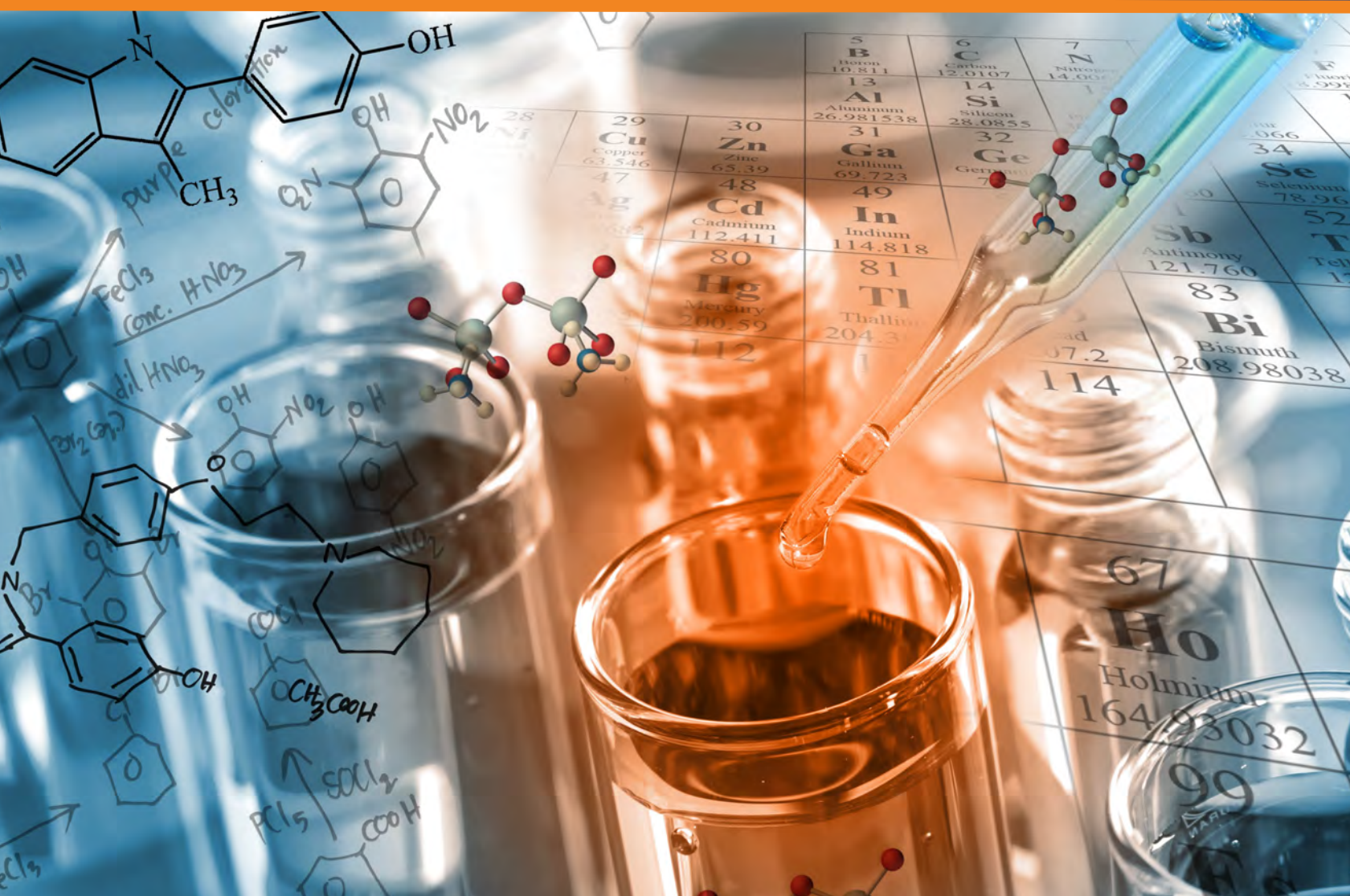




CHAVI-ID

Duke Center for HIV/AIDS Vaccine Immunology
and Immunogen Discovery



Duke CHAVI-ID Update

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

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The CHAVI-ID 2016-2017 Highlights

