THE CSTE WASHINGTON REPORT

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EDITOR'S NOTE"Filarial diseases are treatable, but the current treatments were discovered decades ago," says NIAID Director Anthony S. Fauci, M.D. "There is an urgent need for new discoveries in this area because of the limitations of the current drugs, including toxicities and the development of resistance."
The *B. malayi* genome reveals dozens of potential new targets for drugs or vaccines and should provide new opportunities for understanding, treating and preventing elephantiasis and similar diseases. "Having a complete genetic blueprint gives us a better understanding of what genes are important for different processes so you can target them more specifically," says Elodie Ghedin, Ph.D., who led the sequencing project while at

the Institute for Genomic Research, now part of the J. Craig Venter Institute, a not-for-profit research organization based in Rockville, Md. Dr. Ghedin is now a professor at the University of Pittsburgh School of Medicine.0-- additional details are provided in this *Washington Report*.

The *CSTE Washington Report* is provided as an information resource for members of the Council of State and Territorial Epidemiologists on federal legislation and regulation affecting public health and epidemiology in the U.S.

FIRST CONTINUING RESOLUTION MAKING ITS WAY IN CONGRESS – Since none of the 12 appropriations bills funding the federal government agencies and programs has been enacted, a continuing resolution must be adopted before the fiscal year ends on September 30th. Yesterday, the House passed a CR that would fund the federal government through Nov. 16. The vote on the continuing resolution (H. J. Res. 52) was 404 to 14. The Senate is expected to take up the CR before the end of the week. The terms of the CR fund all federal agencies at the FY 2007 through November 16th. Negotiations between Democrats and the White House over increased spending in most of the bills will occur during the period of the CR, but many expect additional, short-term CRs will be needed as the President has vowed to veto all spending over his budget request, even if it is wrapped up in a giant omnibus bill. Indications are now that the Senate will take up its Labor-HHS-Education Appropriations bill soon. The House passed its version in July on a strong 276-140 vote, just one short of a two-thirds majority of those present and voting, which is needed to override a veto.

SENATOR CLINTON INTRODUCES ENVIRONMENTAL HEALTH BILL WHICH INCLUDES CSTE FELLOWSHIP PROGRAM – On September 20, Sen. Hillary Rodham Clinton (D-NY) re-introduced her bill that authorizes the CDC Health Track program. Among the bills provisions are a section which authorizes the CSTE Applied Epidemiology Fellowship Program and provides $2.5 million for non-infectious disease fellows. In introducing her bill, Sen. Clinton stated,

> "The legislation I am introducing today will help us to understand those links. In establishing a coordinated environmental public health network, we can better track chronic diseases like cancer, asthma, and autism. We can establish critical information sharing between the Centers for Disease Control and Prevention and the Environmental Protection Agency, so that those agencies can pool the information that can help researchers and the public identify and address risks. We can increase our resources for biomonitoring, so that we can measure levels of exposure to chemicals. And we can improve our environmental public health capacity, so that we have professionals who are trained to engage in rapid response to environmental health risks across our country."

The bill has been referred to the Health, Education, Labor and Pensions Committee and a companion measure was introduced in the House by Speaker Pelosi on September 24th.

FDA BAN ON SALE OF BABY TURTLES REMAINS INTACT – Congress passed the House version of the FDA bill reauthorizing a series of user fee programs at the Food and Drug Administration (H.R. 3580). A Senate version of the bill had included an amendment adopted during the floor debate that lifted the FDA ban on the sale of baby turtles that currently exists to prevent Salmonella disease in children. CSTE weighed in against the Senate language, urging the House not to incorporate the Senate turtle language, which it did not, and again during conference negotiations to reconcile differences between the bills. In the end, the House version of the bill prevailed. The President is expected to sign it into law.

