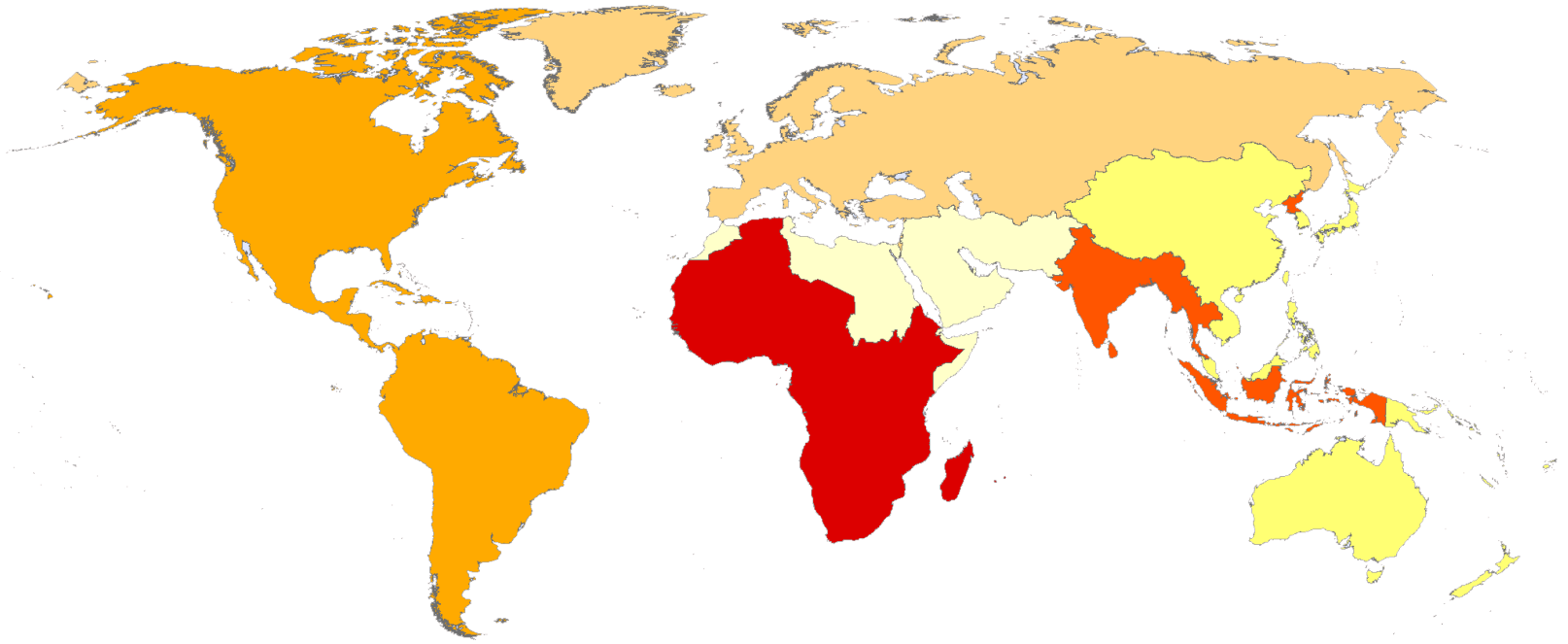




**CHAVI-ID**  
Duke Center for HIV/AIDS Vaccine Immunology  
and Immunogen Discovery



ADULTS AND CHILDREN ESTIMATED TO BE LIVING WITH HIV (2013)

Eastern Mediterranean: 280 K  
Western Pacific: 1.3 M

Europe: 2.1 M  
Americas: 3.2 M

South-East Asia: 3.4 M  
Africa: 24.7 M

PHOTO CREDIT: WHO

# Duke CHAVI-ID Update

A NEWSLETTER BY THE DUKE CENTER FOR HIV/AIDS VACCINE  
IMMUNOLOGY AND IMMUNOGEN DISCOVERY

Vol 4, Issue 1

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Duke CHAVI-ID 4TH Annual Meeting  
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In the News

## Duke CHAVI-ID 4th Annual Meeting

The Fourth Annual Duke CHAVI-ID Retreat and Meeting was held September 23 - September 26, 2015 at the Washington Duke Inn in Durham, North Carolina. Over 200 participants attended the meeting, which included Duke CHAVI-ID members and their lab staff. A total of 78 abstracts were submitted, and posters were presented based on those abstracts.