This has been a busy and productive year for the CHAVI-ID. A major strategy of this CHAVI-ID induction of bnAbs is to define the events and conditions that are present in HIV infection when bnAbs are made, and to recreate these events and conditions in the setting of Env immunization. This CHAVI-ID team over the past 11 years has probed HIV infection and defined key traits that are associated with bnAb induction. From a study of 50 HIV infected individuals with bnAbs and 50 that did not make bnAbs, these traits are high viral load, low blood CD4 T cells, high blood Tfh, low blood T regulatory cells, high PD-1 levels on T regulatory cells and high levels of plasma autoantibodies (Science Immunology 1:aag0851, 2016). From this work, and the work of **Laurent Verkoczy, Fred Alt and Ming Tian** that demonstrate in bnAb knock-in mice that CD4bs, gp41 and V1V2 bnAbs are deleted in bone marrow, and most bnAb B cells that escape first checkpoint deletion are anergic, have come evidence that overcoming immune tolerance checkpoints will be key to inducing bnAbs (Immunol. Reviews 275: 79-88, 2017; Ibid. 275: 89-107, 2017).

For bnAb induction, the CHAVI-ID is studying a number of factors that we believe will be needed to be optimized before bnAbs can be induced. These factors include: 1) the correct immunogen form (minimal immunogen to initiate lineages, correct forms of the trimer to boost), 2) the correct sequence of immunogens, 3) the correct affinity of immunogens for bnAb lineage members, 4) the correct transient modifications of host immunoregulatory mechanisms to favor prolonged germinal center responses, and 5) the correct route, intervals and length of immunizations for bnAb B cell maturation.

Focus 1. Induction of Protective Antibodies. For the work on induction of broad neutralizing antibodies, the Duke CHAVI-ID has made progress in the following areas of work:

Defining the immunologic and virologic events and conditions that occur during HIV-1 induction of bnAbs and then recreating those events and conditions by vaccination.

First, to determine if the remarkable immunogenicity in mice of nucleoside-modified mRNAs formulated in lipid nanoparticles, developed by **Drew Weissman**, would translate to rhesus macaques (RMs), we performed a proof-of-concept study in RMs with Weissman's mRNAs encoding Zika Prm,E. We found the one immunization with mRNA induce high titered and long lasting Zika neutralizing antibodies and protected 100% of RMs from Zika challenge (Nature 543: 248-251, 2017). Thus, we are in the midst of producing and testing our sequential Env vaccines formulated as mRNAs in lipid nanoparticles that encode either full gp160s or stabilized trimers. The mechanism of mRNA enhanced immunogenicity is selective induction of Tfh by mRNA immunization.

Second, we have 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. The paper describing the VH1-46 CD4 binding site bnAb CH235 and all its lineage members, and a new vaccine regimen that derived from this work ([Cell](#), 165: 449-63, 2016). A new set of immunogens similarly have been designed from the ontogeny studies of the V3 glycan antibodies. Moreover, the phenomenon of cooperating lineages has now been found for V3 glycan bnAbs (Sci.Transl. Med 9: eaai7514, 2017) as was found for CD4bs bnAb generation ([Cell](#) 158: 481, 2014). Moreover, **Sam Danishefsky** and his team have synthesized a mimic of the gp120 V3-glycan bnAb site (Sci. Transl. Med 9: eeai7521, 2017) and Munir Alam and Mattia Bonsignori have demonstrated it binds to the germline of the recently described DH270 V3-glycan bnAb B cell lineage (Sci.Transl. Med 9: eaai7514, 2017). **Steve Harrison** will present his new structures of the DH270 lineage in complex with the **Danishefsky** Man₉-V3 glycopeptide, and **Ryan Meyerhoff** will present data demonstrating the Man₉-V3 glycopeptide can induce antibodies to the V3-glycan bnAb epitope in rhesus macaques. While we have a clear understanding of what the antibodies are doing to the evolving TF virus, we have had little understanding of what the TF virus and evolving escape mutants are doing to the evolving antibody lineage to “select” for bnAb B cell lineage members. **Bette Korber** has been working on this problem, as well as on the design of optimal Env regimens for induction of non-neutralizing antibodies.

Third, **Steve Harrison** and **Bing Chen** have found the importance of the cytoplasmic domain for maintenance of trimer structure (Science 349: 191-5, 2015) and the utility of “tier 3” virus Envs in trimer stability (PNAS, 114: 4477, 2017). **Walther Mothes** (Science 346: 759-63, 2014) and **Joseph Sodroski** (MBio 7: e01598-16, 2016) have defined three energy states of the HIV Env and suggest that immunogen design to stabilize the most high energy state is desirable for trimer immunogen design.



