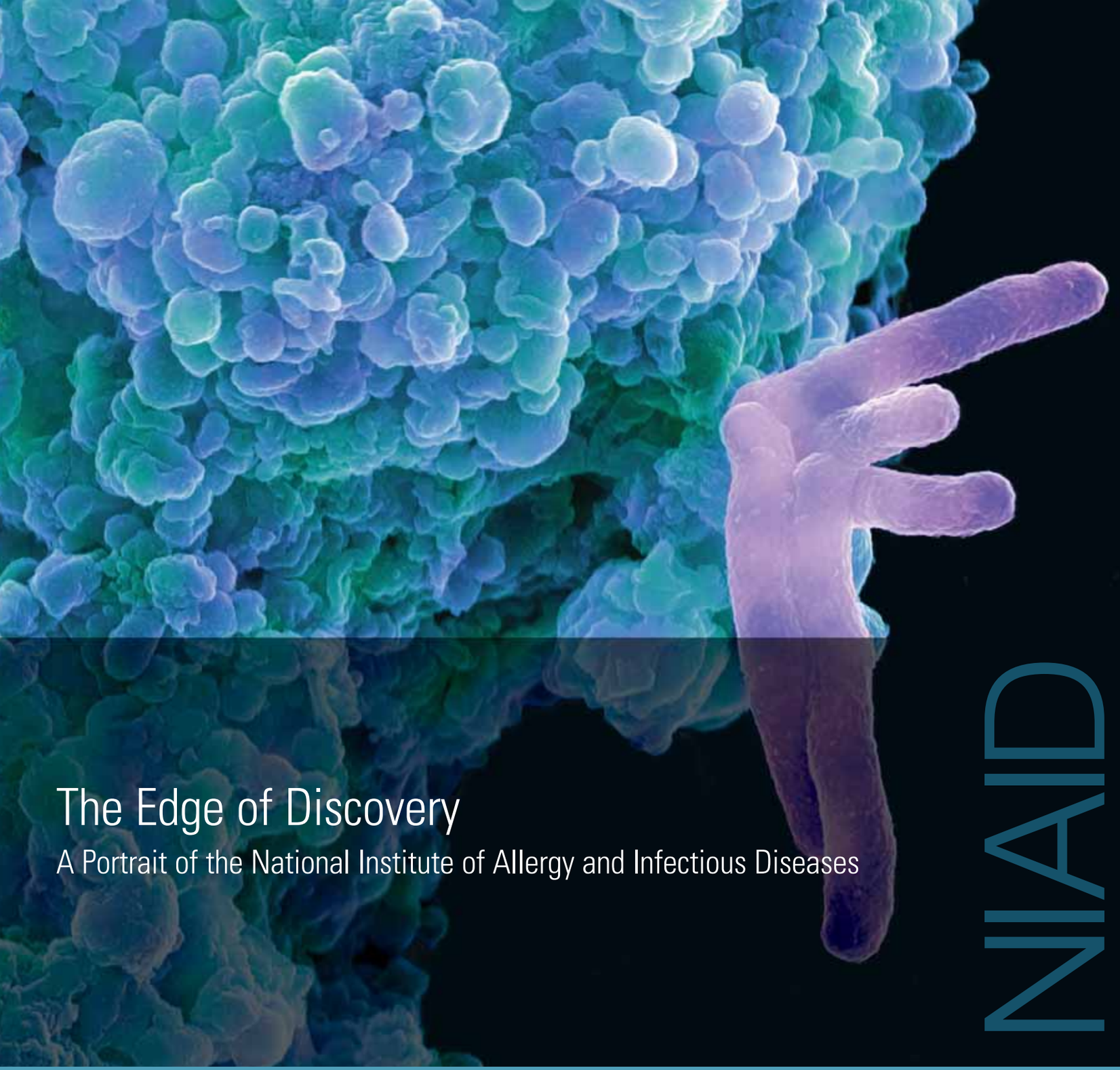


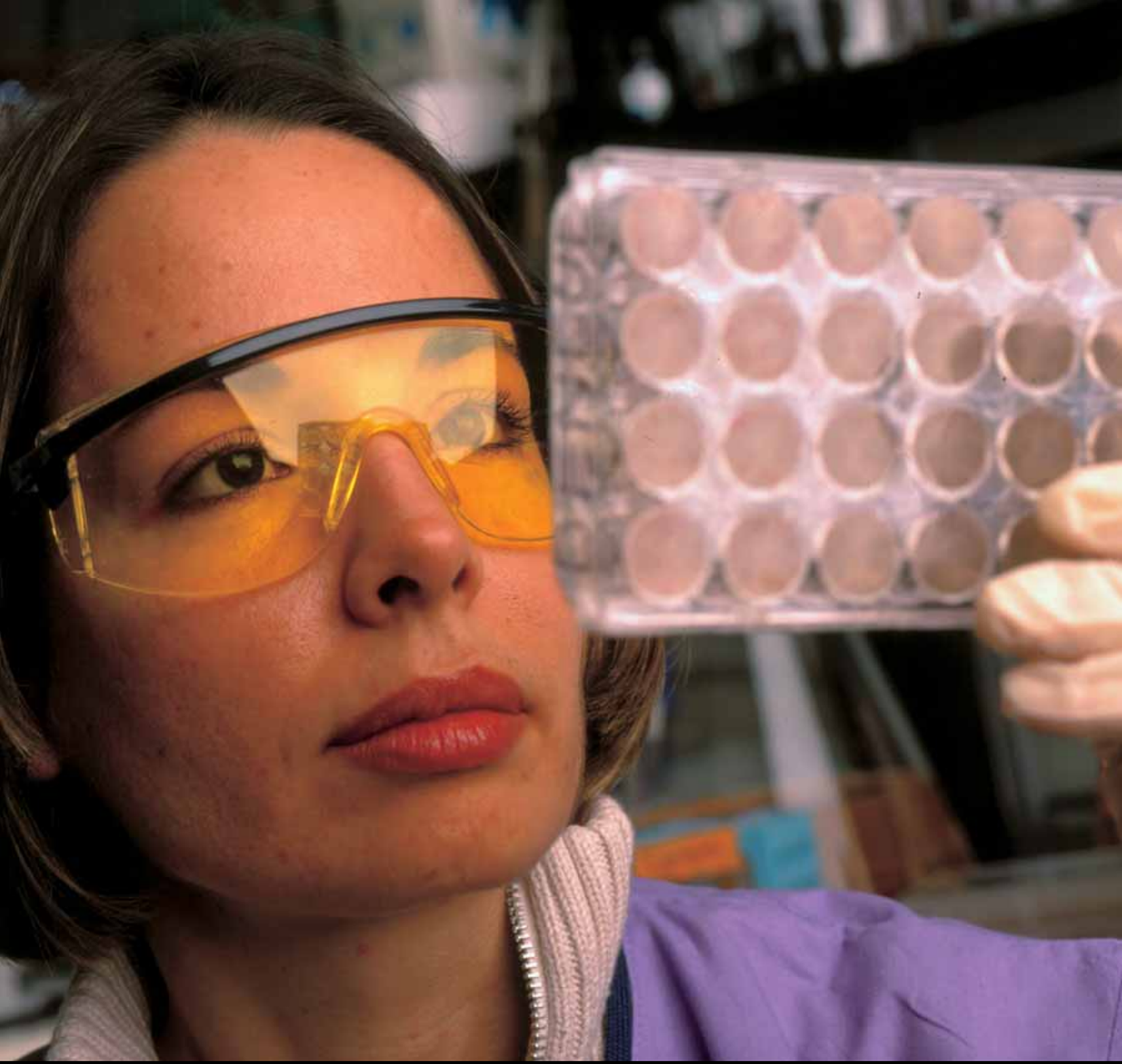
The Edge of Discovery

A Portrait of the National Institute of Allergy and Infectious Diseases

NIAID

National Institute of Allergy and Infectious Diseases

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health



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(Cover) *Mycobacterium tuberculosis* (purple), the organism that causes tuberculosis, invading an immune cell; (above) Ana Goncalvez conducts research on dengue fever at the NIAID Laboratory of Infectious Diseases.

National Institute of Allergy and Infectious Diseases

The Edge of Discovery

A Portrait of the National Institute of Allergy and Infectious Diseases

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

NIH Publication No. 09-6389
June 2009

From the Director

We live in a time when scientific research offers enormous hope and tremendous challenges. Microbiology and immunology, like all sciences, have progressed at an unprecedented rate in recent years. Nonetheless, diseases such as HIV/AIDS, pneumonia, asthma, influenza, malaria, and tuberculosis pose difficult challenges. When it comes to understanding both how the immune system defends against infection and goes awry to cause disease, we still have a long way to go. The reward, however, will be great.