The meeting festivities included the Annual Norman Letvin Memorial Concert, which was performed by the world-renowned Ciompi Quartet to honor the life of Dr. Norman Letvin. The concert was followed by dinner at the Nasher Art Museum in Durham.

## 2015 Poster Session Winners



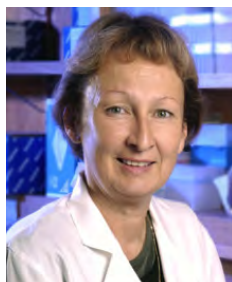
**Pictured (from L to R, Front to Back):**  
Kan Luo, Ryan Meyerhoff, Gilad Ofek,  
Wilton Williams, Kshitij Wagh, Daniela Fera, Tom  
Partridge, Hui Li, Simon Brackenridge, Akshaya  
Ramesh, James Alin, Gerald Learn, Mattia Bonsignori,  
LaTonya Williams, Ted Kreider, David Martinez

## The distinguished guest speakers included:

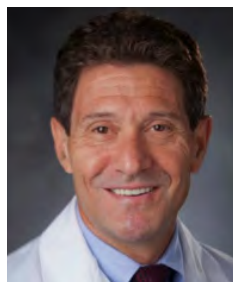
- **Anthony S. Fauci**, Director, National Institute of Allergy and Infectious Diseases, National Institutes of Health
- **Dan Littman**, Helen L. and Martin S. Kimmel Professor of Molecular Immunology, Department of Pathology Professor, Department of Microbiology, Skirball Institute
- **Jaap Goudsmit**, Director and Chief Scientist, President's I & II Crucell Vaccine Institute Academic Medical Center, University of Amsterdam
- **Louis Picker**, Professor of pathology/Molecular Microbiology and Immunology, OHSU School of Medicine and Head of the Division of Pathobiology and Immunology
- **Peggy Johnston**, BMGF, former Director, Vaccine Research Program, DAIDS

## Awards & Recognition

### 2015 Norman Letvin Scholars of the Duke CHAVI-ID



**BEATRICE HAHN, MD**  
University of  
Pennsylvania



**DAVID MONTEFIORI, PHD**  
The Duke Human  
Vaccine Institute

### 2015 Duke CHAVI-ID Outstanding Contributions Award



**JOHN KAPPES, PHD**  
University of Alabama  
at Birmingham



**GERALD LEARN, PHD**  
University of  
Pennsylvania



**TANMOY BHATTACHARYA, PHD**  
Los Alamos National

## 2015 Duke CHAVI-ID Pre-Doctoral Awardees

**TOM PARTRIDGE**  
University of Oxford

**MAXIME VEILLETTE**  
University of Oxford

**NIRMIN ALSAHAFI**  
McGill University

**MATTHEW ZIRUI TAY**  
The Duke Human Vaccine Institute

**SAINTEDYM WILLS**  
The Duke Human Vaccine Institute

## 2015 Norman Letvin Young Investigators Awardees



**KEVIN WIEHE, PHD**  
The Duke Human Vaccine Institute



**HUI LI, PHD**  
University of Alabama at Birmingham

## 2015 Duke CHAVI-ID Post-Doctoral Awardees

**DANIELA FERA, PHD**  
Boston Children's Hospital

**JONATHAN RICHARD, PHD**  
CRCHUM

**ISABELLA PEDOZA-PACHECO, PHD**  
University of Oxford

**LATONYA WILLIAMS, PHD**  
The Duke Human Vaccine Institute

## 2015-2016 CHAVI-ID Accomplishments:

peer-reviewed  
articles  
**50**  
Published  
more than

### Induction of Protective Antibodies

1. Made great progress on mapping two new types of bnAbs—the CD4 mimic antibody type of CD4 binding site antibodies that utilizes the VH1-46 heavy chain, and a V3 glycan bnAb that binds at the apex of the HIV Env trimer
2. Made strides in understanding the nature of glycans on native-like trimers such as membrane-bound trimer
3. Developed new rhesus VH and VL loci maps that are critical to our field's rhesus macaque antibodyome work
4. Made a major breakthrough on construction of Simian-Human Immunodeficiency Viruses (SHIVs) by optimizing the Envs for binding to rhesus CD4
5. Made steady progress in engaging bnAb germline lineages and in inducing both autologous and heterologous neutralizing antibody lineages
6. Began testing immunization with sequential Envs as a strategy for recreating with vaccination the events that occur in infection
7. Gained the ability of a wide range of Env immunogens in vivo to engage the germlines of multiple bnAb germline B cell receptors (BCR)
8. Developed the concept of Vaccine Transient Immune Modulation (vTim) and our hypothesis of how to safely re-create this immunologic milieu in the setting of vaccination

