

Discovery

The Newsletter of
the Institute of
Human Virology

FROM LABORATORY TO CLINIC



ROBERT C. GALLO, M.D.

Director of the Institute

Message From The Director

The Institute remembers Delegate Howard Peters Rawlings

In November, the Institute of Human Virology lost a great friend and supporter. Delegate Howard Peters Rawlings, a founding member of the IHV's board of advisors, had been a member of the



Del. Rawlings

Maryland House of Delegates since 1979 and was chairman of the Appropriations Committee. He passed away at the age of 66 and hundreds attended his funeral, paying tribute to a teacher, politician, fearless fighter and gentleman who championed higher education and was a mentor and inspiration to many.

My first impression of Pete Rawlings was a lasting and true one. He was a man large in stature, deep of voice, yet gentle, concerned, intelligent and determined to make good things happen. These characteristics imbued him with a presence of a strong protective masculinity that fostered growth -- and security -- in the most tender of times.

We at the Institute know from first-hand experience the care and nurture that were a part of Rawlings' nature and legacy. The IHV was founded just seven years ago and "Pete" was unwavering in his support of both the scientific research and clinical care conducted at the Institute and the global reach that our work encompasses. But he also saw the depth and devastation of the AIDS epidemic right here at home and urged local officials -- and the community -- not to forget the patients in our own back

yard. That sense of urgency is as crucial today as it was almost a decade ago -- Maryland, let us not forget, ranks third nationally for new HIV infections and, a surprise to most, has an infection rate that rivals that of sub-Saharan Africa. That is something we don't see recognized or discussed nearly as often as we should.

But it is through the help of compassionate souls such as Rawlings, who take to heart the true loss of what has become the world's deadliest pandemic

Del. Rawlings has long been a friend, supporter, advocate and watch dog for both the Institute of Human Virology -- and AIDS patients everywhere.

in history and push for and indeed insist on progress in AIDS research, prevention and educational outreach and actual patient care -- that we make true progress in the fight against AIDS. Two decades after the discovery of HIV, the impact of HIV/AIDS continues to be minimized -- but Rawlings saw how close this epidemic hits home and he advocated for those who can't advocate for themselves. Just months before he passed away, Rawlings spoke in support of the Institute's undying mission, just as he had many times before, and rallied for international commitment to putting an end to an epidemic whose worst is yet to come. He made this comment:

"AIDS is ravaging much of humankind. The health and well-being of future generations depends on scientific
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Sayed Abdelwahab, Ph.D.
Research Associate

A Long-awaited Weapon Against HIV: Simulated Human Exposure

An ancient military proverb on the art of waging war advised "know your enemies better than you know your friends." In the ongoing battle against HIV, a major stumbling block to understanding the effects of HIV on humans was the inability to study the initial, direct responses of susceptible immune CD4+T cells. The secret to kick-starting (activating) these immune cells once they were removed from the body was unknown, as were the cellular changes that might result.

A dramatic edge for HIV research arises from the research of Sayed Abdelwahab in the IHV's Vaccine Research Division. Using a method for inducing activation of cultured human naive CD4+ T lymphocytes, he has analyzed the cellular changes that accompany activation of previously unexposed cells.

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Cyclic Therapy Clinical Trial Supports Reduced Antiviral Therapy

For millions of HIV-infected persons, drug therapy simply to hold HIV in check can be financially, physically, and psychologically draining. Triple drug combina-



Anthony Amoroso, M.D.

tions, upward of 10 pills a day, fatigue, secondary infections or diseases, and drug toxicities make compliance a daunting prospect. Missing even 5% of drug doses can result in HIV rebounding to pre-treatment levels. Anthony Amoroso, M.D., began wondering whether certain patients could skip several weeks of therapy, take upward of 50 percent less drugs, and still avoid viral rebound. It couldn't happen fast enough.

Amoroso is an Assistant Professor in the University of Maryland Biotechnology Institute and the University of Maryland School of Medicine, as well as Director of the HIV Care and Infectious Disease Clinic at the Baltimore Veterans Administration Hospital. Since May 2002, he has been conducting a clinical trial with HIV-infected patients that uses a "cyclic therapy" design in conjunction with a drug combination that delivers a four-fold punch against HIV.

Patients with pre-stabilized infections are first given the compound hydroxyurea, plus three more "standard" antiviral drugs, for four weeks. Then, still giving hydroxyurea, the three antivirals are discontinued for two weeks, followed by multiple cycles of "one week on-two weeks off" the antivirals, for a total of eight cycles.

There are major improvements in Amoroso's study over previous "treatment interruption" studies, which ultimately produced extensive viral rebound. Amoroso's "ace in hand" is the use of hydroxyurea, a chemical typically used to arrest the growth cycle of cells. "Hydroxyurea limits the massive HIV replication that occurs in highly activated and dividing target T cells," says Amoroso. "It also increases beta-chemokines (immune-modulating compounds), which have been shown to block HIV infection in laboratory cells, with potentially significant implications for patients."

