of this life-saving therapy was a new drug called a protease inhibitor that targeted HIV, the virus that causes AIDS.

While this discovery was groundbreaking, it was only a partial fix, and a quarter century after the first cases of AIDS appeared, the disease still kills more than 15,000 Americans every year and millions more across the globe.

The problem is that HIV rapidly learned to "outsmart" protease inhibitors by constantly mutating, or shuffling, its genes. These genetic mutations alter the physical structure of the virus, which allows it to survive the effects of HIV-killing medicines.

Score another one for the scientists. Chemist **Arun Ghosh** of Purdue University in West Lafayette, Indiana, has crafted a drug that HIV cannot counterattack. Ghosh designed a molecule that attacks the HIV protease "backbone," a part of the virus structure that remains basically unchanged as the virus' genes mutate.

The drug was first tested in animals and then shown to be safe for use in human patients. In June 2006, the U.S. Food and Drug Administration approved it as an AIDS treatment, now marketed as Prezista™.

Ghosh's work provides a new treatment option for the 40 million people worldwide who are infected with HIV.—*A.D.*

Worm Sperm Illuminate Male Infertility

Problems with sperm are the most common causes of male infertility, which accounts for about 30 percent of all cases of reproductive failure in the United States.

Sperm may be immature, abnormally shaped, or unable to move properly. Sometimes, sperm are produced in very low numbers or not at all. Scientists do not understand the root causes of many of these issues that affect a man's ability to father a child.

Male infertility is often caused by abnormal sperm that cannot fertilize an egg.

In a study supported by a National Institute of General Medical Sciences Minority Opportunities in Research program, San Francisco State University biologist **Diana Chu** and her team used roundworms to unravel the mystery. Like human sperm, worm sperm is packaged into bundles of protein and DNA.

Working with **Barbara Meyer** at the University of California, Berkeley, Chu used chemical techniques to isolate the worm sperm proteins, more than a thousand in all. Chu then used a powerful microscope to view the proteins that associate with worm sperm. After follow-up study, she found several that appear to be important for keeping the sperm healthy.

Chu and Meyer generated a list of 132 worm proteins that are critical for the worms' ability to reproduce. Over half of those proteins have human versions that have never before been tested for their roles in infertility.

The findings offer a promising resource for finding new infertility treatments and birth control approaches for men.—*A.D.*

Protein Linked to Cleft Lip and Palate

A developing child's face takes shape in early pregnancy, as the upper lip and palate (the roof of the mouth) grow together on either side of the tongue. When these tissues don't meet up properly, a gap remains. This is called cleft lip and/or cleft palate.

Surgery can often repair the facial structure of a child born with this condition. However, scarring can be a problem, as can difficulties with eating and speech.

Researchers believe that, like many birth defects, cleft lip and cleft palate are caused by both hereditary and environmental factors, and scientists have already identified several suspect genes. Now, geneticists **Cynthia Morton** and **Richard Maas** of Brigham and Women's Hospital in Boston, Massachusetts, have provided an important clue that may help explain previous findings.

Morton and her team examined DNA from a blood sample obtained from a 5-year-old child born with a cleft lip and palate but no other known health problems. The scientists noticed an abnormal chromosome in the child's cells; it contained a gene that had been split. Since genes provide the instructions for making proteins that do important jobs in the body, a broken gene usually results in a protein that doesn't work properly or at all.

More experiments revealed that this gene normally produces a protein that acts as an activation switch for other proteins known to be important for formation of the lip and palate.

Further study of how these proteins interact to produce the birth defect will help scientists better understand, diagnose, and treat it.—*A.D.*

Will Fight for Food

From birth to death, our lives follow a complicated recipe of nature and nurture. While heredity affects our personality and health, how we live—our environment—plays a huge role as well. Nonetheless, identifying genetic traits that influence our actions may help us learn how to manage unhealthy behaviors.

ED KRAVITZ

"High aggression" fruit flies resort to boxing over territory and food.

One way researchers are studying genes and behavior is by using model organisms that have similar genes and biochemistry to people. Recently, behavioral geneticist **Trudy Mackay** of North Carolina State University in Raleigh used fruit flies to look for genes that might be linked to aggression.

Hungry flies will battle over food—kicking, chasing, and boxing their peers in an effort to get their fair share. Some fight vigorously, whereas others are quite polite. The fact that different fly strains vary considerably in this behavior told Mackay that it might be at least partially inherited.

To learn more, she assembled three groups of flies of high, low, and average aggression. Mackay bred the groups of flies separately for 28 generations, choosing the most aggressive males in the "high" group and the least aggressive males in the "low" group to start each new generation. This step enriched the population for genetic variants that make flies more or less feisty.

Since the flies' behavior changed little over a period of about a year, Mackay deduced that only a small component (about 10 percent) of the variation in aggression could be attributed to variation in genes.

Although small, that 10 percent may hold significant clues toward understanding the biology of aggression. In follow-up experiments, Mackay found 15 fruit fly genes clearly linked to aggressive behavior. Several of the genes have counterparts in humans, which may help scientists understand such behavior in people.—*A.D.*