The National Institute of Allergy and Infectious Diseases (NIAID) conducts research that will lead to new ways to prevent, diagnose, and treat infectious and immune-related diseases. Unlike many other research institutes, however, NIAID faces an additional challenge: the diseases we fight rapidly change and adapt on a global scale. Entirely new infectious diseases emerge with unfortunate frequency, such as AIDS in the early 1980s and SARS in 2003. Known pathogens emerge in new locations, such as West Nile Virus in North America, or reemerge in areas from which they had been eradicated. Still others acquire new and dangerous properties, such as extensively drug-resistant tuberculosis and methicillin-resistant *Staphylococcus aureus*. Because many emerging and reemerging infections have the potential to cause catastrophic harm, NIAID must be ready to respond rapidly with research aimed at understanding new threats and working toward the best possible solutions.

Basic research in microbiology, immunology, and disease pathogenesis is at the heart of how we accomplish our mission. After decades of research, scientists have gained a clear understanding of the big picture. They now are working to unravel the intricate details, because it is these details that will lead to new and better interventions to prevent, diagnose, and treat disease.

We are committed to maintaining a strong foundation of fundamental research, which is conducted primarily at academic institutions. At the same time, however, NIAID takes seriously the pressing need to capitalize on recent scientific findings to develop new treatments as rapidly as possible. To that end, NIAID cooperates extensively with nonprofit organizations, small biotech startups, and established pharmaceutical companies to speed all phases of the pathway from new findings to effective and available treatments. These cooperative arrangements run the gamut from very early explorations of interventions based on new research findings to large double-blind, placebo-controlled trials of vaccines for diseases such as HIV/AIDS and malaria.

NIAID Director Anthony S. Fauci (right) and Deputy Director for Clinical Research H. Clifford Lane.

One of the most striking changes to occur in my years at NIAID is the extraordinary increase in how tightly our work is integrated with biological and medical research in the United States and throughout the world. Although NIAID is the primary Federal research organization for infectious and immune-related diseases on the domestic front, we coordinate closely with other NIH institutes and our HHS sister agencies, including the Centers for Disease Control and Prevention and the Food and Drug Administration. Also, because our mission encompasses global scourges that are major killers in low- and moderate-income countries, we have increased substantially our presence outside the United States.

Our emphasis on global health, and on building research capacity in resource-poor countries, is unquestionably good for public health—our partnerships with scientists abroad speed the development of new vaccines and therapies. It is also in our national interest, in part because diseases that affect other countries now can—and often do—come to our shores, and in part because the stability of our globalized economy depends on good health at home and abroad. Healthy nations are secure and stable nations.

NIAID research is moving ahead rapidly, bringing fundamental new knowledge to light and new vaccines, treatments, and diagnostic tools to people who need them. As I look to the future of research on infectious and immune-related diseases, I am confident that progress will only accelerate. For example, our capacity to decipher the genetic codes of pathogens and their hosts, together with new technological platforms for vaccines, diagnostics, and treatments that can be readily adapted to multiple diseases, make it likely that the next generation will be both healthier and safer. I hope you will enjoy the glimpse of the exciting research in the NIAID portfolio presented in this publication. I also hope you will come to share my optimism that while the problems of infectious and immunological diseases are daunting, we will continue to develop powerful new tools to fight them.

[Signed June 2009]

Anthony S. Fauci, M.D.
Director
National Institute of Allergy and Infectious Diseases

The Immune System in Health and Disease

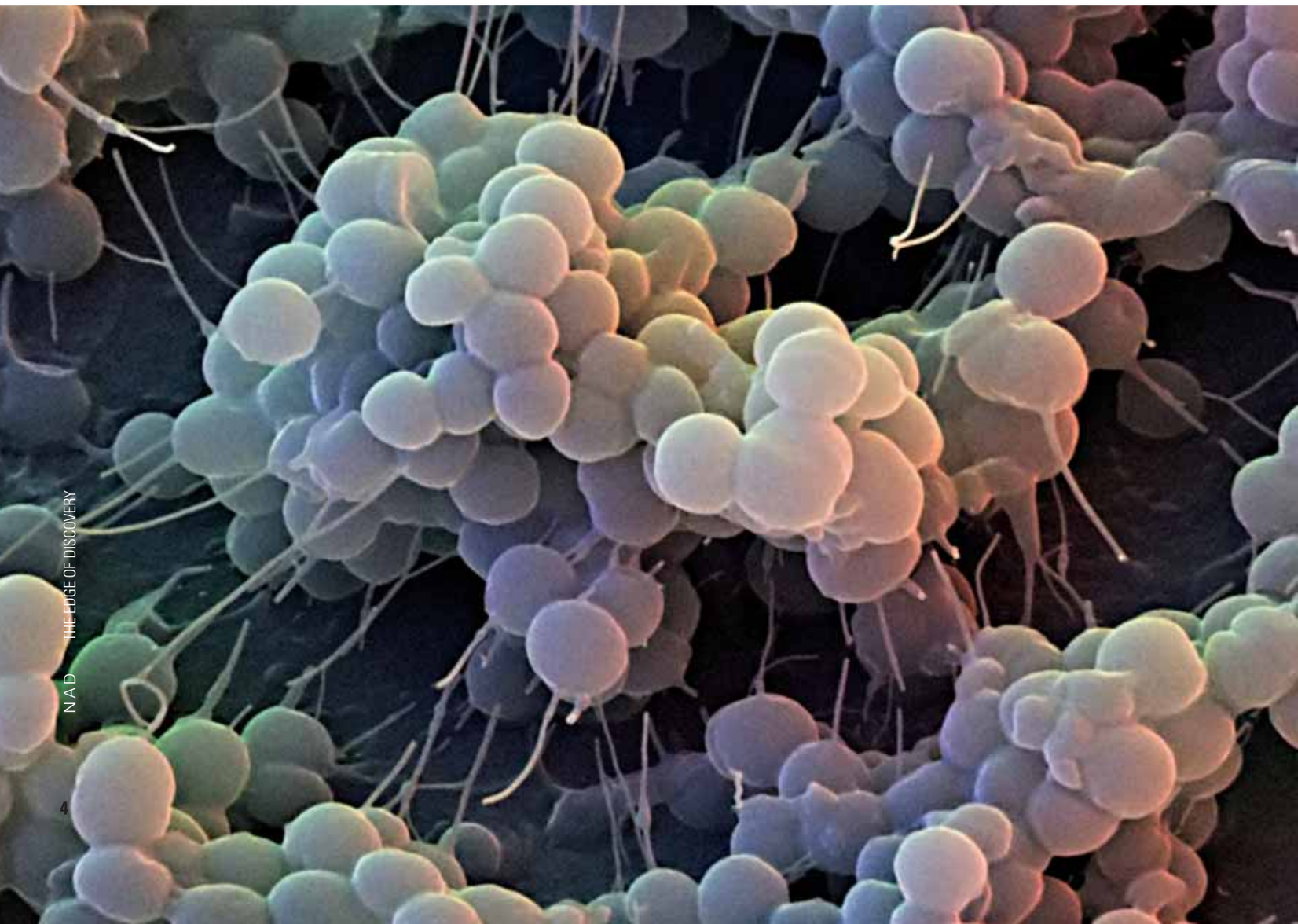
A key NIAID mission is to understand how the immune system keeps us healthy and what happens when it goes awry.

We live in a sea of bacteria, viruses, fungi, and other microbes that, given the chance, could easily do us harm. Fortunately, they rarely get that chance because the immune system provides an astonishingly effective defensive shield.

A primary NIAID goal is to understand *all* the many mechanisms the immune system uses to fend off infection. Researchers have long since mapped the most important of these and have a solid, basic understanding of how the immune system distinguishes what belongs in the body and what does not. But researchers do not yet understand many, if not most, of the detailed molecular mechanisms that collectively make the system so effective. That makes basic scientific study of immune mechanisms one of NIAID's top priorities. That basic research effort is progressing rapidly, spurred on by potent new scientific tools such as sequencing the entire genome of people and pathogens and powerful computer models that can reveal how tightly networked immune mechanisms keep pathogens at bay.

Like any powerful defense system, however, the immune system can harm what it is meant to protect. Autoimmune diseases such as lupus, type 1 diabetes, and rheumatoid arthritis occur when immune defenses attack the body itself. Allergic diseases and asthma occur when the immune system overreacts to substances in the environment. Transplant rejection is also an unwanted, if understandable, immune reaction. Although the immune system is only doing its job when it attacks transplanted cells, tissues, and organs—they are, after all, foreign—physicians are working to disable this response without undercutting a person's ability to fight off infection. For that reason, a second key NIAID goal is to find new ways to cope when the immune response itself causes problems.

The insights gained from basic immunology research are laying the groundwork for future treatments of immune-related disorders. In the meantime, NIAID research programs are helping us improve today's treatments for autoimmune disorders, allergic diseases, asthma (see sidebar), and transplant rejection.



For example, autoimmune disorders, allergic diseases, and transplant rejection all share a common thread: they result from the immune system's failure to tolerate cells or substances that we would like it to leave alone. To unravel that thread, NIAID sponsors the Immune Tolerance Network (ITN), a research consortium that conducts clinical trials of new tolerance-based therapies and provides sophisticated laboratory tools for detailed scientific studies of samples from patient volunteers. The ITN is developing powerful new therapies for allergies and transplant survival. The science of manipulating the immune system to create tolerance is still in its infancy, and fully mastering it will require integration of both basic science and clinical studies. But through its many programs targeting immune-related diseases, NIAID is working to reduce the burden of these illnesses while learning about the underlying mechanisms that cause them.