FOOD SAFETY BILLS INTRODUCED – Three Food Safety bills were introduced on September 20th. Rep. Frank Pallone (D-NJ), Chairman of the Health Subcommittee of the Energy and Commerce Committee introduced the Consumer Food Safety Act (H.R. 3624) which would establish a comprehensive program to ensure the safety of food products intended for human consumption which are regulated by the Food and Drug Administration. Provisions include assistance to states to develop food safety programs and a requirement that CDC create a food safety surveillance system, among other provisions. No authorized funding level is specified. Rep. John Dingell (D-MI), Chairman of the Committee on Energy and Commerce Committee introduced the Food and Drug Import Safety Act of 2007 (H.R. 3610). This bill is aimed at improving safety of imported food through research to develop new testing technologies, user fees to support the oversees inspection of food, and other purposes. A summary of the bill is posted on the Energy and Commerce Committee website: http://energycommerce.house.gov/. Sen. Tom Harkin (D-IA) introduced S. 2077, a bill to establish a program to assure the safety of fresh produce intended for human consumption, and for other purposes. It has been referred to the Committee on Agriculture, Nutrition, and Forestry. Text of the bill is not yet available.

AHRQ AND FDA TO COLLABORATE IN LARGEST STUDY EVER OF POSSIBLE HEART RISKS WITH ADHD MEDICATIONS -- Two U.S. Department of Health and Human Services agencies will collaborate in the most comprehensive study to date of prescription medications used to treat attention deficit hyperactivity disorder (ADHD) and the potential for increased risk of heart attack, stroke or other cardiovascular problems.

Researchers supported by the Agency for Healthcare Research and Quality (AHRQ) and the U.S. Food and Drug Administration (FDA) will examine the clinical data of about 500,000 children and adults who have taken medications used to treat ADHD to determine whether those drugs increase cardiovascular risks.

Because medications used to treat ADHD can increase heart rate and blood pressure, there are concerns about the drugs' potential to increase cardiac risks. It is also thought these risks may be different for adults and children, but more evidence is needed about the long-term effects of using ADHD medications.

The planned analysis follows an FDA-sponsored preliminary study that compiled information from large health care databases on prescription drug use, inpatient care, outpatient treatment, and health outcomes, including death. Based on that effort, researchers identified people who took ADHD drugs during a 7-year period ending in 2005. AHRQ, which sponsors research on clinical effectiveness and safety, will team with FDA to complete the analysis of the data.

"This study highlights one of AHRQ's most important missions: to collect and analyze scientific evidence that will help patients, policymakers, and clinicians make the best possible decisions," said AHRQ Director Carolyn M. Clancy, M.D. "This partnership with the FDA is a great way to move closer to answering important clinical questions that affect children and adults who have ADHD."

"Case reports have described adverse cardiovascular events in adult and pediatric patients with certain underlying risk factors who receive drug treatment for ADHD, but it is unknown whether or not these events are causally related to treatment," said Gerald Dal Pan, M.D., director of FDA's Office of Surveillance and Epidemiology. "The goal of this study is to develop better information on this question."

The study will be coordinated by Vanderbilt University researchers on contract through AHRQ's Effective Health Care program. Data analysis will be performed by researchers at Vanderbilt, Kaiser Permanente of California, the HMO Research Network and i3 Drug Safety, as well as from FDA and AHRQ. The analysis will include all drugs currently marketed for treating ADHD. The study will analyze the risks of all the drugs as a whole, and risks of the drugs grouped by class.

The analysis will take about 2 two years to complete. Results are expected to be important not only to patients, their families and health care providers, but also to government insurance programs. Medicaid, Medicare, and the State Children's Health Insurance Program provide reimbursement for drugs prescribed for ADHD. This information could also be used to inform product labeling, which is used by health care providers when making treatment decisions.

ADHD is a behavioral disorder that, in many patients, causes hyperactivity, and may have a significant impact on school performance and social functioning. According to the National Institute of Mental Health, ADHD affects approximately 3 percent to 5 percent of school-age children and about 4 percent of adults.

Use of ADHD drugs has increased in recent years among children and adults. A recent AHRQ analysis of medication expenditures found three ADHD drugs—Concerta, Strattera, and Adderall—ranked among the top five drugs prescribed for children ages 17 years and younger. About $1.3 billion was spent on those drugs in 2004, the study estimated. Adult use is also believed to be increasing.