The CHAVI-ID 2016-2017 Highlights

Moreover, we now have been able to induce heterologous tier 2 neutralizing antibodies and **Kevin Saunders** will present RM and rabbit studies in which tier 2 autologous and heterologous neutralizing antibodies were induced. A fundamental question for the field is whether there is a state of the HIV-1 Env ("State 1") that, if stabilized, will be a better immunogen to induce bnAbs than the stabilized SOSIP trimer. Our current hypothesis is that to induce bnAbs we will have to optimize both Env structure and control of host tolerance mechanisms with Vaccine Transient Immune Modulation (VTIM) (Science 344: 588, 2014; Immunol Reviews 275:79, 2017).

Fourth, George Shaw has made a major breakthrough on construction of Simian-Human Immunodeficiency Viruses (SHIVs) by optimizing the Envs for binding to rhesus CD4 (PNAS 113: E3413-22, 2016). He has now made over 15 different transmitted/founder (TF) SHIVs and is analyzing TF Env evolution. In the CH505 and CH848 SHIV-infected RMs, remarkably, he has demonstrated virus evolution near identical to virus evolution in the human from whom the TF virus was isolated. **Wilton Williams** at Duke has now shown neutralizing antibody development is similar in the SHIV-infected macaques and **Shaw** and **Williams** will present these data. The SHIV results are critical because they demonstrate the recapitulation of both virus and neutralizing antibody ontogeny in outbred rhesus macaques, and in doing so, validate the sequential Env immunization strategy.

Fifth, we have made steady progress in understanding the host controls of bnAb development. **Garnett Kelsoe** and **Todd Bradley** will present progress in reshaping the B cell repertoires using Vaccine Transient Immune Modulation (VTIM). However, we realize that use of such proof of concept checkpoint inhibitors such as CTLA4 Abs may be of use scientifically but likely will not practical for use in large numbers of vaccinees. Rather, we have initiated a genome-wide transcriptome study to probe the molecular mechanisms of the immune response in those that make broadly neutralizing antibodies versus those that do not, in order to be able to selectively release only bnAb B cell lineages from tolerance controls. **Todd Bradley** and **Isabela Pedroza-Pacheco** will present these new transcriptome analysis results and their functional significance. **Garnett Kelsoe** has found that a commonly used malarial drug, chloroquine, can release bnAb B cells from bone marrow and circumvent the first tolerance checkpoint (Cell Reports 18: 1627-1635, 2017).

Sixth, the work of **Laurent Verkoczy** and **Fred Alt** have placed the Duke CHAVI-ID in a position to evaluate Env immunogens for their ability to engage the germinal centers of multiple bnAb germline B cell receptors (BCR) in vivo. **Fred Alt** has made the following bnAb germline homologous recombinant mice: VRC01 (CD4 mimic CD4 bs VH1-2), DH270 (V3 glycan), DH512 (MPER gp41), VRC26 (V1V2 glycan) and CH235.12 (CD4 mimic CD4 bs VH1-46). **Laurent Verkoczy** has made the following bnAb knock-in mice: 2F5 gp41 MPER mature and germline, 4E10 MPER mature, CH01 V1V2 glycan germline, CH31 CD4 mimic CD4 bs VH1-2, and CH103 CD4 bs HCDR3-binder germline. **Fred Alt** is collaborating with **John Mascola** and **Peter Kwong** and their immunogens that can engage the VRC01 germline BCR, and **Laurent Verkoczy** is collaborating with **Rogier Sanders**, **Peter Kwong**, **Bill Schief**, and **Dennis Burton** to test a wide spectrum of Env constructs in the Duke CHAVI-ID mice. **Alt and Verkoczy** will review the results of immunizations in their mice.

Induction of non-neutralizing, protective antibodies

The primary goal of this work is to improve on the efficacy seen in the RV144 vaccine trial that used ALVAC-AE prime and ALVAC + AIDSVAX B/E boost.

The **overall goals** of this study are to develop a globally effective HIV vaccine.

The rationale for the study is based on the observations:

- RV144 V2 antibodies correlate of decreased transmission risk (NEJM 366: 1275, 2012);
- RV144 V2 Abs focused on K169 (Immunity 38: 176, 2013);
- RV144 viral sieve analysis showed if challenge virus had K169, efficacy 48% (Nature 490: 417, 2012).

Thus, if "easy-to-induce" K169-targeted V2 abs protect, then a goal is to increase the specificities of V2 Abs induced (increase the specificities of all FcR-mediated anti-viral responses). To this end, CHAVI-ID will pursue development of the following in collaboration with MHRP, DAIDS, Sanofi. Here, with **Bette Korber**, "ADCC mosaic Envs" have been designed that optimize the coverage for global diverse ADCC eptiopes. These Envs are currently being tested them in small animals regarding epitopes induced and comparing the induced immune responses with more complex Env mixtures.