### Induction of Protective T Cell Responses

1. Developed centralized HIV genes for coverage for CD4 and CD8 T cell response breadth for multiple HIV isolates and have a clinical trial in place comparing consensus vs. mosaic Env immunogens as well as clinical trials planned for the next generation centralized immunogen for CD4 and CD8 breadth
2. Developed new work on the CHAVI-ID conserved/mosaic and 5'-LTR vaccines in attenuated RhCMV vector and work on the mechanism of CD8 T cell killing via HLA E
3. Found critical insights into the mechanisms of bnAb induction when they are made (cooperating B cell lineages), and the nature of the immunologic milieu that is present when bnAbs are made (release from tolerance controls)
4. Determined a remarkable new area of research directly related to HIV vaccine development that has come from the 2011 CHAVI study in the Journal of Experimental Medicine that demonstrated that the initial antibody response to HIV was derived from pre-existing memory B cells that were gp41 reactive but also gut flora reactive

## Researchers Unravel Pathways of Potent Antibodies that Fight HIV Infection

SOURCE: CELL  
MARCH 3, 2016

One of the most crucial and elusive goals of an effective HIV vaccine is to stimulate antibodies that can attack the virus even as it relentlessly mutates.

Now a research team, led by investigators at the Duke Human Vaccine Institute and the Vaccine Research Center of the National Institute of Allergy and Infectious Diseases (NIAID), has tracked rare potent antibodies in an HIV-infected individual and determined sequential structures that point to how they developed.

The details form a blueprint that will help guide researchers as they try to build an experimental vaccine that recreates the pathway that gives rise to the important broadly neutralizing antibodies.



**We have followed a less potent neutralizing lineage in this particular individual before, but now we have found a far more potent antibody and have been able to study its development over six years. With sequential structures, we can see the changes that occurred in both antibody and virus.**

Mattia Bonsignori, MD | Lead author

The work was aided by the identification six years ago of a person in Africa whose HIV was diagnosed within weeks of infection and who provided blood samples to researchers periodically from the time of diagnosis, allowing researchers to examine in real time the co-evolution of the virus and the body's immune response.

Using high-resolution electron microscopes and building structural models, the scientists were able to see the antibodies binding to the HIV envelope and the complicated structural changes that occurred in the antibody and the virus.

“We could visualize this complex dance between the virus and the antibody and understand exactly how the virus was teaching the antibody to be a broadly neutralizing antibody,” said Peter D. Kwong, Ph.D., chief of the Structural Biology Section at the NIAID Vaccine Research Center.

Kwong said understanding that interaction has been an important piece of the puzzle for vaccine development, because HIV mutates so rapidly. Broadly neutralizing HIV antibodies have been isolated from chronically infected people, giving HIV vaccine developers hope that they could stimulate production of such antibodies in healthy people as protection against the virus.

Haynes said the research team's insights would be tested in animal models. He said a second key to creating an effective vaccine is understanding how the body's immune system often thwarts development of broadly neutralizing antibodies. Work to solve that is ongoing.

In addition to Haynes and Bonsignori, study authors from Duke include Feng Gao, Kevin Wiehe, S. Munir Alam, Todd Bradley, Morgan Gladden, Kwan-Ki Hwang, Sheelah Iyengar, Amit Kumar, Xiaozhi Lu, Kan Luo, Michael C. Mangiapani, Robert J. Parks, Hongshuo Song, David C. Montefiori, Michael A. Moody, Garnett Kelsoe, and Hua-Xin Liao.

Dr. Kwong was joined by authors from the NIAID Vaccine Research Center, part of the National Institutes of Health, including co-first authors Tongqing Zhou and Lei Chen, and M. Gordon Joyce, Gwo-Yu Chuang, Priyamvada Acharya, Robert T. Bailer, Allen Cao, Aliaksandr Druz, Ivelin S. Georgiev, Young D. Kwon, Mark K. Louder, Baoshan Zhang, Anqi Zheng, Brenna J. Hill, Rui Kong, Cinque Soto, Daniel C. Douek, and John R. Mascola.