(left) *Staphylococcus epidermidis* bacteria can cause illness in people with compromised immune responses; (above) Venkat Yedavalli studies HIV in the NIAID Laboratory of Molecular Microbiology.

A Long Commitment to Asthma Research

Asthma, a temporary narrowing of the airways to the lungs that causes wheezing, coughing, and difficulty breathing, affects about 20 million people in the United States. It is the most common chronic condition among children and disproportionately affects children in poor urban areas. It can be deadly, too. Within the United States alone, asthma sends about 1,000 people to the hospital and kills about 11 people every day. The causes of asthma are not completely understood. Respiratory allergies play a leading role, but genetics, nutrition, viruses, and air pollution are all supporting actors. And for reasons unknown, asthma incidence among children has more than doubled since 1980.

NIAID has specifically targeted asthma since 1971. The Asthma and Allergic Diseases Cooperative Research Centers program, now in its fourth decade of continuous support, is responsible for multiple important advances in the basic science of asthma and helped establish the clinical study of allergy and asthma as a growing academic discipline.

In 1991, NIAID launched the National Cooperative Inner-City Asthma Study, a community-based approach to understanding the medical, social, environmental, and demographic reasons why asthma takes a heavier toll among the urban poor. A second phase, launched in 1996, continued those investigations and began to test ways to reduce asthma symptoms. In 2002, NIAID followed up with a new effort, the Inner-City Asthma Consortium. Bringing together scientists at several major research centers across the United States, the consortium conducts clinical and epidemiological studies of asthma; one study follows a group of very young children as they grow, to understand exactly which environmental triggers are most important and what can be done to prevent the onset of asthma.

A child in the Children's National Medical Center asthma clinic, site of an NIAID-sponsored asthma study.

Global Health Research

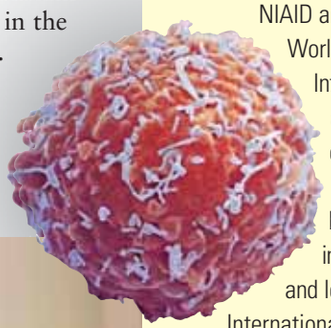
Partnerships around the world are a crucial part of NIAID's research strategy for infectious and immune-related diseases.

Throughout the world, pathogens are an omnipresent threat. One quarter of all deaths worldwide are caused by infectious diseases. Three infectious diseases alone—malaria, tuberculosis, and AIDS—account for about 1 out of every 13 deaths, mostly among children and young adults. That burden destroys families, stresses social institutions, and restricts economic growth.

Political leaders in many countries have come to understand that controlling infectious diseases not only saves lives but is essential for building a strong global economy and maintaining international stability. That growing awareness helped spark the creation of ambitious initiatives to limit the impact of infectious diseases. Those efforts include the President's Emergency Plan for AIDS Relief, the Global Fund to Fight AIDS, Tuberculosis, and Malaria, and other initiatives sponsored by national governments, philanthropic and faith-based organizations, private companies, and multilateral organizations.

NIAID's role in improving global health is to support basic and clinical research needed for the prevention, diagnosis, and treatment of infectious diseases. Most of that work is carried out in NIAID-operated laboratories or by scientists at U.S. research institutions. But because the public health challenges created by infectious diseases are so scientifically complex and talented scientists are widely dispersed, NIAID supports investigators working in about 90 countries, including countries that bear the greatest infectious disease burden. Our strategy is to forge lasting partnerships with researchers around the world and enhance the research capacity of the countries and institutions in which they work (see sidebar). These partnerships provide extraordinary opportunities for research on vaccines, drugs, and new diagnostics to benefit local populations where the research is done.

The effort already has yielded substantial dividends, with a promise of more to come. For example, U.S. investigators and their colleagues in Uganda, India, Kenya, and elsewhere have demonstrated that simple antiretroviral-based prevention interventions can greatly reduce the transmission of HIV from mothers to their children before and during delivery and during breastfeeding. And within the next decade, collaborative international development and testing of vaccine candidates to prevent malaria, tuberculosis, AIDS, and other globally important infections could lead to products that will substantially reduce the global infectious disease burden. NIAID is deeply committed to collaboration, innovation, and building sustainable infectious disease research capacity in the United States and throughout the world.



(left) Children in Pursat Province, Cambodia, site of an NIAID-sponsored clinical study of malaria. According to the World Health Organization, malaria kills about 750,000 children under age five every year; (above) Vu Nguyen and Holly McClellan, researchers in the NIAID Laboratory of Malaria Immunology and Vaccinology; (above right) An immune system cell; (right) A participant in a study of genetic resistance to malaria in Kenieroba, Mali, displays his study identification card. His health will be monitored by NIAID investigators for five years.

Partnership in Mali

One of NIAID's most successful international collaborations is based in Bamako, Mali. NIAID's relationship with Mali began in the 1980s, when NIAID and Malian scientists began a collaborative study of the mosquitoes that transmit malaria. Although the partnership was productive, shortages in trained personnel and modern infrastructure hampered the work. To provide a stronger base for research, NIAID joined with the Faculty of Medicine at the University of Bamako to create the Malaria Research and Training Center (MRTC). Dedicated in 1989, the MRTC was given a dual mission: to conduct world-class malaria research and to permanently strengthen Mali's research capabilities.

The partnership has thrived ever since. With support from NIAID and others, including the government of Mali, the World Health Organization, and the U.S. Agency for International Development, the MRTC has become a premier biomedical research institution, directed and staffed by Malian scientists. In recent years, as the center's interests have expanded beyond malaria to include HIV and tuberculosis co-infection, as well as the tropical diseases filariasis and leishmaniasis, NIAID designated the MRTC as an International Center of Excellence in Research.

In addition to providing support for research and training, NIAID continues to work with the University of Bamako as it builds essential scientific infrastructure—expanding and modernizing laboratories, building a network of community-based field research sites, upgrading information technologies, and helping improve grant-management and scientific communication skills. With ongoing support from the government of Mali, the MRTC allows scientists from Mali, the United States, and other countries to work together on some of the world's most challenging infectious disease problems.

Emerging and Reemerging Infections

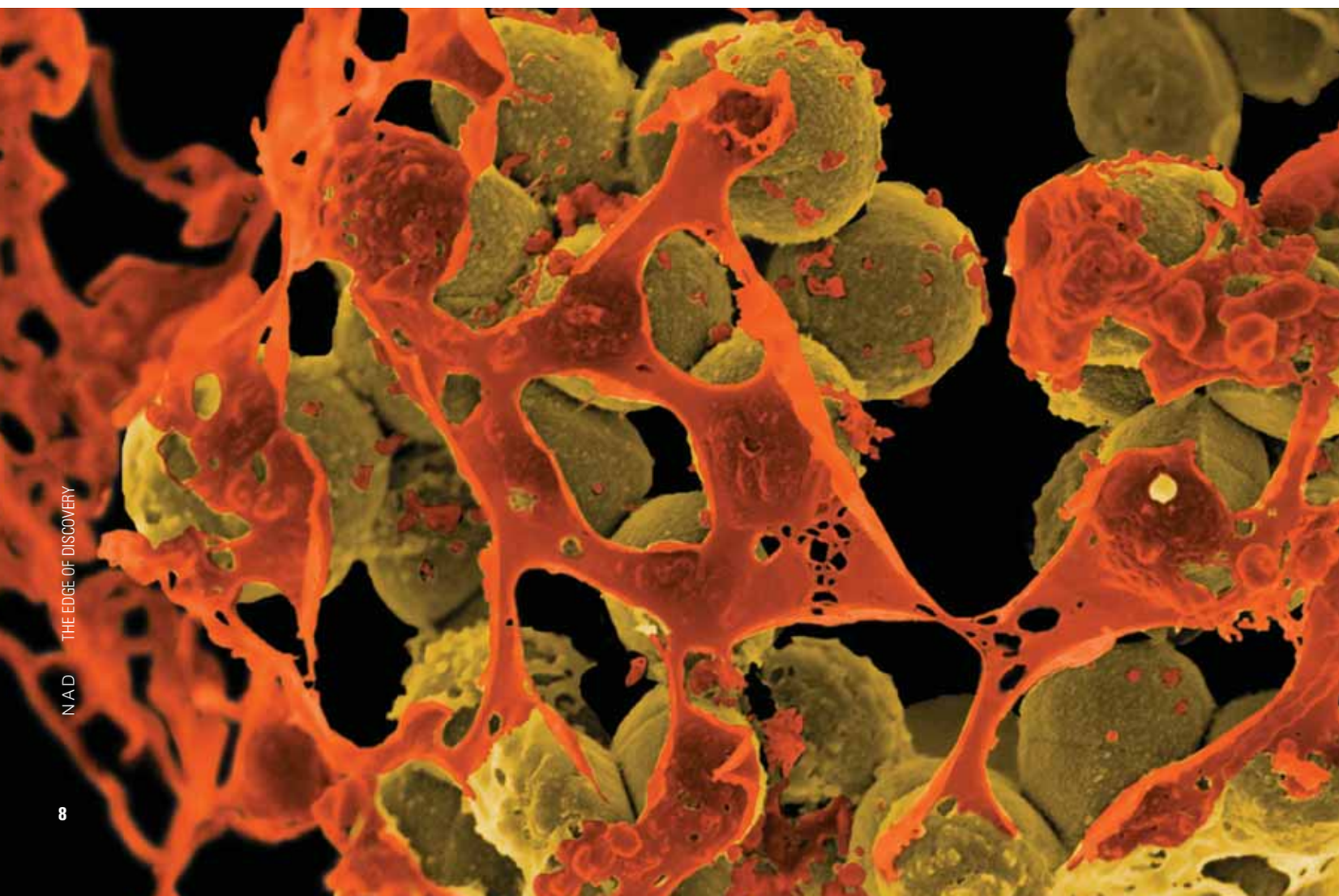
Infectious diseases emerge and reemerge around the world with startling frequency. NIAID research is a key element in the global effort to limit the damage.

