Columbia researchers

By Elizabeth Reza
Spectator Staff Writer

The Columbia School of Physicians and Surgeons, together with affiliates Harlem Hospital and St. Luke's-Roosevelt Hospital are spearheading projects on the cutting edge of AIDS research.

The initiatives include clinical work with patients already infected with Human Immunodeficiency Virus (HIV), studies of mother-to-child transmission, the progression of AIDS in children, historical studies which follow the progression of the virus in the Harlem population, psychiatric studies which examine the effect of AIDS on neurological development and functioning, and studies which chart the natural history of HIV in gay men and intravenous drug users. Each involves the cooperation of a multitude of different departments across the spectrum of disciplines.

Clinical

A clinical study which represents a new approach to treating infections was launched at the beginning of October, according to Director of Presbyterian Hospital's AIDS Program Dr. Jay F. Dobkin, CC '68.

In the study, a new agent, soluble CD4, is being injected into the blood stream of AIDS patients who are already being treated with an antiviral drug Zidovudine (AZT) in hopes that it will prolong the period of AZT's effectiveness in suppressing viral activity, Dobkin said.

"That's attacking the virus at two separate and important points of its life cycle," said Professor of Medicine Dr. Leonard Chess, who is the principle investigator of a multidepartment project titled "Basic Molecular and Cellular Mechanisms Important in AIDS Pathogenesis."

CD4 is a receptor agent which exists naturally in the human body on the surface of the T4 cells, which are white blood cells that help fight infection. CD4 is important in antigen recognition because it discriminates viruses from cells, and when triggered, it activates the lymphocytes to perform their virus fighting functions, according to Chess. It was first cloned by Columbia Professor of Biochemistry Richard Axel in 1985, he added.

Chess said he began CD4 studies over a decade ago, before anything was known about AIDS, because it is such a critical agent in the body's immune system.

During later studies, it was found that only CD4 positive cells were infected with HIV, and that no infection resulted when antibodies which blocked the CD4 activity were administered, Chess said.

"That suggested that CD4 might actually interact with the virus and allow interaction," Chess said.

What he said he discovered is that the CD4 coating on the T4 cells binds with the outer coating of the virus, and allows the virus to enter the T4 cells and kill them.

"Cells critical for recognizing foreignness are being destroyed and patients are dying of infectious agents that are normally relatively benign," Chess said.

In fact, AIDS targets those cells which express CD4 on their surface, Axel said, a paradox when one considers that these are the cells that normally fight infection.

"We established that CD4 is the receptor for the virus, or at least a key in infection," Chess said.

Because of these results, drug companies have manufac-

tured soluble CD4 which lacks the chemical link that would normally bind it to the surface of the T4 cell.

Laboratory experiments have demonstrated that HIV binds with the soluble CD4, keeping it from binding with the CD4 on T4 cells, which are left unharmed, according to Chess.

Under these circumstances, lab studies have shown that the T4 cell is 100,000 times less likely to be infected by HIV, according to Axel, showing it to be tremendously effective.

The aim, therefore, is to block interaction of the CD4 with the HIV without inhibiting its effectiveness in fighting other viruses, Chess said.

Studies conducted on experimental drugs such as CD4 are conducted in three phases.

In the first phase of the soluble CD4 study, it was determined that injections of CD4 into the blood stream were non-toxic, Chess said.

"You know it doesn't hurt people, but does it do any good?" Chess asked.

Therefore, the second phase of the study, which began earlier this month, gauges the efficacy of the drug.

According to Dobkin, patients who received the highest doses of CD4 in the first phase of the study seemed to show a positive reaction.

"It certainly wasn't spectacular and not basis to say the drug is effective and no more studies are needed," Dobkin said.

In the current stage of the study, 30 AIDS patients, in addition to receiving AZT, are being injected with soluble CD4 over the course of six months. Physicians will be gauging viral activity in the patients to determine whether the soluble CD4 is having beneficial effects, Dobkin said.

The patients participating in this study are ambulatory, relatively healthy individuals, according to Chess.

