HIV Vaccine Research at Duke University: A Continued Quest to End the Epidemic

Introduction

In the 1980s, in the early days of the acquired immunodeficiency syndrome (AIDS)—then called gay-related immunodeficiency disease—a frequent response to the disease was to deny its relevance to the general population or to deny its existence at all.

However, this was not the case for the dedicated patient care providers and basic scientists at Duke who understood the seriousness of the expanding epidemic of this new disease and rapidly began to focus on patient care, discovery research, implementation of novel therapeutic regimens, and ultimately working on preventive vaccine development. In the ensuing years these efforts have grown tremendously in scope and scale, and have propelled Duke to the forefront of a concerted, worldwide scientific quest to end the global AIDS epidemic.

Duke investigators, led by Tom Palker and me, worked with the National Cancer Institute team led by Robert Gallo to demonstrate that HIV-1
was the causative agent of AIDS. Once the human immunodeficiency virus (HIV) was isolated, the search for therapeutic interventions and implementation of these therapies for patients quickly ensued at Duke. Kent Weinhold and Dani Bolognesi worked with Burroughs Wellcome in an effort that resulted in the development of the first therapeutic agent, azidothymidine (AZT), available for the treatment of AIDS. Catherine Wilfert, Samuel Katz, and Ross McKinney with their team in Duke Pediatrics led the effort to control HIV infection in children, and they were instrumental in bringing the first treatments for AIDS to HIV-1 positive pregnant women to prevent mother-to-child transmission. David Durack, John Hamilton, John Bartlett, and the Duke Division of Infectious Diseases & International Health worked to develop management and treatment regimens for AIDS patients. Duke investigators, led by Thomas Matthews and Dani Bolognesi, went on to discover a novel drug for the treatment of AIDS, T20 (Fuzeon), that also defined a new class of drugs: fusion/entry inhibitors for treatment.

The following section highlights the work performed at Duke that has been critical to the national HIV vaccine research effort and discusses how this early work has provided a foundation for the increasingly interdisciplinary work needed for vaccine development for pandemic infectious diseases.

**The Early Days of Human Retroviral Research at Duke**

Dani Bolognesi and I were recruited to the study of AIDS by Robert Gallo at the National Cancer Institute, National Institutes of Health in Bethesda, Maryland. (Figure 1) Gallo had recently described the first human retrovirus, called the human T-cell lymphotropic virus type I (HTLV-1), that caused a malignancy of T lymphocytes (termed “adult T-cell leukemia”) sporadically seen in certain geographic areas, such as the southern coast of the United States, the Caribbean, and southern Japan around Nagasaki and the island of Kyushu. Soon after Gallo’s first isolation of HTLV-1, Joseph Moore and I were referred a patient from Florida who was Japanese and 14 years of age in 1945 when the atomic bomb was dropped on Nagasaki. She survived the blast and married an American sailor and immigrated to the United States with him after the war. In 1980, she came to Duke to see us because at that time I was studying the origin of malignant cells in a spectrum of T-cell malignancies—from acute leukemia to chronic malignant T-cell syndromes such as cutaneous T-cell lymphoma. The patient had a unique syndrome of ulcerating skin lesions and painful arthritis of her hands, knees, and ankles. Having read Gallo’s recent paper on the new adult T-cell leukemia syndrome and realizing that the patient did not match other known disease patterns, I took cells from the patient’s blood and joints and put them in tissue culture under conditions that would grow a retrovirus if it was present.

At this time Duke and all other institutions in the United States had no infectious disease isolation facilities except the high-security isolation facilities at Frederick, Maryland, run by the U.S. Army. Moreover, I had just arrived at Duke from training at the NIH, and no laboratory was ready for me here when I arrived. Russ Kaufman also arrived at Duke from the NIH at the same time as myself, and we shared a makeshift laboratory for our first two years at Duke. Therefore, to work on my patient’s leukemia cells, I enlisted the help of Richard Metzger and Dani Bolognesi—two established investigators in the Departments of Immunology and Surgery, respectively. Metzger was a pioneer in transplantation research at Duke and was working with Bernard Amos in Immunology to perfect human organ transplantation. Bolognesi was a PhD virologist who had mapped the structure of animal retroviruses and was working on a human cancer vaccine. I said to them, “I have a patient that I think has HTLV-1 infection, and I need your labs to help me isolate the virus.” Both scientists were excited to help; Metzger turned over his tissue culture lab to me, and Bolognesi called Gallo and arranged for all the reagents to be sent to me to determine if the virus was present in my patient’s cells.
The patient’s cells were non-reactive with all the antibodies against HTLV-1 when they came directly from her body, but after stimulating the T cells with a factor called interleukin-2, the virus burst forth from the cells and were easily identified under the microscope. We also demonstrated the virus in her joints as the cause of her severe arthritis, and she turned out to be the first patient in whom the syndrome HTLV-1-associated arthritis was described. This is a form of arthritis now recognized to be common in Japan that was previously diagnosed as rheumatoid arthritis.