When safe and effective antibiotics came on the market in the 1940s, it seemed that infectious diseases would soon no longer be a threat to most people. The microbial world, though, is nothing if not resilient. New pathogens have emerged regularly to infect the human population, and familiar ones have reemerged with new properties that allow them to evade our defenses and adapt to new environments. Drugs that could once control tuberculosis, malaria, and common bacterial infections are failing as resistant strains evolve. And the anthrax attacks in 2001 reminded us of our vulnerability to deliberate biological attacks.

As a result, emerging infectious disease threats, whether from nature or deliberate human action, remain a high priority. Among NIH institutes, NIAID has primary responsibility for research on emerging and reemerging infections, including pathogens and biological toxins that might be deliberately used to harm human health. Because these threats are unpredictable, we must be ready to respond quickly with research to meet any microbial challenge. To do that, NIAID pursues a threefold strategy: conduct basic research on microbes and host immune defenses, build programs to conduct research on dangerous pathogens safely, and support targeted development of new vaccines, therapies, and diagnostic tools.

Basic research is the foundation. Scientists still have much to learn about how infectious pathogens interact with immune defenses and about how microbes emerge and adapt. Only by filling in these blanks can researchers develop the next generation of medical countermeasures. The explosive growth of genomics—the science of genes and their function—is accelerating research into how microbes invade, how the host responds, and what determines the outcome of the resulting showdown.

NIAID is building a national network of secure research labs, staffed by highly trained scientists. These labs will mobilize in the event of a public health emergency and provide state-of-the-art facilities for carrying out infectious disease research safely. They will also train young scientists and act as a "melting pot" for the ideas that will lead to advances in fighting emerging and reemerging infections.



To translate the findings of basic research into new ways to fight pathogens as rapidly as possible, we are moving beyond the traditional "one bug, one drug" approach of the past to develop vaccines, diagnostics, and therapeutics that can tackle many pathogens at once. For example, diagnostic tools now in development can identify dozens of pathogens in a single sample and rapidly identify drug sensitivities. Also on the horizon are vaccines that will protect against whole families of microbes, and drugs that rapidly stimulate broad-spectrum immune responses. NIAID supports new and creative ways to thwart pathogens that have grown resistant to existing drugs, as well as new studies of older drugs that may yet prove effective against resistant infections.

Emerging and reemerging infections will always be with us. The task for NIAID is to build a strong foundation of the basic, applied, and clinical research needed to counter them and to be nimble enough to respond with speed and precision to new threats as they arise.

(left) Methicillin-resistant *Staphylococcus aureus* (MRSA, brown) surrounded by cellular debris—MRSA resists treatment with many antibiotics; (above) Robert Hohman and Cynthia Dowd search for tuberculosis drugs in the NIAID Research Technologies Branch; (right) Improvised hospital at Camp Funston, Kansas, during the 1918 influenza pandemic.

Influenza

For all its familiarity, influenza is a vicious virus. Although many respiratory infections cause similar symptoms—fever, fatigue, aches and pains, sore throat, congestion—seasonal influenza hits harder and lasts longer than a typical cold. Relying on small changes in its genetic sequence to overcome last year's immunity, the virus sickens 5 to 15 percent of the U.S. population each winter. It puts between 200,000 and 250,000 people in the hospital. Thirty to forty thousand people die after becoming infected. It costs the economy more than 10 billion dollars a year.

And that is just an average season. Sometimes the virus changes more dramatically. The result is an influenza pandemic, with much higher rates of illness, hospitalization, and death. The influenza pandemics that began in 1957 and 1968 were serious, killing, respectively, about 2 million and 700,000 people worldwide. The 1918–1919 pandemic, however, was catastrophic: it killed more than 50 million people, including more than 500,000 in the United States, with terrible social and economic fallout worldwide.

Given this history, we have to be ready for the next influenza pandemic. In fact, scientists and public health officials the world over are now worried that the deadly H5N1 avian influenza virus that has killed millions of wild and domestic birds—and more than 60 percent of the few hundred people it has infected—could spark the next pandemic.

The NIAID role in pandemic preparedness is to conduct both basic and applied research to bolster our antiinfluenza toolkit. In basic research, for example, NIAID scientists have deciphered the genetic code of the deadly 1918 virus, which revealed that it started as an avian virus that adapted to human hosts through a series of genetic changes. That work is providing clues to the changes that the H5N1 virus undergoes to become easily transmitted between people. And in applied research, NIAID supports the advanced development of flu vaccines that can be made in large quantity much more quickly when the next pandemic virus announces its presence.

A Selection of NIAID Research Advances

The path from a laboratory to a patient's bedside is a long one. NIAID research and collaborations fuel discovery, build on past progress, and lead to new drugs, vaccines, and other interventions.

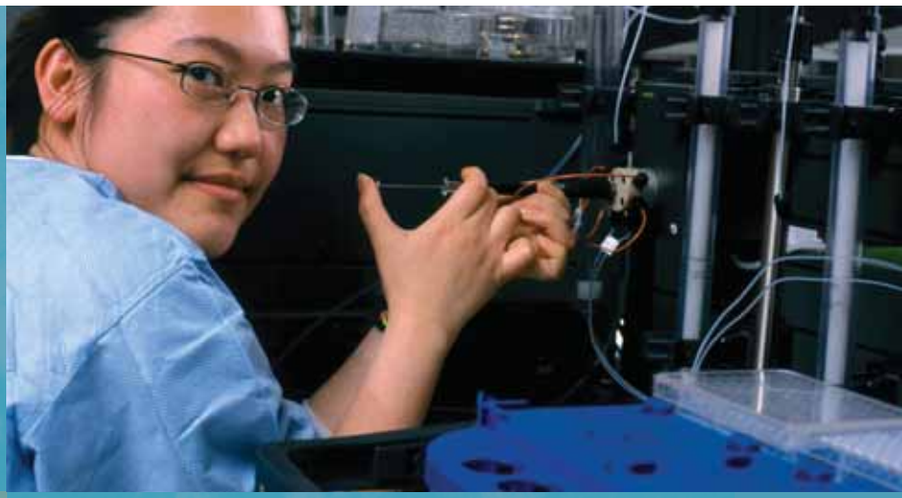
Medical research travels a long road. Its ultimate objective is to find new ways to fight disease. But the path from first discovery to new treatments always seems to twist and turn, with many blind alleys and strange detours.

In the late 19th century, Louis Pasteur and other microbiologists proved that microbes cause infectious diseases. Since then, basic science has been the bedrock on which new cures for infectious diseases are built. But turning a basic insight into a new medical intervention requires years of hard labor: invention, experimentation, innovation, animal testing, refinement, human testing, licensing. Going back to the drawing board when things do not work out is an essential part of the process—setbacks often lead to deeper understanding and, eventually, success.

Many terms describe the stages of the research pathway. Basic research. Applied research. Clinical research. Translational research. Preclinical development. Clinical development. Phase I, II, and III human trials. Regulatory review. Approval. The precise boundaries between the stages matter less than the journey itself.

The road invariably begins with discovery, a bit of insight won from long, hard hours in the laboratory. Then a glimmer of how that insight might provide a way to interfere with a disease process—a new way to treat HIV or a new vaccine to prevent pneumonia. The idea might then get picked up, extended, and tested in another laboratory.

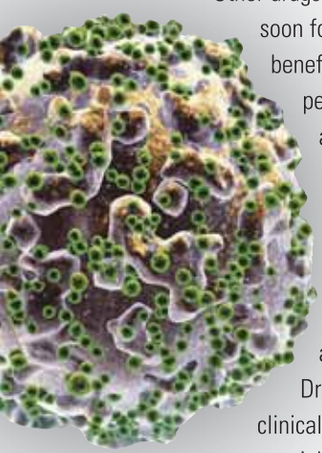
An academic researcher or a small company might create a prototype. Then another company might make a more polished product and carry out more testing in complex model systems, including animals. If all looks good, testing in human volunteers begins. The first goal in human testing is to make sure the intervention is safe. Then come more safety studies and a first look into whether it might work in people. Then full-scale testing to show it does work. Regulators participate throughout the process. If everything checks out, a new way to find, prevent, or treat disease becomes available.



