

Duke CHAVI-ID

Update



A newsletter by the Duke Center for HIV/AIDS Vaccine Immunology and Immunogen Discovery

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Duke CHAVI-ID in the
News

1-3

Duke CHAVI-ID
Additional Updates

4-5

Recent Duke
CHAVI-ID Publications

6

Event Calendar

7

Diversion of an HIV Vaccine Immune Response by Antibodies Reactive with Gut Microbiome

July 30, 2015

A recent HIV vaccine trial testing the HIV envelope as an immunogen was unsuccessful for protection against HIV infection. A new study has found that this vaccine selectively recruited antibodies reactive with both the HIV envelope and common



intestinal microbes — a phenomenon previously reported by the same investigators to occur in the setting of acute HIV infection.

The finding by a Duke Medicine-led research team suggests that a successful vaccine approach would need to somehow mask this easily induced, but ineffective antibody response, or stimulate a different antibody response altogether.

“With this study, we wanted to know whether a vaccine induced the same diverted, ineffective antibody response that occurs with acute HIV infection,” said Barton F. Haynes, M.D., director of the Duke Human Vaccine Institute and senior author of the study appearing online in *Science Express* on July 30.

“We know that the intestinal microbiome can influence the types of antibodies that develop after birth when the microbiome is established,” Haynes said. *(Continued on next page)*

Duke CHAVI-ID in the News

“Our study raises the hypothesis that the microbiome imprinted the immune system to make these cross-reactive antibodies. It suggested that one way to improve the antibody response may be to block the undesired HIV sites during vaccination, or to vaccinate earlier in life to imprint the immune system on desired HIV regions.” Haynes said the experimental vaccine induced antibodies that targeted a region of the HIV virus called gp41, which is part of the virus’s outer envelope. But these antibodies were non-neutralizing and were not able to stop the virus from infecting CD4 T cells.

What’s more, the gp41 region is a molecular mimic of some intestinal microbiome bacterial and self antigens that the body’s B cells are trained on, raising the hypothesis that the vaccine essentially stimulated a diversion that kept the immune system busy, allowing the virus to flourish.

“It’s another way that the virus evades the immune system,” Haynes said. “It gives the virus a leg up in escaping the early antibody response, by primarily inducing antibodies that cannot neutralize HIV.”

Because the microbiome serves as a training ground to teach the immune system how to fight pathogens, HIV’s ability to mimic common microbiota suggests that a successful HIV vaccine approach might also include early childhood immunizations. This could provide a way to prime the immune system to better identify and attack HIV.

“The keys to inducing a successful HIV antibody response may be to mitigate or get around the virus’s ability to divert preexisting B cells that are cross-reactive with intestinal microbiota,” said lead author Wilton B. Williams, Ph.D. “We are currently exploring early vaccination strategies and exploring new designs of the HIV viral envelope to induce the correct antibodies.”

In addition to Williams and Haynes, study authors from Duke include M. Anthony Moody; S. Munir Alam; Feng Gao; Kevin Wiehe; Ashley M. Trama; Kathryn Jones; Ruijun Zhang; Hongshuo Song; Dawn J. Marshall; John F. Whitesides; Pinghuang Liu; Matthew Z. Tay; Kelly Seaton; Xiaoying Shen; Andrew Foulger; Krissey E. Lloyd; Robert Parks; Justin Pollara; Guido Ferrari; Jae-Sung Yu; Nathan Vandergrift; David C. Montefiori; and Georgia D. Tomaras.

They were joined by Thomas B. Kepler, Kaitlin Sawatzki and Axin Jua of Boston University; Magdalena E. Sobieszczyk and Scott Hammer of Columbia University; Shelly Karuna, Peter Gilbert, Doug Grove, Nicole Grunenberg, Julie McElrath, Lawrence Corey, Cecilia Morgan, and Janine Maenza of Fred Hutchinson Cancer Research Center; John R. Mascola, Barney S. Graham and Richard A. Koup of NIH Vaccine Research Center; Gary J.



Antibody Response Linked To Lower Mother-to-Child HIV Transmission

June 9, 2015

How most babies are protected from acquiring HIV from their infected mothers has been a matter of scientific controversy. Now researchers at Duke Medicine provide new data identifying an antibody response that had long been discounted as inadequate to confer protection.

Mother-to-child transmissions account for about 250,000 HIV infections per year worldwide, despite greatly expanded access to antiretroviral drug regimens that can interrupt transmission into low-resource settings.

(Continued on next page)

Duke CHAVI-ID in the News

Ongoing problems with access to the drugs, late initiation of the drug regimens during pregnancy, and acute maternal infection during pregnancy and breastfeeding all contribute to the ongoing infant transmission.

Even in the absence of antiretroviral drug regimens, however, the majority of newborns are naturally protected against HIV, despite chronic virus exposure. The Duke research team sought to define what is different in the babies who become infected compared to those who don't.