In May 2006, based on a review of anecdotal reports of heart attack, stroke and sudden death among patients taking usual doses of ADHD medications, the FDA asked drug manufacturers to revise product labeling to reflect concerns about possible adverse

events. Drug manufacturers have created patient Medication Guides for individual products to help patients understand risks.

FDA and AHRQ recommend that individuals using or being considered for treatment with ADHD drug products work with their physician or other health care professional to develop a treatment plan that includes a careful health history and evaluation of current health status, particularly for cardiovascular and psychiatric problems, including assessment for a family history of such problems.

NIH-FUNDED SCIENTISTS SOLVE GENETIC CODE OF PARASITIC WORM THAT CAUSES ELEPHANTIASIS -- "Filarial diseases are treatable, but the current treatments were discovered decades ago," says NIAID Director Anthony S. Fauci, M.D. "There is an urgent need for new discoveries in this area because of the limitations of the current drugs, including toxicities and the development of resistance."
The *B. malayi* genome reveals dozens of potential new targets for drugs or vaccines and should provide new opportunities for understanding, treating and preventing elephantiasis and similar diseases.

"Having a complete genetic blueprint gives us a better understanding of what genes are important for different processes so you can target them more specifically," says Elodie Ghedin, Ph.D., who led the sequencing project while at the Institute for Genomic Research, now part of the J. Craig Venter Institute, a not-for-profit research organization based in Rockville, Md. Dr. Ghedin is now a professor at the University of Pittsburgh School of Medicine.

When a mosquito bites someone infected with *B. malayi*, it ingests microscopic worms that develop into infectious larvae. These larvae are then deposited onto the skin of the next person bitten. Once the parasites penetrate the skin, they wend their way to the body's lymphatic system — a network of fine vessels and organs that drains fluid from the body's tissues and plays a key role in coordinating the immune response by concentrating immune cells in the lymph nodes. Male and female worms cluster, intertwining in the draining vessels just below the lymph nodes, and mate. A fertile female may produce 1,000 or more larvae a day and grow to be three or four inches long.

This filarial union can cause severe disease. Because they most often position themselves in front of vessels draining liquid from the lymph nodes, the worms can effectively obstruct the drainage. This causes the surrounding tissues to fill with fluid and swell to elephantine proportions.

As the disease progresses, tissues in the swelling arms, legs or scrotum can die or become infected, turning black and oozing puss. Making matters worse, the fluid accumulation can lead to permanent disfigurement over time as the swollen limbs become solid masses with connective tissue, blood vessels and nerve endings. Reducing the bulbous tissue may require major surgery.

Female *B. malayi* worms can live up to eight years in the human body. This longevity complicates elephantiasis treatment because existing drugs for treating the disease target the larvae only and do not completely kill the adult worms. The drugs often must be taken for years, and the worms can cause massive immune reactions when they die, releasing foreign molecules in the body.

The worm's longevity is curious because it lives for years in the shadow of the lymph node, where immune cells meant to clear the body of infections congregate. One way the worm survives is by releasing chemicals that dampen the human immune response. *B. malayi* is so good at this that most people who are infected have no symptoms: The worms can live in their bodies for years without their even knowing it.

Understanding how this particular parasite has adapted to humans may yield medical benefits far beyond those places where elephantiasis is common, according to collaborator Alan L. Scott, Ph.D., of the Bloomberg School of Public Health at Johns Hopkins University. Worms can be viewed as foreign tissue transplanted into the human body. But unlike baboon hearts or pig kidneys, which the immune system quickly rejects, worms can survive for years in the body. Discovering how they do so may someday benefit transplant surgery, according to Dr. Scott.

Along with NIAID, J. Craig Venter Institute, and Johns Hopkins, collaborators on the project included researchers from the University of Edinburgh; New England Biolabs; the University of California, Davis Genome Center; Smith College; Imperial College, London; the University of Dundee; Divergence, Inc; Washington University; Lyon College; The Australian National University; the University of Toledo; the New York Blood Center; the Hospital for Sick Children in Toronto; the University of Göttingen; and the University of Alabama.

