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Selected Science Advances, 2007-2008

The National Institute of Allergy and Infectious Diseases (NIAID) conducts and supports basic and applied research to better understand, treat, and ultimately prevent infectious, immunologic, and allergic diseases. In the past year, NIAID has conducted and supported many basic and clinical research studies that have improved our understanding of disease and advanced the quest for new treatments and prevention strategies. Some of the most exciting discoveries are highlighted below.

Hope for HIV prevention

Ever since HIV was identified as the cause of AIDS in 1983, scientists have worked feverishly to develop a means to prevent it. Even as scientists continue to pursue the "Holy Grail" of an AIDS vaccine, work continues to identify other means of prevention. Two NIAID-sponsored clinical trials examining the effect of adult male circumcision in preventing HIV infection yielded findings so clear and compelling that the trials were stopped earlier than planned. The trials, conducted in Kenya and Uganda among nearly 8,000 men between 18 and 24 years old, mirrored similar results from an earlier trial in South Africa and showed that circumcised men have a 50 percent lower risk of becoming HIV infected through heterosexual intercourse than their uncircumcised counterparts. It is not yet known whether removal of the foreskin in males will lower the risk of HIV transmission to their sex partners, but studies are now being conducted to answer this question. A vaccine that prevented half of all HIV infections would be considered a major victory. Thus, the discovery that medically supervised circumcision of adult males can cut the rate of HIV infection in half is certainly cause for cautious optimism, if not celebration.

New clue to HIV vaccine puzzle

Developing an effective HIV/AIDS vaccine requires finding a way to stop the virus in its tracks, before it makes its way into the immune cells it targets for destruction. A key to the puzzle is a protein — gp120 — that sits on the surface of the virus and latches onto the immune cells that HIV ultimately infects.

Scientists have looked at the blood of people who seem able to delay the crippling effects of HIV and have found that many of them have specific virus-fighting molecules, known as neutralizing antibodies, that seek out the HIV surface protein. One of these, known as b12, binds to the HIV surface protein. An effective vaccine likely will need to stimulate these neutralizing antibodies.

Now NIAID researchers have taken a detailed picture at the atomic level of the b12 antibody bound to the gp120 HIV surface protein. This picture reveals that the antibody recognizes the same part of gp120 that the virus uses to latch onto and enter immune cells. The researchers believe that this site serves as a region of vulnerability that can be targeted by vaccine developers.

Cause of Job's syndrome revealed

The cause of Job's syndrome, a rare, genetic immune disease marked by the appearance of recurring infections and skin problems such as boils and severe rashes, has eluded physicians for more than 40 years. Unraveling its cause has been difficult because only 250 cases have been reported since it was first described in 1966. But careful detective work carried out by scientists at NIAID and in Tokyo reveals that mutations in a single gene underlie the disease. Job's syndrome, also known as hyper-IgE syndrome, tends to run in families, so the researchers looked for differences in immune proteins and genes that affect the way immune cells work. They found the mutations in a gene known as *STAT3*, which is part of a pathway that is involved in inflammation.

This discovery provided an important clue to investigators who were studying immune cells in patients with Job's syndrome. STAT3 is required for the production of Th17 cells, which fight infection by *Staphylococcus* bacteria and certain fungi. The researchers then discovered that people with Job's syndrome lack Th17 cells, which increases their susceptibility to *Staph* and fungal infections. Knowing the genetic cause of Job's syndrome may eventually lead to new ways to diagnose, treat, and prevent the disease.

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health
National Institute of Allergy and Infectious Diseases

Dengue-causing mosquito genome decoded

In the United States, mosquitoes usually are considered a mere annoyance, particularly among outdoor enthusiasts. But mosquitoes carry deadly infections to more than half the people in the world, infecting them with pathogens that cause malaria, dengue fever, West Nile fever, and other infectious diseases.

A few years ago, researchers sequenced the genome of *Anopheles gambiae*, a major carrier, or vector, for the malaria parasite. Then in 2007, NIAID-funded researchers completed the genomic sequence of *Aedes aegypti*, the mosquito responsible for spreading dengue fever, yellow fever, and chikungunya fever. Although the two mosquito species share about 2,000 genes, the *Ae. Aegypti* genome is five times bigger than that of *An. gambiae*. The researchers found an increase in the genes that help the *Aegypti* mosquitoes detect odors, which may explain why the different species prefer different victims. The study may help researchers genetically alter mosquito species so that they are unable to transmit disease and may help in developing tests to detect and monitor insecticide resistance.

Once-defunct malaria drug shows renewed promise

Although malaria has afflicted humans for at least 50,000 years, effective treatments were not developed until the early 1900s. Thanks to the discovery and wide availability of chloroquine, a cheap drug that kills the malaria parasite, and the widespread use of DDT, which kills the mosquitoes that transmit malaria, malaria was wiped out in the United States and many other western nations and drastically reduced in many tropical regions of the world. However, in the 1950s, *Plasmodium falciparum*, the parasite that causes malaria, began to develop resistance to chloroquine, and DDT fell out of favor because of its impact on the environment. As a result, malaria began to resurge, and today it kills 1.3 million people each year, mostly children in Africa.