Because of his prior work with HTLV-I, and the relatively uncharacterized nature of the clinical manifestations of the disease, Gallo immediately suspected that the cause of this new disease might be an unusual response to the HTLV-1 virus or perhaps a new retrovirus. He called me one day and asked me to move to Frederick, Maryland, and help him determine the cause of this new disease. He said, “You are an immunologist, a clinician, and have isolated a human retrovirus. You have combined unique qualifications, and we need you.” At this time, I was a single parent of a two-year-old daughter and could neither move nor devote the time to help lead an effort on the new disease. When I told Gallo this, he then said, “You have to work on this disease; it will become the greatest pandemic of our time!” To that I said, “I will have to stay in Durham, but I will help and join the team.”

We began at Duke by organizing studies on a new population of susceptible patients—those with hemophilia. With Tom Palker at Duke and Gil White at the University of North Carolina at Chapel Hill, we set up studies in a facility at Duke with a biosafety level IV laboratory for cancer viruses with what is called a Blickman Line—an isolation cabinet with gloves for the operator to stand outside the sealed cabinet and to manipulate the samples while being separated from the air around the samples. From this work we identified two patients who had antibodies in their blood that cross-reacted with HTLV-1 and were found by Gallo to have the new virus, initially called HTLV-III and now called HIV-1.2 Gallo’s work paralleled the work by Luc Montanier and colleagues at the Pasteur Institute in Paris; a year earlier, Montanier had isolated a virus called LAV, which eventually came to be called HIV-5.

The Duke Human Vaccine Institute
The roots of the Duke Human Vaccine Institute (DHVI) began in 1985 soon after the discovery of HIV-1. In order to tackle this newly emerging infectious disease, Dani Bolognesi and I formed a working group at Duke University Medical Center with Kent Weinhold, Tom Matthews, and Tom Palker. Not everyone at Duke was supportive of AIDS research efforts, but one of the greatest supporters of this effort at Duke was David Sabiston, the chair of Duke Surgery from 1964 to 1994. Sabiston raised $5 million to build the Surgical Oncology Research Facility in 1986, where all AIDS research at Duke was performed, and supported both Bolognesi and me throughout those early and difficult years. (Figure 2) In 1990 Bolognesi and I established the Duke Human Vaccine Institute to support interdisciplinary efforts across Duke to develop vaccines and therapeutics for HIV and other emerging infections that threatened the health of our nation and our world. In a real sense, neither the early work of the Duke Center for AIDS Research and DHVI nor any of the other AIDS basic research at Duke could have been performed without the support of David Sabiston.

Early HIV-1 Vaccine Research
Some of the most elegant work on both HTLV-1 and HIV-1—regarding how these human retroviruses overcame the host cells and “hijacked” the machinery of the host cell to the viruses’ benefit—was the work of Warner Greene and Bryan Cullen in the Division of Rheumatology and Clinical Immunology of the Department of Medicine. Their work played a major role in helping the field understand how human retrovirus genes worked to subvert the host immune system.
Since the beginning of the AIDS epidemic, a major focus of DHVI investigators has been the development of a safe and effective HIV vaccine. The initial efforts in HIV vaccine development were led by Dani Bolognesi, who was working on a cancer vaccine at the time of recognition of the AIDS epidemic and who convinced the National Cancer Institute to change his grant in midstream to an HIV vaccine development grant. At the time of the re-competition of that grant, Tom Palker and I joined Bolognesi, Kent Weinhold, Tom Matthews, and Al Langlois and successfully received a new grant in 1986. David Montefiori later joined the team and became a key national leader in the area of neutralizing antibody work. Early on, Bolognesi teamed with Peter Fischinger and Gallo at the NCI to first focus on the outer-coat protein of HIV, gp120, and showed the ability of gp120 to be a vaccine candidate that could induce antibodies that could prevent infection of the laboratory-grown strains of HIV that were being used by the field. Bolognesi teamed with Scott Putney of Repligen Inc. and our group to define an early target for a vaccine, the V3 loop of the envelope gp120.10,11 With Tom Palker, we converted this region into a vaccine candidate first synthesized by Tony Moody and Richard Scearce in my laboratory, and John Bartlett in the Division of Infectious Diseases carried out the first clinical trial of this HIV vaccine developed in a basic science laboratory and taken directly to the bedside.12 Soon thereafter, Bolognesi, Matthews, and others in the field found that the strains of HIV grown in the laboratory were not like the strains infecting people in the real-life settings, prompting the realization that the field was using the wrong strains of HIV-1 for testing vaccines—a major setback.