By using the two drugs simultaneously, Chess said he is

hopeful that they will be able to see greater inhibition of HIV caused by smaller doses of the drugs.

AZT, which is toxic in high doses, works by blocking the transcription of HIV's genetic material into DNA which can be integrated into the DNA of the host T4 cell.

Administering the two drugs together, but in lower doses, has proven effective in laboratory experiments, Chess said.

Dobkin said he is optimistic that the study might yield results quickly, but that it is unlikely they would be positive enough to establish CD4's potential as an effective medication for AIDS patients. Most likely, it would pass on to a larger Phase III study which would hopefully show that soluble CD4 is more effective or as effective as current treatments, he added.

Current research on soluble CD4 is funded by the drug companies which are manufacturing it. But if CD4 were to ever go on the market, it would probably be more expensive per gram than AZT, because it can only be produced through expensive methods, Chess said.

AZT costs about $4,000 per year. But through the AIDS Drug Assistance Program, a federally and state funded program, students who are infected with HIV can receive the medication at no cost, according to Paul Douglass, co-director of the Columbia Gay Health Advocacy Project. In New York state, AZT is available at no cost to all residents with incomes below $42,000 per year.

It will also be important to develop a method which will deliver the CD4 by a means other than injection, Dobkin said, since the logistics of having to continually inject the massive doses of CD4 that would be necessary are impractical.

A related problem with CD4 is that is rapidly destroyed in the body, according to Axel.

"If derivatives of soluble CD4 are developed that are stable, one might anticipate that it would inhibit viral infection in the

organism," Axel said.

One alternative method of delivering a substance such as soluble CD4 to the body that is being investigated is the idea of transplanting genes from CD4 to an artificial secretory organ and than implanting that "organoid" in the body, Dobkin said.

Research on CD4 could take decades to finalize, Dobkin said.

"The problem with AIDS research is that it's an atmosphere that's high pressure. Stuff is picked up and discarded too readily," he added. "The expectations are very high and at times unrealistically high about how fast you can move."

CD4 is also being investigated by several other research teams outside the Columbia community.

Pediatric Research

There are three major initiatives in pediatric research regarding AIDS currently underway at Columbia, according to Associate Professor of Clinical Medicine Dr. Jane Pitt.

The AIDS Clinical Treatment Group (ACTG) of the National Institute of Allergies and Infectious Diseases sponsors 13 pediatric centers across the nation where researchers are investigating various methods to treat infants and children who are HIV positive.

Children are defined as persons 13 years old or younger.

In New York City alone, there are about 400 children infected with HIV, according to Principal Investigator Anne Gershon.

Women are the fastest growing demographic group nationwide, making mother-to-child transmission an increasingly dangerous health hazard.

In one study, the patients are receiving AZT in addition to immunoglobulin, a class of proteins that contain antibodies, Pitt said.

"There is some evidence that antibodies seem to offer some protection to children infected with HIV," Gershon said.

The study is closed, unlike other pediatric studies which continually admit new patients, and involves only three very young infants, Gershon said.

In addition to the immunoglobulin administration, some of the children will soon be receiving CD4 as a part of a phase one study which hopes to establish that CD4 linked with immunoglobulin lasts longer in the body, Pitt said.

A second clinical study which will begin within the year will involve giving an immunoglobulin with many anti-HIV antibodies to newly delivered babies, with the goal of altering infection rate, Pitt said.

It has been found that some mothers with AIDS have a certain antibody against HIV and these mothers seem not to transmit HIV to their babies, Pitt said.

This study seeks to discover whether infants can be treated with this same antibody, she added.

"The object of the high titre [measurement of antibody concentration] is to cure the HIV infection or prevent other infections," Gershon said.

In less than a year, Pitt said the HIV Center for Clinical and Behavioral Studies plans to launch a study which will use Dideoxyinosine (DDI) and Dideoxycytidine (DDC), two new anti-HIV drugs that are currently available to adults only.