In addition, the three antivirals used -- Tenofovir, Sustiva, and 3TC -- were carefully chosen for their ability to infiltrate HIV "reservoirs" (cells that are not dividing, but serve as hideouts for inactive but potent HIV), reduced toxicities, similar time courses of action in the body, and, in the case of Tenofovir, greatly enhanced effectiveness when combined with hydroxyurea.

Amoroso is excited by preliminary results. "Of seven patients who have participated in this on-going trial, all but one has maintained complete viral suppression," he says, "and that's using one-third the amount of traditional anti-viral drugs." His patients boost his enthusiasm. "They want to stay in this trial, even though they've finished. Most of them had 'pill fatigue' and chronic toxicities when they began, and now they want to keep going." Pending results, Amoroso plans a new study with a "one week on-three week off" cycle.

"The ultimate goal is to make drug therapy more accessible, less toxic, and less costly, to HIV-infected people around the world," Amoroso states.

Simulated Human Exposure, continued from page 1

"We have developed a system for characterizing the early changes in CD4+ T cell phenotypes (collective physical properties) and functions over the course of activation, comparing various antigens (foreign substances that elicit immune response)," he says. "No one has successfully done this, so extensively, for human cells, until now."

Abdelwahab credits his success to hard work and to human dendritic cells, the only cells capable of stimulating naïve T cells in culture. Found in mucous membranes lining body cavities (e.g., the gut wall), dendritic cells engulf antigens, mince them up, and then present them to T cells, an approach similar to waving a "red flag" at a bull. Naïve T cells respond directly to this stimulus with an established sequence of primary immune responses, including initial growth and division, followed by controlled cell death, and finally the establishment of "memory" or recall for the antigen. "We can basically simulate human exposure to HIV, now," says Abdelwahab.

The most profound applications of this system encompass "use as an in vitro screening system for HIV vaccines, prior to clinical trials, to assess the likelihood that a person will respond," Abdelwahab states. "It can also be used to screen for adjuvants (substances that boost immune reactions to antigens), by asking whether cellular responses are enhanced in their presence." Certain adjuvants could promote a greater magnitude of defense against HIV.

Abdelwahab is especially excited by the latest discovery enabled by his system. He and his colleagues discerned that, following activation, certain populations of activated CD4+ T cells secrete an evolving array of anti-HIV-1 suppressive factors, possibly able to retard and prevent HIV infection. "These factors are chemokines (molecules that modulate immune responses)," says Abdelwahab, "and their secretion by select cells may help explain why those T cells are protected while others become infected." He hopes this knowledge may lead to new and improved strategies for designing HIV vaccines, and shed light on how a human host can control viral infections.

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Spotlight: Staffan Hildebrand, IHV Board of Advisors



Staffan Hildebrand

renowned documentary film director, Staffan Hildebrand is also Creative Director of the Sweden-based, Karolinska Institute's "Face of AIDS—Global Documentation Center." Describing his role as one of "unbiased film chronicler of the global HIV/AIDS epidemic," Hildebrand has been bringing his unique and personal perspective to the IHV Board of Advisors since asked to join by IHV Director Robert Gallo in January 2001.

Hildebrand accepted the challenge to create a film archive documenting the course of the AIDS epidemic from Hans Wigzell, President of the Karolinska Institute and the Nobel Prize Committee, 16 years ago. "I knew on the bus ride home from our meeting at the Institute that my life was about to change," Hildebrand says. "Wigzell told me this would be a 'life assignment' of 20-30 years in duration, and he was a visionary."

Robert Gallo was "the first scientist I met after I accepted this assignment, in 1987," states Hildebrand, "and he gave me his entire day to help with

my global documentation project." Hildebrand has documented Gallo's work since, and is a staunch supporter and friend.

Traveling around the world to HIV/AIDS epicenters, Hildebrand films the people behind the statistics. He has seen the despair of villagers in Nigeria, slum-dwellers of Bangkok, and urban poor of Baltimore. At each IHV Board meeting he shows a new film, "focused on developing countries and aimed at enhancing the global perspective," he states. "In a sense, I help 'push' Gallo's vision and ideas." He views his primary role as "a communicator and bridge-builder" between scientists and the HIV/AIDS community.

Hildebrand is most impressed with the trail-blazing example set by the IHV for other Institutes, especially in bringing scientists into the HIV/AIDS trenches. "Their courage in entering Nigeria and setting up four

Centers of Excellence may be the most important development," he says firmly. "People were saying 'there are no scientists in Africa' and now that isn't so."

As for himself, Hildebrand is no stranger to commitment. "Even the times when this project went without funding, I took more commercial work to keep it going. I had promised Wigzell, and I never gave up. In the end, I knew I'd be proud of this."

Prof. William Walmsley Hall



The IHV would like to welcome William Walmsley Hall, Director of the National Virus Reference Laboratory of Ireland and Chair and Head of the Department of Medical Microbiology, University College Dublin (UCD), to its Board of Advisors.