More Recent HIV-1 Vaccine Research
Over the years, the HIV-1 vaccine development effort has been long and complicated due to the extraordinary nature of HIV diversity and the ability of HIV to evade host immune responses. Nonetheless, studies demonstrating the ability of cytotoxic T cells (killer T cells) to control HIV replication as well as high levels of neutralizing antibodies to protect against HIV infection (provide sterilizing immunity) have bolstered HIV vaccine developers and suggested that an immunogen that induces broadly reactive killer T-cell responses and B-cell neutralizing antibodies that work against the type of viruses that circulate in the community (so-called primary isolates) could be helpful in stemming the AIDS epidemic. To this end, the DHVI Development Team has a broad-based program to develop a number of experimental immunogen constructs for testing in animals and in humans.

In the late 1990s, although we demonstrated that the V3 loop could induce antibodies that were effective against a few primary isolates, we were discouraged by the realization that the V3 loop vaccines were not going to be effective against the majority of primary HIV-1 strains. Nonetheless, the V3 loop work led to the discovery that the V3 loop was a key component of binding the HIV-1 envelope to the HIV-1 co-receptors CCR5 and CXCR4, and its structure determines the type of co-receptor to which HIV-1 binds.

By 2004 we were at a major impasse and did not know how to think about the problem of why broad neutralizing antibodies were not routinely made by the immune system. We began to look at the few broadly neutralizing antibodies that had been isolated by others in the field over the years from rare patients with HIV-1. These few human monoclonal antibodies had the traits of binding to conserved vulnerable regions (Achilles’ heels) of the AIDS virus, but we noticed that they also had characteristics of antibodies that were “self-reactive” and were frequently removed by the immune system as potentially harmful to the body. We asked if indeed these antibodies were self-reactive and indeed they were,13 and we postulated that indeed the reason these antibodies were not made was because HIV-1 had evolved such that its vulnerable Achilles’ heel regions were mimics of self-protein regions, and to make a protective antibody response to these regions required a special kind of antibody that normally the body doesn’t want to make.14 While we are still working on this hypothesis to determine
if we can use the principles to safely induce the right kind of antibodies with a vaccine, this notion of requirement of self-reactivity of broad neutralizing antibodies opened up for us a new way of thinking about this difficult problem.

Duke investigators now play an integral leadership role in the new Global HIV-AIDS Vaccine Enterprise. The enterprise is a collaboration of independent organizations around the world dedicated to accelerating the development of a preventive HIV vaccine. The first collaborative project under the enterprise was the $300-million Center for HIV-AIDS Vaccine Immunology (CHAVI), funded by the National Institute for Allergy and Infectious Diseases (NIAID) in July 2005 to create a consortium of investigators from academic institutions worldwide, which I lead from the Duke Human Vaccine Institute. Members of the CHAVI Scientific Leadership Group are Myron Cohen at UNC, David Goldstein and myself at Duke, Joseph Sodroski and Norman Letvin at Harvard, George Shaw at UAB, and Andrew McMichael at Oxford.

The goal of CHAVI is to test new vaccine strategies to overcome key immunological roadblocks in HIV vaccine design, and to work faster, in an unprecedented collaborative way. Now in its fourth year, this virtual consortium currently comprises more than 100 investigators worldwide. In 2006, the Bill & Melinda Gates Foundation provided $287 million to fund the second scientific arm of the enterprise, the Collaboration for AIDS Vaccine Discovery (CAVD). The CAVD awarded a consortia grant to me and Garnett Kelsoe in Duke’s Department of Immunology to work on developing novel strategies for inducing neutralizing antibodies against HIV, a major obstacle in the development of an effective HIV-1 vaccine, and awarded David Montefiori in the Department of Surgery a CAVD center grant to provide neutralizing antibody technology to the field and to work on the neutralizing antibody problem. CHAVI and the two CAVD grants are the major implementation projects under the Global HIV-AIDS Vaccine Enterprise that were funded at Duke. CHAVI also funds collaborative research sites in Uganda, Malawi, Tanzania, South Africa, and the United Kingdom—helping Duke to increase its global outreach.