In this study, children who cannot tolerate AZT will be

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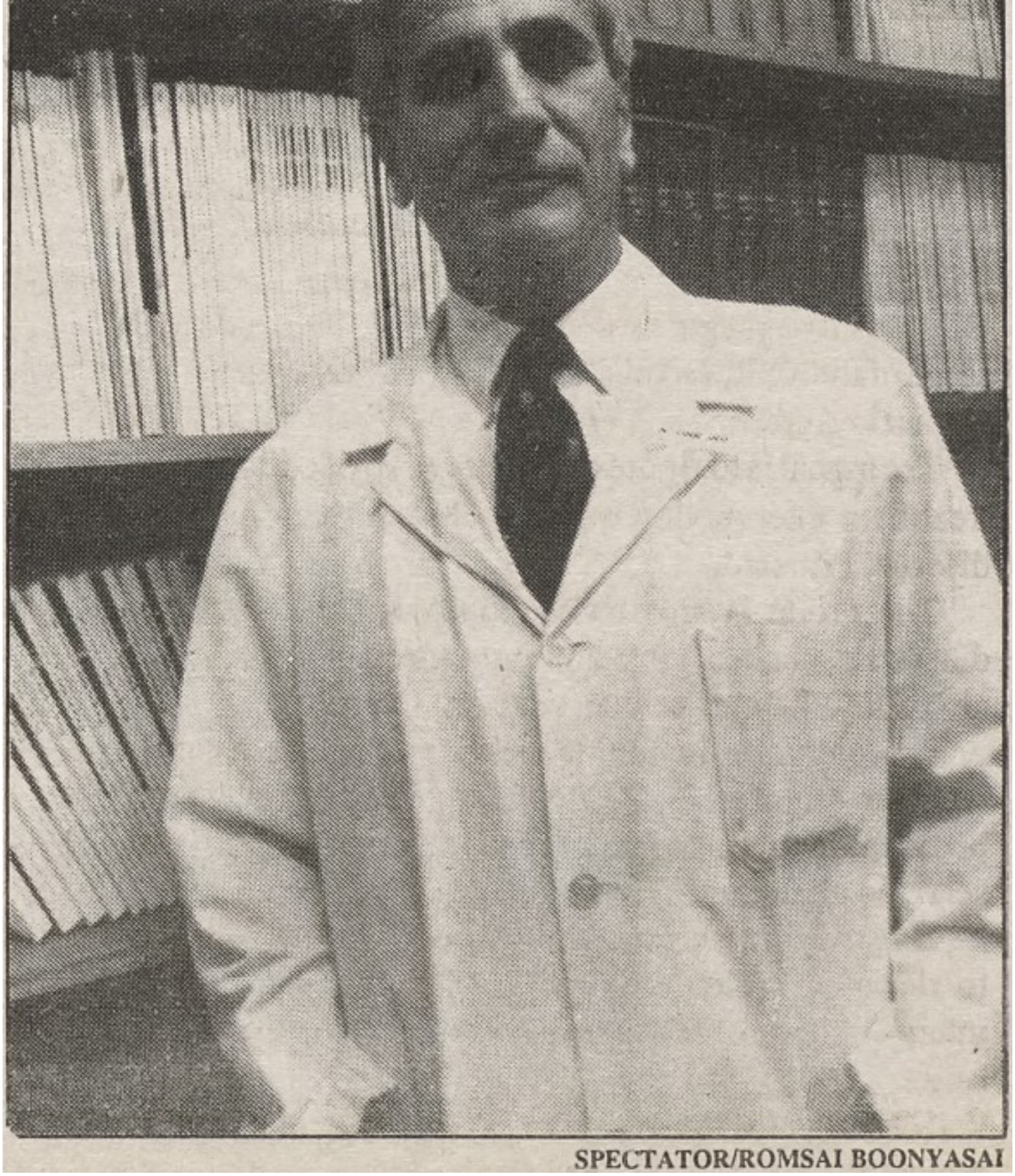
Dr. Anne Gershon, principal investigator at the AIDS Clinical Treatment Group



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Dr. Leonard Chess, professor of medicine at Columbia Presbyterian Medical Center