"We know that mothers pass antibodies to fetuses in-utero, but a true understanding of how maternal antibodies were contributing to protection had never been established," said Sallie Permar, M.D., Ph.D., associate professor of pediatrics at Duke and lead author of a study published online June 8, 2015, in the *Journal of Clinical Investigation*.

Permar and colleagues at the Duke Human Vaccine Institute and the Fred Hutchison Cancer Research Center analyzed data from a U.S. study in the 1990s that predated therapies such as AZT. The study included mothers and babies, yielding information about risk factors and transmissions in a pre-treatment environment.

By profiling the immune responses of mothers in this early study, the researchers were able to pinpoint the differences between those who transmitted the virus to their infants, and those who did not.

Among mothers whose babies were shielded from infection, they found a strong antibody response to a particular region on the HIV virus envelope (the HIV envelope third variable or V3 loop) that has been considered too variable and too inaccessible to be a relevant target for a neutralizing antibody.

"That was very surprising," Permar said, "because this type of weak neutralizing antibody response, which had previously been thought to be inconsequential for HIV transmission, could potentially be effective in preventing mother-to-child transmission. And there are current HIV vaccine candidates, such as recombinant HIV envelope protein immunization, in early-stage clinical testing that can elicit this type of response."

Permar said the team's study raises a compelling question about why the V3 neutralizing antibody response seems to be enough to reduce mother-to-child transmission, yet is not protective in other modes of HIV transmission.

"The difference in mother-to-infant transmission might be that the infant is only being exposed to the mother's virus, and the infant is born with antibodies that are transferred from the mother," Permar said. "The presence of antibodies that were raised against the mother's virus prior to exposure to the same virus makes the infant transmission setting very different from that of other modes of HIV transmission. So how well the mother's antibody can neutralize her own virus could be the key to whether the baby is infected."

Permar said additional research at Duke will focus on testing newer experimental HIV vaccines to raise this potentially protective antibody response in mothers to neutralize her virus and thereby protect the baby.

"We hope this will be a major clue to making a vaccine to effectively prevent all mother-to-child HIV transmission, since these antibodies are the type that our current experimental HIV vaccines can boost," said M. Anthony Moody, M.D., a co-author and chief medical officer in the Duke Human Vaccine Institute. "For protecting unborn and newborn children, we may be closer to testing a vaccine that can induce this type of common HIV-specific antibody response for its ability to protect infants than previously thought."

In addition to Moody and Permar, study authors include Youyi Fong; Nathan Vandergrift; Genevieve G. Fouda; Peter Gilbert; Robert Parks; Frederick H. Jaeger; Justin Pollara; Amanda Martelli; Brooke E. Liebl; Krissey Lloyd; Nicole L. Yates; R. Glenn Overman; Xiaoying Shen; Kaylan Whitaker; Haiyan Chen; Jamie Pritchett; Erika Solomon; Emma Friberg; Dawn J. Marshall; John F. Whitesides; Thaddeus C. Gurley; Tarra Von Holle; David R. Martinez; Fangping Cai; Amit Kumar; Shi-Mao Xia; Xiaozhi Lu; Raul Louzao; Samantha Wilkes; Saheli Datta; Marcella Sarzotti-Kelsoe; Hua-Xin Liao; Guido Ferrari; S. Munir Alam; David C. Montefiori; Thomas N. Denny; Georgia D. Tomaras; Feng Gao; and Barton Haynes.

Funding included grants from the National Institute of Allergy and Infectious Diseases, part of the National Institutes of Health (5-UM1-AI100645, 5-P30-AI064518).

Duke CHAVI-ID Additional Updates

A DART[®] protein to clear the pool of latently HIV-infected cells

(EMNBARGOED FOR RELEASE UNTIL

9/28/2015) Upon HIV-1 infection and integration into the host genome, some of the central memory CD4⁺ T cells are likely to transition back to a resting state that is not permissive for virus gene expression. These resting CD4⁺ T constitute the pool of latently infected cells that are not recognized and eliminated by the immune system. Even though antiretroviral therapy can suppress HIV-1 to undetectable levels, it is not effective in eliminating the pool of latently infected cells.

The strategies currently used to reactivate the latent virus reservoir rely on both concomitant administration of anti-retroviral therapy and immune responses to eliminate the infected cells. The latter is not as efficient in recognizing the infected cells. A team of investigators led by Guido Ferrari, Barton Haynes (Duke University Medical Center), Scott Koenig (MacroGenics), and David Margolis (University of North Carolina-Chapel Hill) have designed antibody-based Dual-Affinity Re-Targeting proteins that can recognize HIV-1 envelope on the surface of the infected cells and simultaneously recruit cytotoxic CD3⁺ T cells to engage and kill HIV-1-infected cells. Importantly, these novel HIVxCD3 DARTs mediated in vitro clearance by CD8⁺ T cells of latently infected CD4⁺ T cells that had been treated to induce latent virus expression. Therefore, DART proteins could provide the immune system with the necessary specific help to improve the elimination of the latently infected cells. These molecules will be soon tested in clinical trials to evaluate their ability to clear the latent viral reservoir.