Professor Hall, whose research interests are in human retrovirology and specifically the Human T Lymphotropic Viruses (HTLV), obtained his Ph.D. from Queen's University Belfast, Northern Ireland and M.D. from Cornell University Medical College in New York. Prior to returning to Ireland in 1996, he spent his entire academe in the United States where he was Assistant and Associate Professor of Medicine at Cornell; Associate Professor and Head of the Laboratory of Medical Virology and Senior Physician at the Rockefeller University in New York. Prof. Hall is Board Certified in Internal Medicine and Infectious Diseases in the U.S. and is a Fellow of the Royal College of Physicians in the UK and the Royal College of Physicians in Ireland.

Since his return to Ireland, Prof. Hall has been responsible for the funding and development of the Centre for Research in Infectious Diseases (CRID) at UCD.

Prof. Hall was President of the International Retrovirology Association from 2001-03 and has been elected Fellow of the American Academy of Microbiology. He currently serves on the Editorial Boards of Journal of Neurovirology, AIDS Research and Human Retroviruses, Neuropathology, Journal of the Acquired Immunodeficiency Syndrome (JAIDS).

Remembering Del. Rawlings, *continued from page 1*

progress and a new approach to prevention and treatment of this disease. I applaud the advances of the IHV in what must become a worldwide endeavor to address this international crisis." Del. Rawlings has long been a friend, supporter, advocate and watch dog for both the Institute of Human Virology -- and AIDS patients everywhere.

"When the IHV was in its infancy and had several very outspoken critics, Rawlings was our champion in Annapolis," recalls Michael Goldrich, the IHV's chief operating officer shortly after its opening in 1996. "He truly believed in the noble purpose of the IHV and would not let

critics judge us too soon. With his leadership and counsel, we weathered the political storm and the IHV today serves more than 4,000 patients. Many, many African Americans in the Baltimore area who suffer from HIV and are now helped by the IHV's clinical program owe a debt, without realizing it, to this great man."

Joseph Bryant, a scientist who heads the IHV's Animal Core Division, recognizes Rawlings for both his compassion and contribution to the cause. "I am so glad I had the opportunity to share with others the gift of meeting and getting to know Pete Rawlings. He was in the same mold as that of Dr. Martin Luther

King Jr., who stated, "When I die, don't mention all of the accolades and honors that were stored on me. I'd like to be remembered as a person who tried to help his fellow man. The Institute of Human Virology will always remember Pete Rawlings for who he was and what he stood for."

Like citizens across the state of Maryland, members of the IHV are ever grateful that our paths crossed, that we were able to know Pete and to be friends with him. One of his legacies is the success of the IHV, but that is just one of many. He was a concerned citizen who made the world a better place.

THE INSTITUTE OF HUMAN VIROLOGY (IHV) at the University of Maryland was established to create and develop a world-class center of excellence focusing on chronic diseases and virally linked cancers. The IHV is dedicated to discovery, research, treatment, and prevention of these diseases and cancers. Its unique structure seeks to connect cohesive, multidisciplinary research and clinical programs so that new treatments are streamlined from discovery to patient. The IHV serves patients locally and the scientific community globally.

RV-144 Prime-Boost Efficacy Trial Begins in Thailand

RV-144, an HIV vaccine efficacy trial, has begun in Thailand, sponsored by the Royal Thai and U.S. governments. It is seeking to determine if a combined vaccine regimen (CVR) comprised of two vaccine candidates— one designed to stimulate a cellular immune response and another to stimulate humoral and augmented cellular immunity – will provide a measure of protection not likely to be achieved by using either component alone.

There is common conception that effective HIV vaccines may require both cell-mediated and antibody-mediated immune responses. No single vaccine candidate currently being studied can adequately provide such a full constellation of immune responses. However a “prime-boost” approach, in which two different candidates are used sequentially, is capable of achieving this goal.

The vaccine components used in this trial are 1) Aventis Pasteur’s ALVAC-

HIV canarypox vector (vCP1521), containing genes of HIV, and 2) VaxGen’s envelope glycoprotein gp120 (AIDSVAX) used together in a CVR in “prime-boost” configuration. ALVAC vectors have been extensively tested for safety, and are designed to induce cellular immune responses to HIV. The envelope glycoprotein was designed to induce antibody responses and has been tested alone in two efficacy trials, but failed to demonstrate any efficacy by itself. However, the new efficacy trial is designed to test the concept that cellular immune responses induced by ALVAC in combination with antibody responses and augmented CD4 T helper responses induced by the CVR will prove efficacious. The CVR has been demonstrated to elicit a broad based immune effector profile, including antibodies and a cellular (CD4+ T cell and CD8+ cytotoxic T-lymphocyte) responses.

In addition to the CD8+ T cell response induced by the ALVAC vaccine

component, the immune response profile of the prime-boost approach is different from that induced by each component alone. These include qualitative changes in CD4+ T cell response, in that it induces different and broadened cytokine profiles, as well as broadened T helper epitope recognition and induction of additional antibody effectors mechanism like antibody dependent cellular cytotoxicity (ADCC).

The hypothesis that cellular immune responses can protect against HIV has not been tested even though it is the foundation of most experimental approaches to vaccination. Thus, the first efficacy test of vaccine candidates that elicit this repertoire of both cellular and humoral immune responses will be a major step forward. This is the principle being tested in RV-144, a community based trial that will assess the CVR’s efficacy in 16,000 volunteers in Southeast Thailand.



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