Additional authors include co-first author Zizhang Sheng, Chaim A. Schramm and Lawrence Shapiro from Columbia University; Gabriel Ozorowski and Andrew B. Ward from The Scripps Research Institute;



**Now we've been able to go back and see what happened. We hope we can recreate this pathway but because it is so tortuous, it will be difficult.**

Barton Haynes, MD, PhD | Director, DHVI

James C. Mullikin from NIH Intramural Sequencing Center; George M. Shaw and Beatrice H. Hahn from the University of Pennsylvania; Peter T. Hraber and Bette T. Korber from Los Alamos National Laboratory; Scott D. Boyd and Andrew Z. Fire of Stanford University; and Thomas B. Kepler of Boston University.

The research received support from NIAID through the Center for HIV/AIDS Vaccine Immunology and Immunogen Discovery (UM1 AI100645); the Scripps CHAVI-ID (UM1 AI1006630); and the Scripps HIVRAD (P01-AI1047220). The International AIDS Vaccine Initiative also provided funds for the study.

## Immune Responses Provide Clues for HIV Vaccine Development

SOURCE: DUKE NEWS AND COMMUNICATIONS  
OCTOBER 21, 2015

Recent research has yielded new information about immune responses associated with—and potentially responsible for—protection from HIV infection, providing leads for new strategies to develop an HIV vaccine. Results from the RV144 trial, reported in 2009, provided the first signal of HIV vaccine efficacy: a 31 percent reduction in HIV infection among vaccinees. Since then, an international research consortium has been searching for molecular clues to explain why the vaccine showed this modest protective effect.

A new review outlines findings that hint at the types of immune responses a preventive HIV vaccine may need to induce. The article was co-authored by leaders in HIV vaccinology, including Anthony S. Fauci, M.D., director of the National Institute of Allergy and Infectious Diseases, part of the National Institutes of Health, and lead author Lawrence Corey, M.D., of the Fred Hutchinson Cancer Research Center.

Analyses of RV144 volunteers revealed that particular vaccine-induced immune responses, including production of certain antiviral antibodies and CD4+ T cell responses to HIV's outer shell, or envelope, correlate with reduced HIV infection. Many RV144 vaccinees produced antibodies in the immunoglobulin G (IgG) family that bind to sites within part of the HIV envelope called V1V2. These antibodies were linked to protection against acquiring HIV. However, high levels of a different type of envelope-binding antibody belonging to the IgA family were associated with a lack of protection against HIV infection. Evidence suggests that IgA may block the protective action of IgG. Recently, monkey studies testing vaccine regimens different from those in RV144 have supported the notion that enhancing protective antibody activity may increase vaccine efficacy.

Guided by findings from human and monkey studies, researchers are working to improve upon the efficacy of the RV144 vaccine regimen. They are investigating strategies to increase the magnitude and durability of vaccine-induced immune responses associated with protection from HIV infection, as well as developing vaccines to elicit production of antibodies that are broadly neutralizing against a variety of HIV strains. As development of an effective HIV vaccine continues, efforts stemming from the modest success of the RV144 trial have "produced a momentum and series of immune targets that will hopefully lead to an effective global vaccine effort," the authors conclude.

## DART Protein Shows Potential as Shock-and-Kill Strategy Against HIV

SOURCE: DUKE NEWS AND COMMUNICATIONS  
SEPTEMBER 28, 2015

DURHAM, N.C. – A unique molecule developed at Duke Medicine, the University of North Carolina at Chapel Hill and MacroGenics, Inc., is able to bind HIV-infected cells to the immune system's killer T cells. It could become a key part of a shock-and-kill strategy being developed in the hope of one day clearing HIV infection.

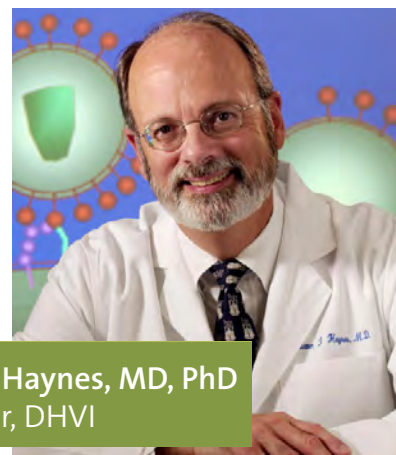
The molecule is a type of bi-specific antibody known as a Dual-Affinity Re-Targeting protein, or DART®. It was engineered by MacroGenics, using HIV-targeting antibodies discovered at Duke. Employed increasingly in cancer research, bi-specific molecules have shown effectiveness in helping the immune system recognize and clear tumor cells. In this case, pre-clinical models demonstrate that DART creates a fatal union between HIV-infected cells and killer T cells.

