he dream of developing a vaccine against HIV/AIDS is shared by many scientists throughout the world. That dream moves closer to reality for Abraham Pinter, PhD, of the Public Health Research Institute (PHRI) at NJMS, who recently received a five year, $15.9 million grant from the NIH’s HIV Vaccine Research and Design (HIVRAD) program to conduct research in HIV vaccine development.

Pinter is among an elite group of researchers worldwide who are studying the development of a vaccine for HIV. With this grant, he’ll direct an international team of researchers from as far away as New Orleans, Los Alamos, Seattle and South Africa—all working towards this common goal. Receiving such a highly competitive grant positions the PHRI/NJMS team at the forefront of HIV/AIDS research.

“This is an exciting opportunity,” says Pinter. He explains that the group’s goal is to develop a new approach to producing a prophylactic, or preventive, vaccine. “Once someone is infected and the virus becomes established, it is difficult for the immune response to control the infection. But if an appropriate neutralizing antibody response can be produced by vaccinating people before they are exposed to the virus, there is a much greater chance that these antibodies will be able to block infection.

“There has been great difficulty in developing a successful vaccine for HIV, compared to other viruses,” says the scientist. “Our lab has identified one important reason why. It is known that HIV mutates when it spreads, and for many years, it’s been believed that the main difficulty with HIV vaccines is that such mutations rapidly lead to the loss of neutralization targets. We discovered that HIV uses a more effective method for protecting itself, which doesn’t require mutations at the target sites.”

Through this mechanism, called conformational masking, the virus forms a structure which covers up the antibody targets so they are no longer accessible to the antibodies. Pinter explains that many neutralization targets are in regions that the virus needs for replication, and therefore mutations at these sites may reduce the ability of the virus to spread, and thus come at a cost. Conformational masking can protect multiple targets at once, without requiring mutations at the antibody-binding sites themselves. “There may be other viruses that do this as well, but the viruses for which we do have vaccines, such as polio and influenza, don’t use this mechanism.”

A related discovery was that the masked structures contained a new class of neutralization targets that are actually more sensitive...
to antibodies than the standard sites that have been studied for years. These new targets are present in the natural trimeric structure on the surface of the virus, but are not retained after the proteins are solubilized and purified. “Since most early antibody and vaccine studies used soluble viral proteins, this class of targets was completely missed until recently.” The realization of the importance of these new targets, called Quaternary Neutralization Epitopes, and the identification of potent monoclonal antibodies and broadly-reactive patient sera that recognize such targets, led to Pinter’s blockbuster grant.

Pinter’s lab at PHRI currently includes a core of approximately 12 researchers, and he’s in the process of recruiting additional scientists for the demanding work ahead. The grant also allowed Pinter to assemble a group of internationally respected collaborators to work on this project. “Each collaborator was selected for their ability to bring something unique to the project,” he says. For example, the South African scientists, Lynn Morris, PhD, and Carolyn Williamson, PhD, have done important work in identifying HIV patients with this type of antibody response. One of their studies monitors people who are at high risk to infection by HIV. “This team is actually trying to find the uninfected person right about the time they become infected. This allows scientists to carefully characterize the evolution of the virus—to see how the virus mutates and how this leads to changes in the antibody response,” explains Pinter. “That’s difficult to do in this country, where treatment with anti-viral drugs is standard and the rate of infection is much lower.” Another collaborator, Shiu-Lok Hu, PhD, studies how chimeric viruses called SHIVs (formed between HIV and a related monkey virus known as SIV, Simian Immunodeficiency Virus) infect monkeys and cause an AIDS-like disease. A critical aspect of the grant will involve inserting the new vaccine targets into SHIVs and testing the immune response in animals.

Pinter, a life-long native of Brooklyn, spent the early part of his career working with murine and feline leukemia viruses at New York’s Memorial Sloan-Kettering Cancer Center. “These animal retroviruses were important tools for studying cancer, but were not responsible for diseases in humans. In the early eighties, when scientists discovered HIV, it quickly became clear that these were related to the retroviruses and when we moved to PHRI in 1985 we switched our major focus to this new virus.”

Meet the Collaborators

A list of Pinter’s collaborators reads like a global “Who’s Who” in the world of HIV/AIDS research. The list includes researchers at the Wits Health Consortium in South Africa, the University of Washington in Seattle, Tulane University in New Orleans, and the Los Alamos National Laboratory in New Mexico.

At NJMS/PHRI:
Aymeric deParseval, PhD, head of the molecular biology core
Chavdar Krachmarov, PhD, head of the viral immunology core

Outside collaborators include:
Lynn Morris, PhD, chief specialist scientist and head of the AIDS Unit at the National Institute for Communicable Diseases (NICD) in Johannesburg
Carolyn Williamson, PhD, associate professor in the Division of Medical Virology, Institute for Infectious Diseases and Molecular Medicine, University of Cape Town Health Sciences Faculty
Shiu-Lok Hu, PhD, professor of pharmaceutics and microbiology at the University of Washington and Head of the AIDS-Related Research Core at the Washington National Primate Research Center
James Robinson, MD, professor of pediatrics, Division of Infectious Diseases, at Tulane University School of Medicine
Gnana Gnanakaran, PhD, staff member in the Theoretical Biology and Biophysics Group at the Los Alamos National Laboratory

In 2002, PHRI became part of UMDNJ and the group moved to New Jersey to continue the work. “The merger has worked out well for us,” Pinter says. “We have the advantages of being in a state-of-the-art building, along with access to excellent NJMS facilities and the stability associated with a large university.”

Managing his PHRI research group, and now the collaborations, is enormously challenging. “I’ve known many of our collaborators from their published work and from scientific meetings,” he says. “When I became aware that we were looking at similar targets, I initiated collaborations with these scientists, and this naturally led to the combined grant application.” The group communicates regularly through emails and monthly teleconferences, and their first face-to-face meeting in New Jersey, at PHRI, was held in July. Now that they’re officially a team, Pinter hopes to be able to generate rapid progress towards developing the potential of this new approach. “To be able to work with all these outstanding scientists is a tremendous advantage,” says Pinter. “I hope that this grant will enable us to understand these new targets better, and to learn how to efficiently induce these types of antibodies by immunization. The overall goal of these efforts is to come up with a vaccine product that can be tested in humans, and hopefully produce a protective antibody response.”

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