(left) *Salmonella* bacteria, a common cause of food poisoning, invade an immune cell; (above) Christina Sanford and Tavis Steenbeke in the NIAID Laboratory of Immunoregulation; (right) Catherine Cruz purifying an HIV protein in the Laboratory of Immunoregulation.

AIDS Drugs

After HIV was shown to cause AIDS, scientists immediately began basic research to map its genes and isolate its enzymes. The goal was to understand the virus, the better to fight against it. Originally studied as a cancer therapy, a drug called AZT was found to inhibit reverse transcriptase (RT), a key HIV enzyme. In 1987, AZT became the first AIDS drug licensed in the United States. Other drugs that block the HIV RT soon followed. Unfortunately, the benefits of these drugs for people with AIDS often wane as the virus mutates to a resistant form.



Beginning in 1987, NIAID initiated a search for inhibitors of HIV protease, another key viral enzyme. Drug candidates were soon in clinical trials, and the first licensed protease inhibitor came on the market in 1995.

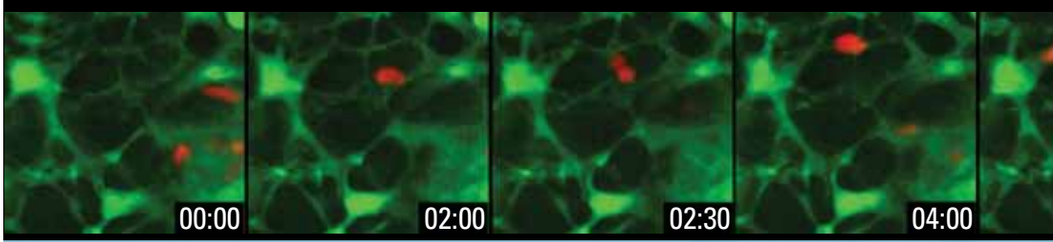
By 1996, researchers in academia and industry had devised a powerful three-drug combination therapy based on two RT inhibitors and one protease inhibitor. Because the drugs struck multiple fronts simultaneously, the virus was much less likely to rapidly become resistant. The AIDS death rate in the United States plummeted, and for the first time, people with HIV could look forward to a life expectancy measured in decades, not years or months.

Today, more than two dozen drugs to fight HIV are licensed, along with several new life-extending combination therapies. More people are receiving HIV treatment than ever before, in all parts of the globe.

That success would not have been possible without the large, long-term basic research effort that uncovered the fundamental molecular mechanisms of HIV infection and the support for clinical studies needed to bring these drugs to market.

(left) HIV (green) budding from infected cell; (right) AIDS drugs helped prevent HIV transmission from this Kenyan mother to her infant son; (below) T cell (red) moving along lymph node filaments (green); (far right) Hyesun Kuehn conducts research on the immune system in the NIAID Laboratory of Allergic Diseases.

Immune System —The Movie



Lymph nodes are the crossroads of the immune system, where roaming immune cells meet and organize a protective response. First, an immune cell called a dendritic cell engulfs an invading pathogen, puts bits of pathogen protein on its surface, and travels to a nearby lymph node. A dormant T cell—a multitalented player in the immune response—becomes active only after it enters the lymph node and physically encounters a dendritic cell bearing the foreign protein to which it is particularly tuned.

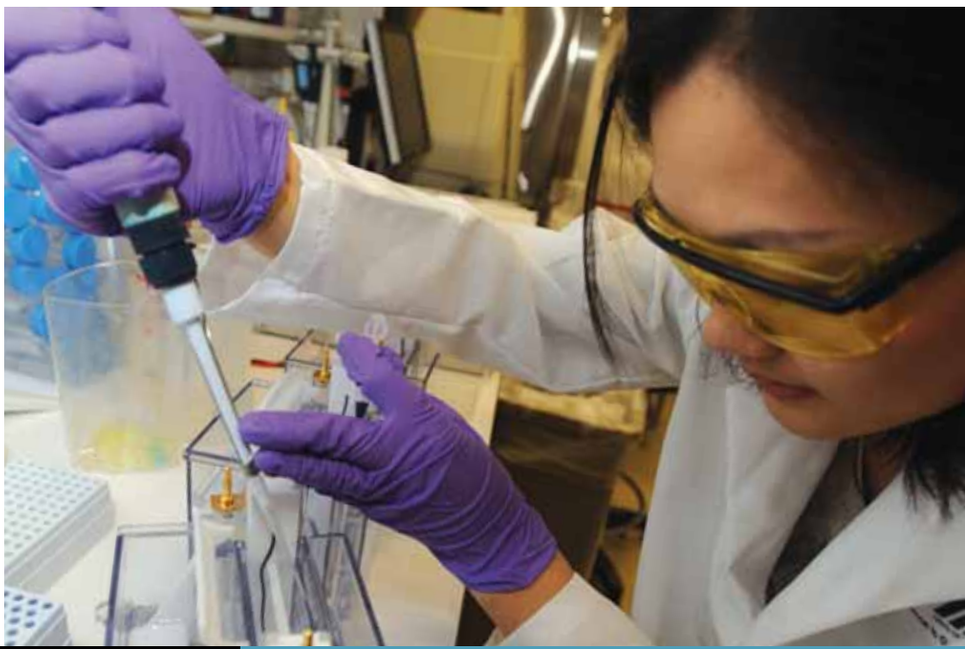
But how do these cells find each other? Aimless bumping around a lymph node might eventually make a match, but when infection threatens, time counts.

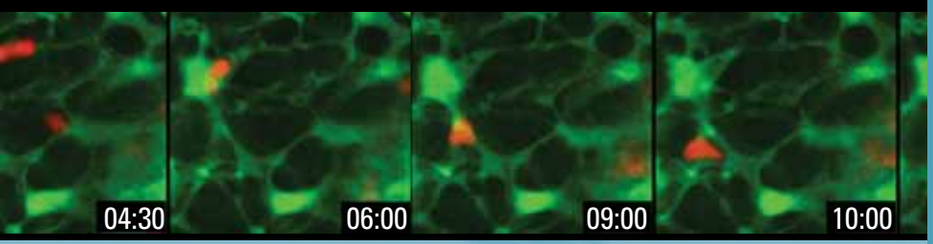
Front-Line Immunity

The immune system is a multilayered defense. The "adaptive" immune system—antibodies and killer T cells—is tailor-made to fight each specific invader. But because these defenses take time to activate, scientists knew that less finely tuned infection-fighting mechanisms must also exist, capable of turning on instantly to fight any pathogen. Beginning in the mid-1990s, studies of these less-specific "innate" immune responses took off and have proceeded at a rapid pace ever since.

For example, in the mid-1990s, NIAID-funded immunologists went looking for the mechanism that tells the innate immune system to activate when a pathogen invades. They used a clue from an unlikely source. A protein in fruit flies called Toll was known to guide the flies' growth and development. Mutations in Toll left the flies vulnerable to fungal infections.

The researchers reasoned that Toll might be a molecular tripwire that activates innate immune responses in flies and other animals. Using the genetic sequence of the fly protein as a molecular fish hook, they found a human protein similar to Toll, which, when properly stimulated, activated many immune responses. Other scientists went on to show that humans and other mammals have a large family of "Toll-like receptors," each tuned to signal the presence of a molecule found only in pathogens. Understanding how this protein family helps kick off the innate response promises to improve our ability to treat infections and increase the effectiveness of vaccines.





In 2006, NIAID scientists used a powerful technique called two-photon laser scanning microscopy to watch immune cells circulate in the lymph nodes of living mice. They saw that T cells (red) move methodically along a network of lymph node filaments made by stromal cells (green). Antigen-bearing dendritic cells (not shown) loiter where the stromal fibers intersect, scattering chemical signals that speed the process along. Scientists can now begin to read the molecular signposts along the filaments and, perhaps, will one day turn those new insights into enhanced responses to infection.

BASIC SCIENCE IS THE BEDROCK ON WHICH NEW CURES FOR INFECTIOUS DISEASES ARE BUILT.

Toward Drug-Free Transplants

Organ transplants have saved countless lives, but recipients must take antirejection drugs for the rest of their lives. These drugs cause a host of undesirable side effects, including increased risk of infection and cancer.

Laboratory studies have shown that mice and other animals can "learn" to accept transplants from unmatched donors if they receive bone marrow cells from the donor as well. A recent NIAID-funded clinical trial showed that this concept works in people, too. Five patients were given both kidney transplants and bone marrow infusions from nonmatched living donors. Four of the patients were able to stop taking antirejection drugs about a year after their transplants. Although the need to carry out a bone marrow infusion on top of a kidney transplant means the protocol is unlikely to be widely used now, it is very encouraging that withdrawal of antirejection drugs is feasible.

Job's Syndrome

Job's syndrome, also known as hyper IgE syndrome (HIES), is a rare genetic disorder marked by recurring infections and skin problems such as boils and dermatitis. It gets its name from the biblical Job, who, among other travails, was "smote with sore boils." With only 250 cases reported since 1966 and a bewildering array of symptoms, pinning down the cause proved difficult.