By 1993, chloroquine was only effective in treating half of all patients, so Malawi turned to other drugs to treat malaria. But by 2001 in Malawi, the genetic mutation that confers drug resistance to the malaria parasite could not be detected. In a recent trial of 210 Malawi children, NIAID-supported researchers found that chloroquine was 99 percent effective at treating children with malaria. The scientists suggest that a temporary halt to chloroquine use in Africa could restore chloroquine as a cheap and effective treatment for malaria, a concept of great interest to many global health experts.

Identification of allergen could help people with allergy and asthma

People who suffer from allergies and asthma know that allergens are everywhere. Even the most fastidious housekeepers are hard-pressed to render an environment free from the bugs, dust, and unidentified substances that can trigger allergic attacks.

In a recent study, NIAID-supported researchers found that chitin, a long sugar chain that gives insects, crustaceans, fungi, and certain worms a hard outer shell, provokes an allergic response in mice. However, when the mice were given chitin that had been pre-digested with enzymes, they did not develop an allergic response. In addition, mutant mice that overproduce an enzyme that breaks down chitin did not develop allergies to intact chitin.

Billions of tons of chitin are produced each year across the globe, especially in oceans, making it nature's second-most abundant biopolymer. Further studies on the role of chitin in human allergies and strategies to break it down may lead to new insights into the cause and treatment of allergy and asthma.

New HIV receptor identified

To get inside immune cells and wreak havoc on the immune system, HIV must first find an entry point. Scientists have identified several immune cell surface receptors that bind the virus and allow it access. Drugs designed to block certain of these receptors have been effective in treating HIV infection and delaying progression to AIDS.

One of the more puzzling aspects of HIV infections is its effect on the gut. Within days of infection with HIV, the virus invades and replicates in the immune cells of the gut and rapidly depletes them. Now NIAID researchers have identified a cell adhesion molecule, which helps cells stick together, as a new receptor for HIV. This receptor, known as alpha 4 beta 7, normally helps guide immune cells to the gut. The finding may eventually help researchers better understand how HIV invades and infects the cells of the immune system and may lead to new strategies for blocking HIV entry.

Organ recipients freed from immunosuppressive drugs

Organ transplants have saved countless lives over the past several decades, but transplant recipients are often doomed to a life fraught with complications. Not only do they face the constant threat of organ rejection and infection, but drugs they must take to prevent rejection can cause a host of undesirable side effects. Studies in mice have shown that organisms can "learn" to accept transplanted tissue if they are first given bone marrow cells. This results in an immune system that contains a mixture of immune cells from both host and donor.

In a recent NIAID-supported clinical trial, five kidney transplant recipients received bone marrow transplants from non-matched living donors. Four of the patients were able to stop taking immunosuppressive drugs 9 to 14 months after receiving a transplant and have remained stable for 2 to 5 years following transplantation. Once perfected and better understood, procedures such as this could be not only life-saving, but life-altering, for the thousands of people who receive organ transplants each year.

Death-defying pathway protects cells from radiation

High doses of radiation kill normal cells, but tumor cells have a remarkable ability to survive our myriad efforts to kill them. Researchers supported by NIAID looked at how tumor cells defy death by radiation and wondered if they might exploit the same tricks to protect normal cells from excessive radiation exposure.

The researchers noted that a protein known as NF-kB regulates a pathway in normal cells that helps protect against infection. This same pathway is always turned on in tumor cells and helps irradiated tumors escape death. The investigators wondered if turning on this pathway in normal cells might also protect them from radiation.

In certain cells of the gut, substances that bind to surface proteins activate the NF-kB pathway. The researchers found that if they injected mice with a single dose of one of these substances, called CBLB502, before exposing them to lethal doses of total body irradiation, the mice survived and were protected from acute radiation poisoning. Pilot experiments showed the drug could also improve the survival of monkeys, and also improved the survival of mice even when administered after irradiation. CBLB502 and similar drug candidates may be beneficial to patients undergoing radiation therapy and may offer protection in nuclear attacks.

Just Say NO: Deadly bacteria finds new way to evade host immunity

One of the most notorious superbugs, *Staphylococcus aureus*, may be about to meet its match. The microbe, one of the most invasive and virulent pathogens to infect humans, has an extraordinary ability to escape attack by the immune system. In addition to its well-known ability to mutate into drug-resistant forms such as MRSA, or methicillin-resistant *S. aureus*, the bug also can resist attack by nitric oxide (NO), a first-line strategy used by the immune system to kill invading pathogens.

Now, NIAID-supported researchers have figured out why. When hit with NO, most *S. aureus* strains ramp up production of an enzyme called lactate dehydrogenase (LDH) that helps the bacteria adapt to the attack. The researchers infected mice with either wild type *S. aureus* strains that have the LDH gene or with strains that lacked the gene. The resulting abscesses in the mice infected with wild-type *S. aureus* were larger and more numerous than those infected with bacteria lacking the LDH gene. These studies suggest that LDH is an important new target for scientists who are developing drugs to combat this deadly infection.

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