

Preclinical Primate Studies Help Bring New Discoveries to Patients

Studies of nonhuman primates are an essential component of translational research, allowing scientists to evaluate potential medical interventions in a nonhuman model before testing proceeds in patients. Many of today's life-saving medical treatments—including polio vaccines, AIDS-fighting drugs, and heart surgery techniques—depended on preliminary evaluation in nonhuman primates.

To enable preclinical animal-based investigations, NCRR supports a nationwide network of eight highly specialized research facilities known as the National Primate Research Centers (NPRCs), which house and care for a variety of nonhuman primates that are important to biomedical research. Each NPRC has experienced staff and appropriate research environments for studying and developing nonhuman primate models of human health and disease. As the articles below illustrate, the NPRCs make essential contributions to preclinical studies of experimental therapies, diagnostic tests, and imaging agents.

Safeguarding New Organs

For thousands of people waiting for kidney transplants, learning they are on top of the list may be good news. Yet soon after transplantation, patients are given a drug regimen that suppresses the immune system to prevent organ rejection. Although immunosuppressants have considerably increased one-year survival rates, these drugs have numerous side effects, including eventual damage to the new kidneys.

Physicians Thomas Pearson and Christian Larsen and their colleagues at the Yerkes NPRC in Atlanta have helped develop a new drug to circumvent this problem. Early clinical trials suggest that the experimental drug, known as belatacept, may be as effective as cyclosporine, the mainstay in immunosuppressive therapy for the past 20 years.

In preclinical studies conducted on nonhuman primates, Pearson and his colleagues found that belatacept effectively reduces the rate of rejection of transplanted kidneys. "The expertise and experience of the Yerkes research staff, as well as the physical facility and resources, greatly augmented the development of belatacept," says Pearson. Belatacept works by attenuating the immune system's activation of T cells that would attack the new kidney.

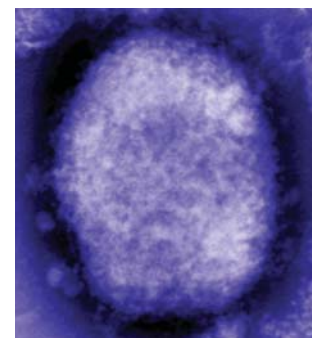
Pearson's preclinical findings laid an important foundation for evaluating the drug in humans. Recent Phase II clinical trials involving 218 kidney transplant patients found that acute rejection and infection frequency were similar whether patients received cyclosporine or belatacept. Those receiving belatacept, however, showed better kidney function than the group receiving

cyclosporine. Also, one year after transplantation, kidney damage known as chronic allograft nephropathy was present in only 20 percent of patients receiving belatacept, compared with 44 percent of cyclosporine patients. "We are hopeful that Phase III trials will show similar results," says Pearson. If it reaches the market, belatacept could lead to improved long-term transplant and patient survival, he adds. (*American Journal of Transplantation* 5:443-453, 2005; *New England Journal of Medicine* 353:770-781, 2005)

—AL STAROPOLI

Diagnostic Tests for Highly Infectious Agents

Scientists at the Oregon NPRC developed a novel series of tests that show evidence of being more sensitive and accurate in diagnosing human monkeypox infections than current tests approved by the U.S. Centers for Disease Control and Prevention (CDC). The studies may lead to improved diagnoses, therapies, and preventive measures for monkeypox and other sometimes-deadly agents that might proliferate in a natural outbreak or a bioterror attack.



The monkeypox virus, shown here, can be deadly to humans. Diagnostic technologies and therapies developed for monkeypox might also apply to smallpox and related viruses.

NPRC researchers Mark Slifka and Matt Lewis traveled to

Wisconsin to examine more than 40 individuals who had been exposed to the monkeypox virus, a close relative of the smallpox virus. In 2003, dozens of people in the Midwest had been exposed to pet prairie dogs infected with monkeypox, and 72 cases of human infections were later reported to the CDC.

The Oregon researchers used a unique series of diagnostic tests to confirm previously unverified human infections. The diagnostic series also identified an additional three individuals whose infections had been undiagnosed because they lacked obvious symptoms. These three people, having been vaccinated against smallpox more than a decade before, were fully protected against monkeypox disease.

Slifka notes that the biocontainment level-3 laboratory associated with the Oregon NPRC is one of the few in the country with the appropriate safeguards, expertise, and authorization to conduct experiments with monkeypox. “Our studies would not have been possible without access to the NPRC or the resources of the General Clinical Research Center, where some blood analyses were performed,” Slifka says. “While this research primarily focused on monkeypox, this same technology could also be used to better detect a smallpox outbreak.” Although smallpox no longer exists in nature, having been eradicated through effective worldwide vaccine programs, the virus is still considered a significant bioterror threat.

The technology and diagnostic platform developed through these experiments has now been licensed to an Oregon Health and Science University spin-off company, Najit Technologies, which specializes in developing effective diagnostics and antibody-based therapies against potential bioterrorism agents, as well as other rare and neglected diseases. (*Nature Medicine* 11:1005-1011, 2005)

—VICTORIA L. CONTIE

Imaging Agent Aids Neurological Diagnoses

A novel brain-imaging agent first conceived more than a decade ago promises to allow early diagnosis of human neurological disorders and is now being evaluated in Phase II and III clinical trials. In the 1990s, Bertha Madras of the New England NPRC helped to create the new agent, called altropane, and demonstrated its clinical potential by using it to diagnose neurological abnormalities in monkeys.

Injected into the body, altropane binds to the dopamine transporter (DAT), a molecule that is produced exclusively by



■ In human studies, the imaging agent known as altropane reveals differences in the brains of a healthy volunteer (top) and in patients with moderate (middle) and severe (bottom) Parkinson's disease.

dopamine-containing cells in the brain, cells that are depleted in Parkinson's disease and are implicated in other neurological disorders. With certain types of brain-imaging scans, radiolabeled altropane reveals the amount and location of DAT molecules in the brain. Because DAT molecules reside almost exclusively on dopamine-producing cells, altropane neuroimaging reveals the density, location, and possibly the function of dopamine-producing neurons.

Working with collaborators David Elmaleh and Alan Fischman at the Massachusetts General Hospital, Madras demonstrated in monkeys that altropane accumulates rapidly and selectively in brain regions rich in dopamine neurons. They also found that altropane could detect a loss of DAT sites—due to a depletion of dopamine-producing neurons—in monkeys

that had a neurological condition analogous to Parkinson's disease in humans. Parkinson's symptoms arise from a progressive loss of dopamine neurons. Once the preclinical studies demonstrated a severe reduction of dopamine neurons in Parkinsonian monkeys, the clinical trials at the Massachusetts General Hospital followed shortly thereafter. An initial clinical study by the team showed that altropane allowed scientists to distinguish between people with and without Parkinson's disease, based on a marked reduction of DAT in the Parkinson's patients. A multicenter Phase III trial of altropane neuroimaging is currently evaluating the technique's ability to distinguish Parkinsonian from non-Parkinsonian tremors.

Altropane also may help to diagnose attention deficit hyperactivity disorder (ADHD), which is characterized by excess DAT in the brain (*Biological Psychiatry* 57:1293-1300, 2005). The team used altropane to detect an increase in DAT density in six adult ADHD patients. A larger study of altropane as a diagnostic agent for ADHD is underway.

—SCOTT J. BROWN