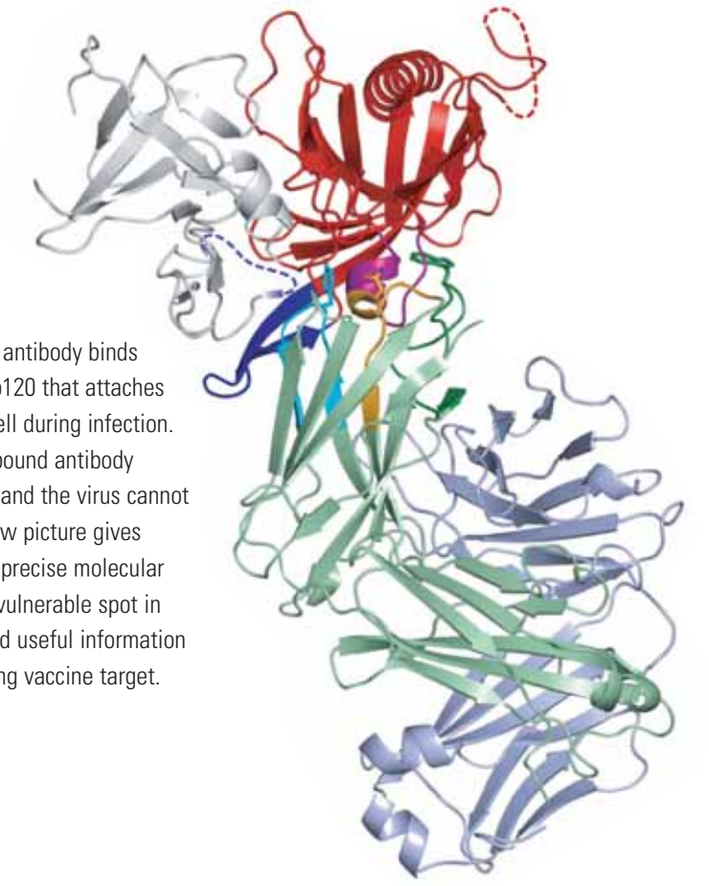
A long and intense collaboration among patients, infectious disease specialists, geneticists, immunologists, dentists, nurses, and statisticians recently led researchers to the cause: mutations in a gene called STAT3, part of a pathway involved in the control of inflammation. Inflammation is one of the first responses of the immune system to a wound or infection. The group found that inflammation is disordered in Job's syndrome—sometimes it is too strong, and other times too weak, leading to the complex syndrome seen in patients. Now that the defect has been unmasked, work toward more effective treatments can begin. Moreover, researchers can use the new insights into what goes wrong in HIES patients to better understand normal immune function.

(top) Surgeons conduct a kidney transplant; (left) *Job and His Wife,* a painting by Albrecht Dürer (1471–1528).

Anti-AIDS Antibody

HIV infects an immune cell when surface proteins on both virus and target bind tightly together. In the 1990s, NIAID-supported scientists isolated rare antibodies that prevent most HIV strains from latching onto their targets. Since then, scientists have been very interested in learning more about how these rare antibodies accomplish this feat.

NIAID researchers recently assembled a freeze-frame, atomic-level picture of one of these rare antibodies—called b12—bound to a protein on the HIV surface called gp120. The image reveals that the antibody binds to the part of gp120 that attaches to an immune cell during infection. The result: the bound antibody gets in the way and the virus cannot latch on. The new picture gives researchers the precise molecular details about a vulnerable spot in HIV infection and useful information about a promising vaccine target.



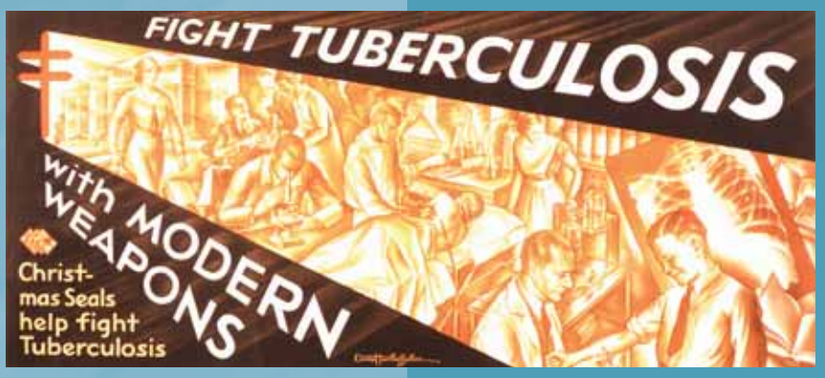
(right) An anti-HIV antibody (green and purple) binds to its molecular target, an HIV protein called gp120 (gray and red).

Searching for TB Drugs

Tuberculosis (TB) kills about 1.7 million people every year. It is notoriously hard to treat, and TB bacteria have evolved that current drugs barely touch.

In the late 1990s, NIAID researchers developed a sweeping "test them all" approach to finding new TB drugs. They churned out tens of thousands of structural variants of ethambutol, a TB drug from the 1950s, and screened them for their ability to kill TB bacteria. Promising candidates were structurally varied again, and again screened. After testing more than 100,000 variations on the original theme, researchers found that a candidate dubbed SQ-109 was among the best. Since 2000, NIAID has partnered with Sequella, a pharmaceutical startup, to conduct more laboratory testing and human trials. Although results so far are good, the gold standard for efficacy—a large placebo-controlled trial with thousands of TB patient volunteers—cannot begin until safety testing is complete.

TURNING SCIENTIFIC INSIGHT INTO A NEW INTERVENTION REQUIRES YEARS OF HARD LABOR.



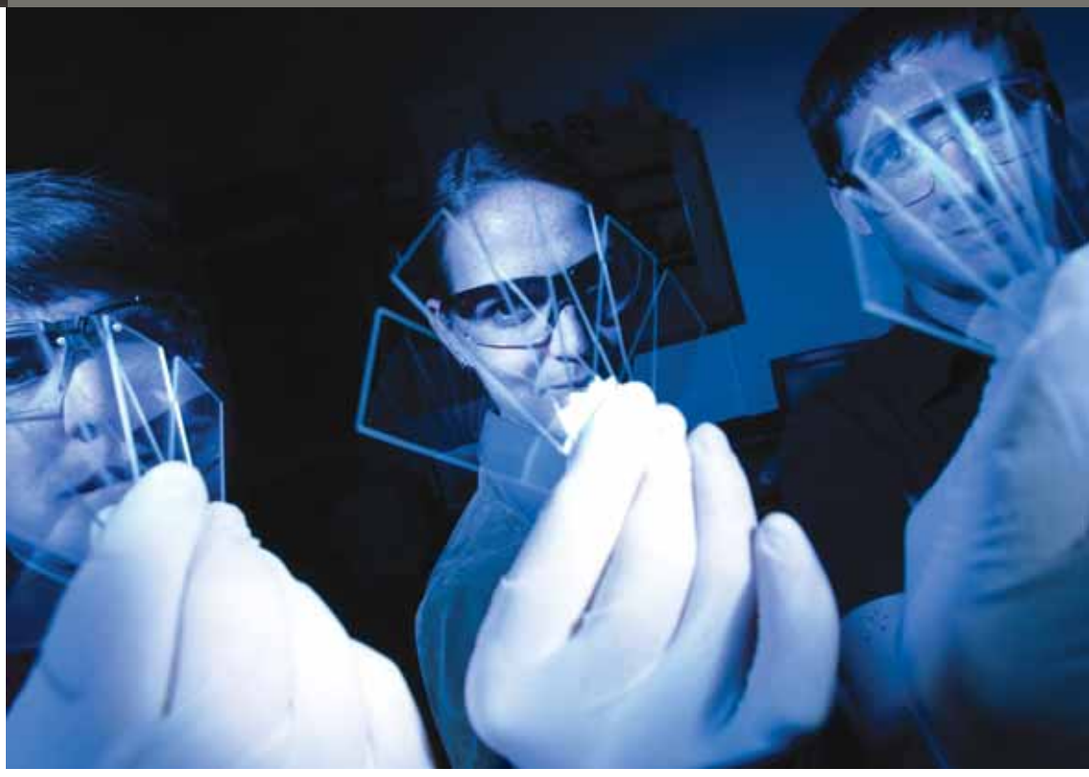
In the mid-1930s, when the American Lung Association made this poster, tuberculosis was a leading cause of death in the United States. In many parts of the world, it still is.

Silencing Autoimmune Signals

When the immune system attacks a person's joints, rheumatoid arthritis (RA) is the cruel result. Years of basic research going back to the 1970s led to the discovery that blocking an immune system signaling molecule called TNF-α could slow the progress of the disease. That finding led in turn to new antibody-based TNF-α inhibitors that work not only against RA but other autoimmune disorders as well.

NIAID intramural researchers are pursuing a new strategy to block TNF-α: disrupt its cellular receptor. The TNF-α receptor is made up of three identical subunits that must stick together to work. The researchers identified the specific places on the receptor subunits that touch as they form the assembled receptor. Then, using an animal model, they showed that injecting soluble forms of just those parts of the subunits can block receptor assembly—the extra copies bind to the single subunits and keep them apart. No receptor, no TNF-α signal. The treatment greatly improved the condition of mice with a disorder similar to RA; the plan now is to move into human clinical trials.