Strain-specific antibodies select for neutralization-resistant HIV-1

Duke CHAVI-ID investigators have elucidated one of the mechanisms likely responsible for the observation that HIV-1 infection occurs primarily with neutralization-resistant viruses. The study, published on September 9, 2015 in the journal *Cell Host and Microbe*, examined the neutralization sensitivity of viruses from individuals that had been recruited in the CHAVI001 protocol that studied acute and chronic HIV-1 infection.

In previous work by the CHAVI team, they had shown that the transmission of HIV-1 usually occurs by a single HIV-1 virion that establishes infection and subsequently diversifies (Keele BF et al. *PNAS* **105**(21): 7552–7557 2008, PMC2387184). For the present

study, the research team isolated antibodies from chronically HIV-1-infected individuals from the CHAVI001 cohort and determined the antibody binding sites. They showed that the antibodies were directed to the V3 loop and CD4 binding site, regions known to be commonly targeted by antibodies during HIV-1 infection. They then tested the ability of these antibodies to neutralize viruses from the previously described class of transmitted/founder strains of HIV-1 as well as other well characterized isolates known to be resistant to neutralization by antibodies. As expected, most of the antibodies were unable to neutralize strains of HIV-1 taken from other individuals.

"But we didn't stop there," said M. Anthony Moody, Chief Medical Officer of the Duke Human Vaccine Institute and first author of the paper. "Using samples that spanned nearly two years of chronic HIV-1 infection, Feng Gao and his team went on to isolate more than 200 viruses from these chronically infected individuals. We then tested the antibodies to determine whether we could see any neutralization by antibodies that developed in the same individuals."

Remarkably, the antibodies that did not neutralize strains of HIV-1 from other individuals were able to neutralize HIV-1 strains taken from the people who made the antibodies. This group of autologous antibodies appeared to be more potent against autologous HIV-1 strains that were also sensitive to antibodies from other people. "This finding was unexpected, because we saw the ongoing evolution of viruses from these individuals and viruses sensitive to the antibodies kept arising, despite the antibodies being there. It suggested that these antibodies were not providing strong immune pressure in the infected individuals, unlike the broadly neutralizing antibodies we had recovered where we saw evidence of complete escape," Moody said. "However, we realized that this neutralization pattern exactly matched the transmitted/founder virus pattern. That led us to think that these antibodies might be providing pressure on the virus during transmission even if it did not provide pressure in the infected person. And, this finding fit exactly with the study of mother-to-child transmission of HIV-1 that we had just reported, where this same class of antibodies correlated with a decreased risk of MTCT."

The MTCT study, examining the Women and Infant Transmission Study was recently reported in the *Journal of Clinical Investigation* (Permar SR et al. *J Clin Invest* **125**(7): 2702–2706 2015) and showed that antibodies directed against the V3 loop and CD4 binding site correlated with a decreased risk of peripartum HIV-1 transmission.

(Cont.) Duke CHAVI-ID Additional Updates

"We realized that because antibodies and viruses are passed together during the transmission event, whether sexual or peripartum, these antibodies might provide an additional degree of selection pressure and might explain the transmission of resistant viruses," Moody said.

The team is currently planning studies to investigate this possibility, including strategies to boost this class of antibodies in pregnant women to reduce MTCT.

In addition to Moody, Gao, and Bart Haynes, the study authors included Thad Gurley, Joshua Amos, Amit Kumar, Bhavna Hora, Dawn Marshall, John Whitesides, Shi-Mao Xia, Rob Parks, Krissey Lloyd, Kwan-Ki Hwang, Xiaozhi Lu, Mattia Bonsignori, Nathan Vandergrift, Munir Alam, Guido Ferrari, Shaunna Shen, Georgia Tomaras, Larry Liao, and David Montefiori at Duke; Andres Finzi at the University of Montreal and McGill University; Gift Kamanga and Mike Cohen at the University of North Carolina at Chapel Hill; Noel Sam at Kilimanjaro Christian Medical Center; Saidi Kapiga at the London School of Hygiene and Tropical Medicine; Elin Gray, Nancy Tumba, and Lynn Morris at the National Institute for Communicable Diseases in Johannesburg; Susan Zolla-Pazner at the Icahn School of Medicine at Mount Sinai; Mirek Gorny at New York University; John Mascola at the Vaccine Research Center; Beatrice Hahn and George Shaw at the University of Pennsylvania; Joseph Sodroski at the Dana Farber Cancer Institut; and Peter Hrabec and Bette Korber at the Los Alamos National Laboratory.