HIV PROTEASE INHIBITORS SHOW POTENTIAL AS CANCER TREATMENTS IN PRECLINICAL STUDIES -- Several protease inhibitors that are used in combination with other drugs to treat Human Immunodeficiency Virus (HIV) infection may also be effective against certain types of cancer, according to researchers from the National Cancer Institute (NCI), part of the National Institutes of Health. Nelfinavir (Viracept®), Ritonavir (Norvir®), and Saquinavir (Invirase®) inhibited growth of several types of cancer cells, with Nelfinavir being the most effective. These results appear in the September 1, 2007 issue of *Clinical Cancer Research*.
The NCI research team investigated HIV protease inhibitors because these drugs are known to inhibit the activation of Akt, a protein that has been implicated in the development of many types of cancer, including non-small cell lung cancer. Using lab studies (called *in vitro* studies) and mouse models, the researchers tested six different protease inhibitors against non-small cell lung cancer as well as a panel of 60 human cancer cell types, in cultures (called cell lines) derived from nine different kinds of malignant tissue. When given in doses that were previously proven to be safe in HIV-infected patients, three of the six protease inhibitors (nelfinavir, ritonavir and saquinavir) inhibited growth of non-small cell lung cancer and every cell type in the set of 60 kinds

of cancer cells.

“There are many common threads between cancer and HIV/AIDS, and this research underscores the value of NCI’s involvement in HIV/AIDS research,” said NCI Director John E. Niederhuber, M.D.

In this study, nelfinavir and saquinavir were more potent than the other HIV protease inhibitors examined. They each had similar abilities to prevent tumor growth, and induce programmed cell death, or apoptosis, which is a normal process that rids the body of old or damaged cells. The molecular structures of these two drugs share a trait that is not found in the other drugs that were tested, and the researchers speculate that this trait might provide an explanation for the relatively higher potency of these two drugs. Nelfinavir was the most effective of all the protease inhibitors tested, and was able to cause two different types of cancer cell death - apoptosis and non-apoptotic cell death. In this study, non-apoptopic cell death was related to induction of stress on part of the cell that synthesizes proteins called the endoplasmic reticulum (ER), which subsequently led to autophagy, a normal process of self digestion that generates energy for the cell under conditions of stress. In the past, other anti-cancer agents have been shown to induce either ER stress or autophagy in a test tube, but in this study nelfinavir was also able to initiate this process in cells that had been transplanted into mice. Other studies have also shown that nelfinavir could induce apoptosis, but non-apoptopic cell death via nelfinavir was a new discovery.

“ER stress and autophagy are cellular processes that are gaining importance in cancer research because we suspect that impaired autophagy may contribute to cancer development,” said Niederhuber. “Markers of ER stress and autophagy will be useful biomarkers for nelfinavir as its clinical development proceeds.”
Nelfinavir was successful in inhibiting growth of both drug-sensitive and drug-resistant breast cancer cells, indicating that this drug could be useful against cancer cells that have acquired resistance to common anti-cancer therapies, such as tamoxifen and trastuzumab. There is also evidence that use of nelfinavir may be able to overcome resistance to radiation.

Based on the results of this study, senior investigator, Phillip A. Dennis, M.D., Ph.D., from the Medical Oncology Branch of the NCI Center for Cancer Research, and his colleagues have just begun a new clinical trial to test nelfinavir in cancer patients. This trial will determine how much of the drug can be tolerated by cancer patients (toxicity), and how the drug behaves in the body and reacts with the tumors (pharmacokinetics). The process of identifying new indications for already approved drugs, called repositioning, takes advantage of existing data on toxicity, pharmacokinetics, and potential side effects. There are several successful examples of this approach, indicating that drug repositioning could complement new drug development, with decreased risks and reduced costs.

“The need for expedited development of effective cancer therapies is critical,” said Dennis. “Repositioning drugs that are already FDA-approved for use in humans could

greatly accelerate the development of new cancer therapies. Our data suggest that, given its wide spectrum of activity and ability to be administered through two different transmission routes [oral and intraperitoneal], nelfinavir could be successfully repositioned as a cancer therapeutic."