(left) Rheumatoid arthritis is an autoimmune disease that affects many tissues and organs, particularly the joints; (below) Researchers with FluChip prototypes.



Diagnosing the Flu

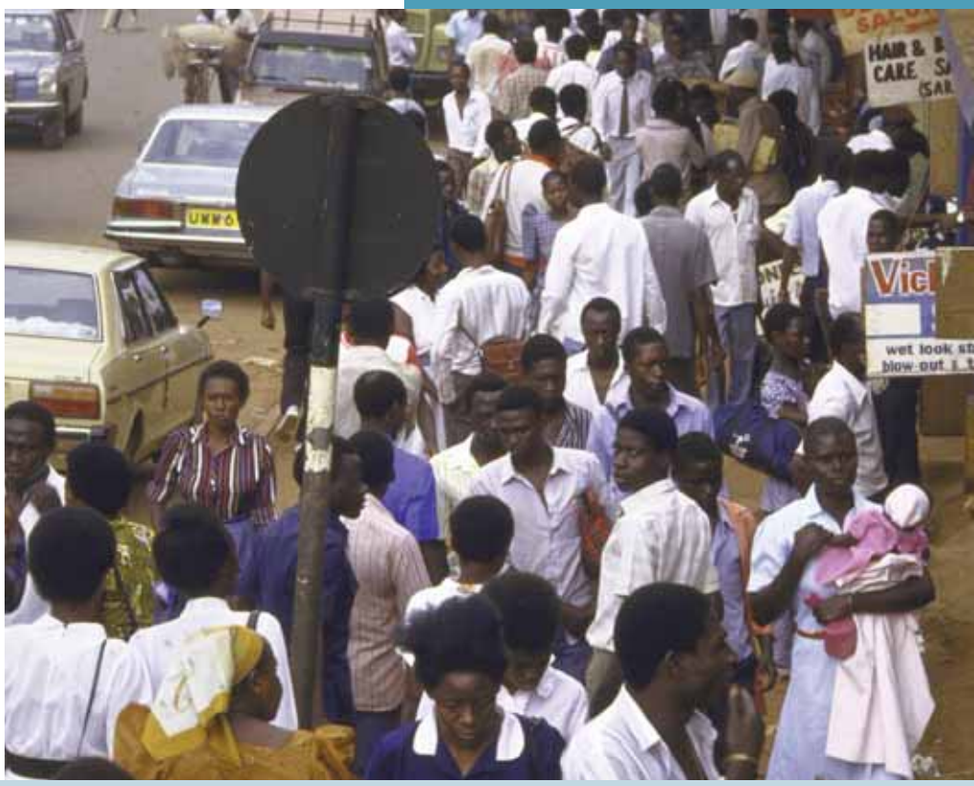
Currently, most influenza strains must be identified in a laboratory miles from a doctor's office—if they are identified at all—and it takes days or weeks to get a final answer. Given the ongoing threat of a flu pandemic, healthcare professionals need a way to find out who might be infected with a new flu strain.

NIAID-supported researchers developed a way to do just that. The method, based on DNA microarray technology, takes just about an hour to complete. To make the microarray—called a FluChip—tiny droplets containing short, fluorescently labeled segments of flu DNA are placed in rows on a glass slide. After some processing, throat-swab samples are spread over the DNA spots. Genetic sequences from flu in the sample bind to any matching sequences on the slide, causing some spots to glow bright yellow. By analyzing the pattern of glowing dots, doctors deduce which strain of flu is present. They can even identify drug-resistant strains. Such tools will let doctors know right away who needs treatment, and thereby help limit the spread of a pandemic flu virus.

Hope for HIV Prevention

Although prevention is always better than a cure, an effective HIV vaccine has proved elusive. But recent NIAID-sponsored clinical trials of the effect of adult male circumcision on HIV transmission were so compelling they were stopped earlier than planned. The trials, conducted in Kenya and Uganda among nearly 8,000 men, showed that men circumcised in the trial were almost 60-percent less likely to become HIV infected through heterosexual sex than their uncircumcised peers. Studies are now under way to find out whether circumcision lowers the risk of HIV transmission to an infected man's sex partners as well. A vaccine with a similar power to limit HIV transmission would be hailed as a major victory. The discovery that medically supervised circumcision of men can cut their rate of HIV infection by more than half is cause for cautious optimism.

AT THE END OF THE ROAD LIES A NEW WAY TO PREVENT, TREAT, AND DIAGNOSE DISEASE.

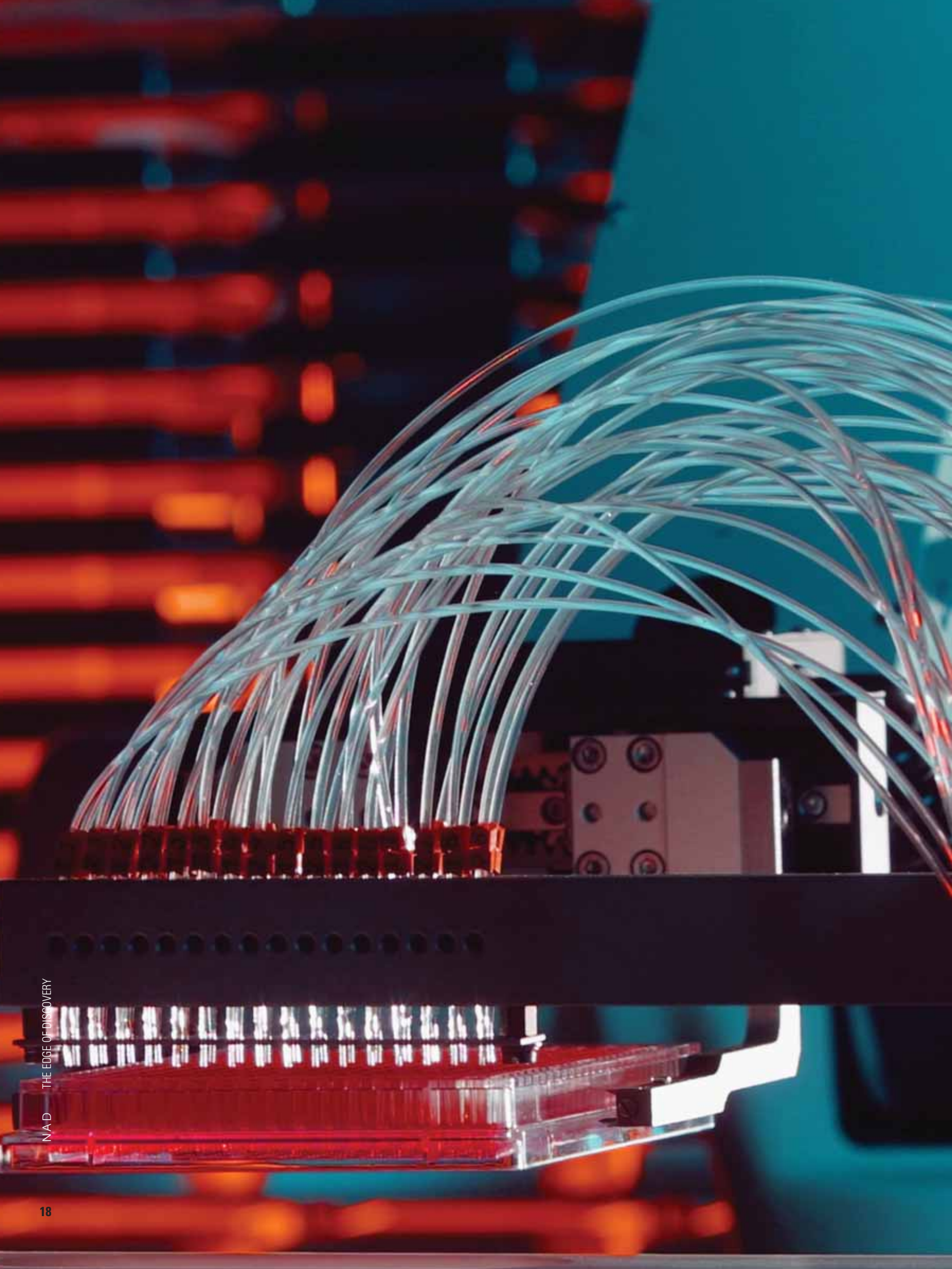


(right) Kampala, Uganda, was the site of an NIAID HIV-prevention study; (below) A child is vaccinated. Vaccines are among the most powerful tools available for improving public health.

Pneumococcal Vaccine

Although its toll is much lower in rich nations, bacterial pneumonia is still a leading cause of death around the world, especially among children. In the 1990s, NIAID helped fund the development of a vaccine against *Streptococcus pneumoniae*, the pathogen responsible for most fatal cases of bacterial pneumonia around the world.