Recent Duke CHAVI-ID Publications

Diversion of HIV-1 vaccine-induced immunity by gp41-microbiota cross-reactive antibodies Wilton B. Williams, Hua-Xin Liao, M. Anthony Moody, Thomas B. Kepler, S. Munir Alam, Feng Gao, Kevin Wiehe, Ashley M. Trama, Kathryn Jones, Ruijun Zhang, Hongshuo Song, Dawn J. Marshall, John F. Whitesides, Kaitlin Sawatzki, Axin Hua, Pinghuang Liu, Matthew Z. Tay, Kelly Seaton, Xiaoying Shen, Andrew Foulger, Krissey E. Lloyd, Robert Parks, Justin Pollara, Guido Ferrari, Jae-Sung Yu, Nathan Vandergrift, David C. Montefiori, Magdalena E. Sobieszczyk, Scott Hammer, Shelly Karuna, Peter Gilbert, Doug Grove, Nicole Grunenberg, Julie McElrath, John R. Mascola, Richard A. Koup, Lawrence Corey, Gary J. Nabel, Cecilia Morgan, Gavin Churchyard, Janine Maenza, Michael Keefer, Barney S. Graham, Lindsey R. Baden, Georgia D. Tomaras, and Barton F. Haynes *Science* aab1253 Published online 30 July 2015 [DOI:10.1126/science.aab1253]

Inhibitory Effect of Individual or Combinations of Broadly Neutralizing Antibodies and Antiviral Reagents against Cell-Free and Cell-to-Cell HIV-1 Transmission Gombos RB, Kolodkin-Gal D, Eslamizar L, Owuor JO, Mazzola E, Gonzalez AM, Koriath-Schmitz B, Gelman RS, Montefiori DC, Haynes BF, Schmitz JE. Inhibitory Effect of Individual or Combinations of Broadly Neutralizing Antibodies and Antiviral Reagents against Cell-Free and Cell-to-Cell HIV-1 Transmission. *J Virol.* 2015 Aug 1;89(15):7813-28. doi: 10.1128/JVI.00783-15. Epub 2015 May 20. PMID: 25995259

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Improving Neutralization Potency and Breadth by Combining Broadly Reactive HIV-1 Antibodies Targeting Major Neutralization Epitopes. Kong R, Louder MK, Wagh K, Bailer RT, deCamp A, Greene K, Gao H, Taft JD, Gazumyan A, Liu C, Nussenzweig MC, Korber B, Montefiori DC, Mascola JR. *J Virol.* 2014 Dec 17. pii: JVI.03136-14. [Epub ahead of print]

Infection of monkeys by simian-human immunodeficiency viruses with transmitted/founder clade C HIV-1 envelopes. Asmal M, Luedemann C, Lavine CL, Mach LV, Balachandran H, Brinkley C, Denny TN, Lewis MG, Anderson H, Pal R, Sok D, Le K, Pauthner M, Hahn BH, Shaw GM, Seaman MS, Letvin NL, Burton DR, Sodroski JG, Haynes BF, Santra S. *Virology.* 2014 Nov 22;475C:37-45.

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Structure and immune recognition of trimeric pre-fusion HIV-1 Env. Pancera M, Zhou T, Druz A, Georgiev IS, Soto C, Gorman J, Huang J, Acharya P, Chuang GY, Ofek G, Stewart-Jones GB, Stuckey J, Bailer RT, Joyce MG, Louder MK, Tumba N, Yang Y, Zhang B, Cohen MS, Haynes BF, Mascola JR, Morris L, Munro JB, Blanchard SC, Mothes W, Connors M, Kwong PD. *Nature.* 2014 Oct 8. doi: 10.1038/nature13808. [Epub ahead of print]

Event Calendar

Annual Retreat and Meeting

October 2 - 5, 2016
October 1 - 4, 2017
September 30 - October 3, 2018

SLG Fall Planning Meeting

October 23 - 24, 2015
October 28 - 29, 2016
October 27 - 28, 2017
October 26 - 27, 2018

Winter Call

January 28 - 29, 2016
January 27 - 28, 2017
January 26 - 27, 2018
January 25 - 26, 2019

AIDS Conferences

HIVR4P
Chicago, IL
October 18-21, 2016

Pre-Scientific Advisory Board Meeting

March 18 - 19, 2016
March 24 - 25, 2017
March 23 - 24, 2018
March 22 - 23, 2019

CHAVI-ID Scientific Advisory Board Meeting

April 18 - 19, 2016
April 24 - 25, 2017
April 16 - 17, 2018
April 15 - 16, 2019

SLG Summer Planning Meeting

June 24 - 25, 2016
June 23 - 24, 2017
June 22 - 23, 2018
June 21 - 22, 2019

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