Over the first four years of CHAVI, the international CHAVI teams working with Duke investigators have identified the characteristics of the virus strains transmitted in HIV infection and have provided the clearest picture to date of the very earliest stages of infection. Also working with an international team, Duke investigators led by David Goldstein of the Duke Institute for Genome Sciences & Policy have discovered new genes that encode the ability to control HIV.

A key to success in HIV vaccine research has been the ability of the Duke scientists to work collaboratively with those outside of Duke, sharing data and ideas. Long-term partnerships with outside collaborators, especially Norman Letvin at Harvard, have been critical to the success of work ongoing at DHVI. Also key to our success at Duke has been the willingness of the superb investigators at the University of North Carolina at Chapel Hill to work on the CHAVI team. In particular, Myron Cohen has led the effort to organize the clinical core of CHAVI that continues to provide the HIV field with key early acute infection samples. While Duke and UNC investigators remain in hot competition regarding sports, particularly basketball, we have joined forces to work very closely together in the global fight against AIDS.

The ability to take products “from bench to bedside” is a hallmark of translational research at Duke. DHVI has taken two HIV vaccine candidates into human clinical trials in collaboration with a corporate partner and the National Institutes of Health. The recent development of centralized HIV-1 genes, led by collaborator Bette Korber at Los Alamos National Laboratory, with Norman Letvin at Harvard and the Duke team of myself, Hua-Xin Liao, and Feng Gao, are being tested now as a new strategy to make vaccines that can overcome the enormous problem of HIV diversity.

Future HIV-1 Vaccine Research
HIV vaccine research at Duke is moving forward to solve the problem of overcoming viral diversity and learning how to induce broad neutralizing antibodies to HIV-1—antibodies the immune system does not routinely make. Though the problems remain daunting, the teams at Duke and around the globe remain committed to work until HIV-1 can be prevented and the epidemic stopped. Duke investigators understand the power and opportunity of the team approach: a new paradigm for successful research in an academic setting. The diseases of HIV, TB, and malaria together cause more than 12,000 deaths per day worldwide and many bottlenecks for the development of preventive strategies for all three diseases remain. Successful research that focuses on overcoming the bottlenecks for the development of HIV, TB, and other infectious disease vaccines can only be achieved with the new types of partnerships that Duke has developed over the years with academia, the U.S. government, private foundations, and companies. In effect, HIV vaccine research has stimulated the evolution of the virtual collaborative laboratory or “collaboratory” approach to solving highly complex and otherwise intractable scientific problems. If the work on HIV continues to succeed at Duke, we likely can expect similar large science team approaches to other complex and difficult problems, such as global warming, clean water, and TB and other global diseases such as pandemic influenza. It is Duke’s unique spirit of collaboration that has supported the development of such a successful virtual collaborative team, and has made Duke a testing ground for this concept of the future.

Acknowledgements

In any discussion of work over 30 years at a major medical university, many key and critical contributors to the work will unavoidably be omitted. For any such oversights, I apologize.
Legends to Figures

Figure 1. Barton Haynes (right) and Dani Bolognesi in 1997.

Figure 2. The Surgical Oncology Research Facility (SORF) built in 1986 by the Department of Surgery in and financed by the late Dr. David Sabiston, then chair of the department. This building supported all HIV research at Duke until the opening of Medical Sciences Research Building II, which has housed the Duke Human Vaccine Institute since 2007.

References


Barton Haynes, F.M. Hanes Professor of Medicine and professor of immunology, has been at Duke since 1973 with only a five-year gap from 1975 to 1980, which he spent training at the National Institutes of Health. He was a member of the Department of Medicine house staff (1973-1975) and has been a faculty member since 1980. He has served as chief of the Division of Rheumatology, Allergy, and Clinical Immunology (1987-1995) and chair of Medicine (1995-2002).

Currently the director of the Center for HIV-AIDS Vaccine Immunology, Haynes founded the Duke Arthritis Center and the Duke Human Vaccine Institute, where he is also director. He was married in 1984 to Caroline Haynes, MD, PhD, the current dean of Student Affairs in the School of Medicine, and has three children, Charlotte, Ben, and Laura.