The vaccine was first shown to be effective in urban areas in the United States and Finland. No one knew, however, how well the vaccine might work in poor, rural parts of the world, where most deaths occur. So NIAID joined with the British Medical Research Council, the Gambian government, the World Health Organization, the Program for Appropriate Technology in Health (PATH), and other organizations to carry out a large clinical trial of the vaccine in The Gambia in Western Africa. The results showed that the vaccine was also effective in that setting, despite a high incidence of malaria and other infections and inadequate infrastructure. The next step is to find a way to get more and better vaccines to the people who need them most.



The Road Ahead

New technologies and sustained commitment are speeding the progress of research on the immune system and infectious diseases.

Like all biomedical sciences, the study of infectious and immune-related disease is in overdrive. Thanks to new technologies, a long-term commitment to research, and generations of painstaking labor, we are deepening our understanding of how the immune system both keeps us healthy and, sometimes, makes us ill. We've never before learned so much, so fast.

Much of today's rapid scientific pace comes from the application of new technologies. High-speed genetic-sequencing methods have allowed scientists to decipher the entire genome not just of human beings, but of thousands of microbes as well. And not just one version of each microbe, either: collecting and comparing many versions of a pathogen's genome reveals a great deal about how the bug makes us sick and how it is evolving. New laboratory techniques, such as microarray analysis, allow a graduate student in a single afternoon to assess the response of every human gene when a person is infected with a specific pathogen. Twenty years ago, a thousand graduate students could not have done that in a decade. Ever more powerful computers allow us to cope with the flood of biological data—genetic, molecular, physiologic, and clinical—pouring out of labs all over the world. The Internet allows scientists to collaborate more effectively and communicate new insights more quickly. Along with a host of other innovations in chemistry, microscopy, robotics, bioinformatics, and other fields, technology fuels much of the scientific fire that burns so brightly today.

Technological innovations alone, though, are not the whole story. The American people, and societies around the world, have steadfastly supported biomedical research and helped educate and nurture the next generation of scientists. With that support, we are moving along at a prodigious rate.

(left) Automated manufacturing of DNA microarrays.

Where to? For one, toward a future in which we can better manage the immune response to help it fight infection and to get it back on track when it goes off the rails.

Consider vaccines. All rely on a bit of immunologic sleight of hand. Expose a person to a dead or weakened pathogen—or even just a bit of a pathogen—and the immune system learns how to defeat the strong, wild version next time around. It is a trick that has been widely practiced since 1796, when Edward Jenner showed that infection with cowpox virus protects against smallpox.

The path to a vaccine is not always smooth. Despite a hundred years of effort, we do not have a vaccine against malaria. But we do have candidates in clinical trials, and others are on the horizon. Moreover, we have complete genetic sequences for all three elements in the malaria equation: the human host, the *Plasmodium* parasite that causes malaria, and the *Anopheles* mosquito that transmits it. Scientists are now using these genome sequences as they try to pry open the parasite's defenses, control the mosquito that spreads it, and artificially ramp up the human immune response. Other manipulations of immune responses might one day tamp down the ones that are at the heart of immune-related disorders or activate nonspecific "innate" immune responses in the face of a natural or humanmade biological assault.

How far in the future these capabilities might lie is impossible to foretell. But we can be sure that with continued effort, our ultimate destination will be a healthier world.

NIAID: Essential Facts

Mission, Research Funding, and Organization

The mission of NIAID is to conduct and support basic and applied research to better understand, treat, and ultimately prevent infectious, immunologic, and allergic diseases. NIAID is one component of the National Institutes of Health, which in turn is part of the Department of Health and Human Services.

Each year the President proposes a budget for NIAID. Congress passes its version of that budget, which is included in the bill funding the Department of Health and Human Services that the President signs into law.

The lion's share of NIAID funding supports extramural research, carried out by scientists based in academic institutions, nonprofit organizations, and private businesses across the country and around the world. Sometimes the support is provided as a grant to carry out an investigator-initiated project, and sometimes it is in the form of a contract for specific research services. Many variations exist within each category to accomplish specific aims. Small Business Innovation Research grants, for example, help small businesses develop new products based on research findings. Training support at research centers funds the education of the next generation of scientists. In all cases, obtaining research support is a highly competitive process. All NIAID research grant applications and contract proposals are peer reviewed—ranked by panels of scientific experts outside NIAID. That review ensures that only the very best are funded.

A smaller portion of the NIAID budget supports intramural research conducted by NIAID-employed scientists and other personnel in NIAID-managed laboratories. Most of the intramural program is carried out on or near the NIH campus in Bethesda, Maryland; NIAID also operates the Rocky Mountain Laboratories in Hamilton, Montana.

NIAID's main advisory body is the National Advisory Allergy and Infectious Disease Council, whose members are drawn from the ranks of distinguished scientists and laypeople from across the country. The Council advises NIAID on policy matters, provides second-level reviews of grant applications, reviews programs, and helps develop targeted funding initiatives.

Administratively, NIAID is organized into seven major divisions. Three of these—the Divisions of Microbiology and Infectious Diseases; Acquired Immunodeficiency Syndrome; and Allergy, Immunology, and Transplantation—are responsible for planning, managing, and overseeing the bulk of NIAID's extramural research portfolio. The Division of Extramural Activities coordinates peer review and manages extramural research policy. The Division of Intramural Research is responsible for most of NIAID's intramural research portfolio. The Dale and Betty Bumpers Vaccine Research Center is dedicated to developing vaccines against HIV/AIDS and other diseases, with a unique mission to move vaccine concepts through preclinical development and into initial clinical trials. The Division of Clinical Research supports and coordinates both intramural and extramural research involving human volunteers. The Office of the Director is responsible for policy planning and operational coordination for the Institute.

For more information about NIAID and NIAID research, please see http://www.niaid.nih.gov.

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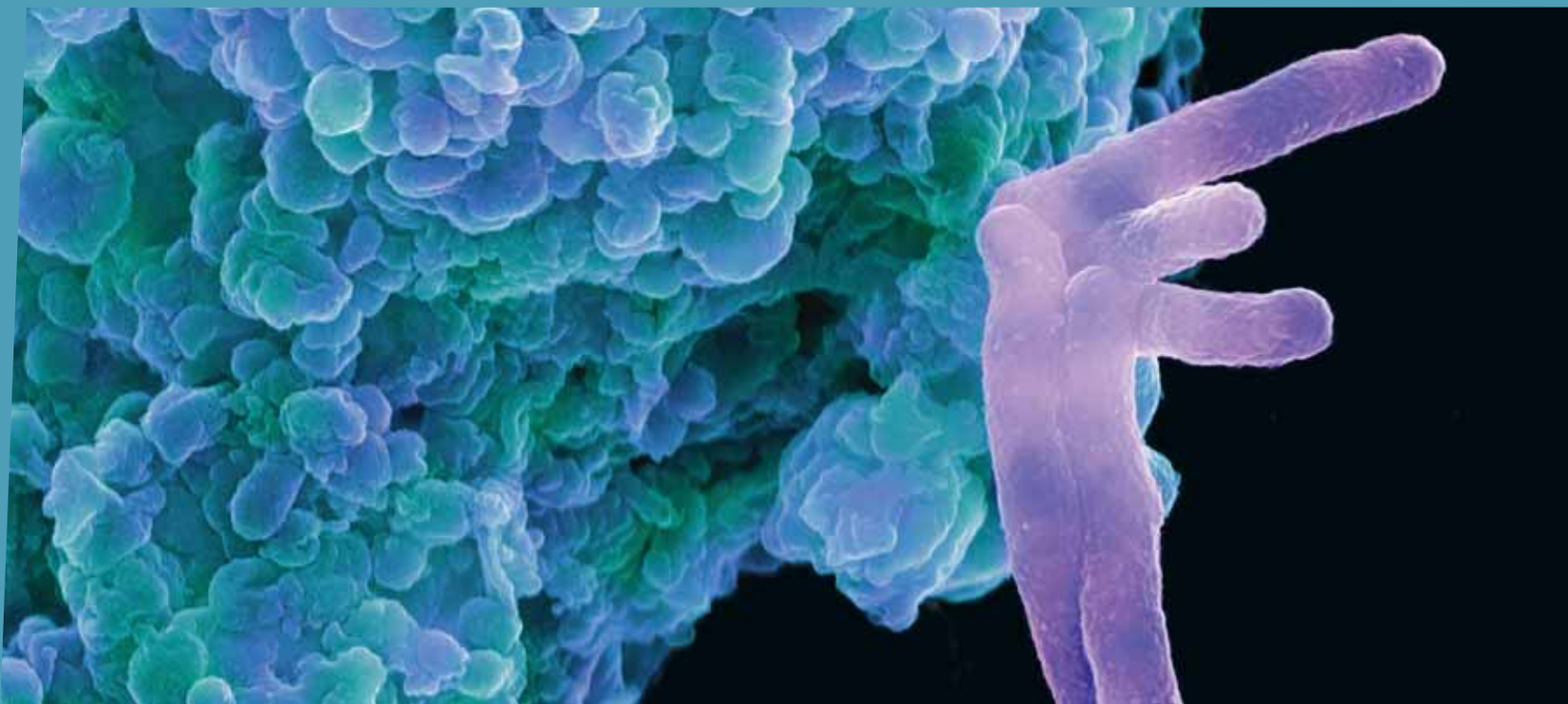

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