When Julia Sung, M.D., lead author and clinical assistant professor in medicine at UNC, used DART molecules in combination with additional agents that wake up latent reservoirs of the virus hiding in the body, the approach showed early promise as a way to clear HIV infection.

"This is an exciting approach that has the potential to clear a pool of cells that are so hard to get rid of -- virus that lies silent and hidden in the host," said Barton Haynes, M.D., director of the Duke Human Vaccine Institute and a senior author of a study describing the molecule in the *Journal of Clinical Investigation*.

“ **These drugs would be combined with other drugs that activate expression of HIV in the cells. As soon as they are awakened, the DART molecules hit them and causes the killer T cells to destroy the virus.** ”

Haynes and colleagues at UNC, the University of Alabama-Birmingham, and MacroGenics report in the Sept. 28 online edition of *JCI* that the DART strategy was highly effective in clearing HIV in laboratory experiments.



Barton Haynes, MD, PhD  
Director, DHVI

To try to model what might happen if patients were treated with DART molecules to clear persistent infection, lymphocytes were taken from patients on HIV therapy. These cells were then re-infected with different HIV virus subtypes, and with viruses previously recovered from the same patient's latent viral reservoir. When the patient cells expressed these various viral strains, DART molecules facilitated CD8 "killer" T cell clearance of the infected cells.

In another pre-clinical modeling experiment in the laboratory, exposing HIV-positive patients' cells to HIV latency reversing agents — drugs which are under development to force dormant HIV out of hiding -- the DART molecules showed potential to be effective immunotherapeutic weapons to clear these latent HIV reservoirs.

"A similar approach is being tested to cure some forms of cancer," said David Margolis, M.D., co-corresponding author and professor of medicine, microbiology and immunology at UNC. "This idea is being repurposed for curing HIV with our partners at Duke and MacroGenics. This paper shows that DART molecules can recognize different strains of HIV, bind to cells, and clear and kill the virus in many different scenarios."

"While the research into DART molecules is still in early stages, it is very exciting to see how these molecules can turn otherwise ineffective T cells into potent killing machines against HIV latently infected cells," Margolis said.

The researchers said the DART approach is especially promising because the molecule recruits from a large pool of T cells, regardless of specificity, creating a broad attack that is not dependent on targeting any single HIV strain.

"Because we are targeting a region of the virus envelope that appears in all mutations of the virus, we think it will make it much easier to be broadly utilized -- at least from our laboratory data," said co-corresponding author Guido Ferrari, M.D., associate professor of surgery and molecular genetics and microbiology at Duke. "These DART molecules will facilitate the recognition. We are eager to see how this translates to human studies."



**This is a great opportunity for MacroGenics to expand our DART platform for therapeutics applications beyond oncology and autoimmune disorders and into infectious diseases. We are encouraged by our proof-of-concept studies that show HIV DART molecules to be potent immunotherapeutic agents with the potential to reduce HIV reservoirs in patients.**

Scott Koenig, MD, PhD | President and CEO, MacroGenics

In addition to Haynes and Ferrari, study authors at Duke include Joy Pickeral; Sherry A. Stanfield-Oakley; Justin Pollara; Celia LaBranche; Mattia Bonsignori; M. Anthony Moody; Robert Parks; Kelly Soderberg; Hua-Xin Liao; and David Montefiori.

Study authors at UNC include Margolis and Sung, along with Carolina Garrido; Nancie Archin; Brigitte Allard; Jennifer Kirchherr; JoAnn D. Kuruc; Cynthia L. Gay; and Myron S. Cohen. Authors at MacroGenics include Koenig and Liqin Liu; Chia-Ying Kao Lam; Yinhua Yang; Paul Moore; Syd Johnson; and Jeffrey L. Nordstrom. Author Christina Ochsenbauer is from UAB.

Haynes, Ferrari, Bonsignori, Moody and Liao have filed patent applications on the two monoclonal antibodies described and related antigens used in the study.

This study received funding from the National Institutes of Health to the Collaboratory of AIDS Researchers for Eradication (U19 AI096113); Center for HIV/AIDS Vaccine Immunology and Immunogen Discovery (UM1 AI10064); the UNC Center for AIDS Research (P30 AI50410); and the Duke Center for AIDS Research (P30 AI64518).

Full funding support and conflicts of interest are disclosed in the published study.



# CHAVI-ID

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