Nucleoside-modified mRNAs as a vaccine platform for induction of ADCC and other FcR-mediated effector functions. While we are designing and testing protein mosaic and Envs, we are starting now a head to head comparison of A244 gp120 protein with **Drew Weissman's** modified mRNA A244 gp120 in macaques. We believe that mRNAs will be as good as proteins for epitopes induced and for Ab durability.



CHAVI-ID Highlights

Focus 2. Induction of Protective T Cell Responses.

First, for development of an optimal T cell vaccine, we have developed centralized (conserved/mosaic) HIV genes for coverage for CD4 and CD8 T cell response breadth for multiple HIV isolates and have just finished a clinical trial (HVTN 106) comparing consensus vs. mosaic Env immunogens. We found that a trivalent mosaic T cell insert is extremely immunogenic and have clinical trials planned for the next generation centralized immunogen for CD4 and CD8 breadth, the HIV conserved/mosaic gene immunogen developed **by Andrew McMichael, Bette Korber, and Tomas Hanke**. McMichael and Hanke have the greatest T cell breadth for vaccine-induced CD8 T cell responses in man of any vaccine tested to date, and we are now moving to get the next generation of the conserved/mosaic vaccine into human trials. We have formed a collaboration with IAVI and the Division of AIDS, NIAID, to move forward with a bivalent conserved mosaic Chimp AdOX1 prime, MVA boost human clinical trial.

Second, two years ago **Louis Picker** and **Scott Hansen** joined our CHAVI-ID to construct an attenuated CMV vector with the **Korber/Hanke** conserved/mosaic insert as well as with **George Shaw's** 5'-LTR vaccine for testing in rhesus macaques. Part of the emerging story of mechanism of eradication of SIV-infected CD4 T cells is the observation that a major effector function of CMV- generated CD8 T cells is via peptide recognition in the context of HLA E. Andrew McMichael and Bette Korber joined with Picker and Hansen to work out the mechanism of HLA E-mediated CD8 T cell killing and the peptides recognized in this type of immune response (Hansen S et al., [Science](#), Epub ahead of print Jan 21, 2016).

Fourth, a remarkable new area of research directly related to HIV vaccine development has come from the 2011 CHAVI study in the ([Journal of Experimental Medicine](#) 208: 2237, 2011) that demonstrated that the initial antibody response to HIV was derived from pre-existing memory B cells that were gp41 reactive but also with reactive gut flora. **Andrew McMichael** has gone on to show now that there is a high frequency of pre-transmission CD4 T cells that are both HIV antigen reactive and recognize commensal bacteria (*J. Exp. Medicine*, 211: 1273, 2014). **Wilton Williams and Bart Haynes** have found from the study of vaccinees that have received the VRC DNA prime rAd vaccine, that 95% of induced HIV+ memory B cells were gp41 antibodies that cross-reacted with gut microbiome antigens ([Science](#) 349: aab1253, Jul 30, 2015). This work has now transitioned to work in neonatal and adult RMs and in the HVTN 106 clinical trial. Vincent Han has now shown the same phenomenon of gp41 immunodominance occurs in both adult and neonatal rhesus macaques when immunized with the DNA prime, rAd5 Env vaccine (*J. Virology* August 9th, 00923-17, 2017)

GMP manufacture capabilities. Because of the delays in producing clinical trials materials, we have established a GMP facility at Duke with **Fred Porter** recruited from GSK/Novartis as the head of GMP manufacturing. The first product to be made GMP will be the CH505 M5 Env that binds to the CH235 CD4bs bnAb UCA (Bonsignori, *M Cell* 65:449, 2016). This GMP run will begin October 31, 2017. The second product to be made is A244 gp120D11 that will begin production in January, 2018. Finally a new set of GMP suites is under construction for occupancy in January 2019, and will give the CHAVI ID both new capacity for protein production and as well, allow us to produce mRNAs under GMP conditions for human clinical trials.



Recent Publications

In order by published date from Aug 2016 to Oct 2017

R. D. Astronomo, S. Santra, L. Ballweber-Fleming, K. G. Westerberg, L. Mach *et al.*, Neutralization Takes Precedence Over IgG or IgA Iso-type-related Functions in Mucosal HIV-1 Antibody-mediated Protection. *EBioMedicine* **14**, 97-111 (2016).

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Y. N. Chan, A. W. Boesch, N. Y. Osei-Owusu, A. Emileh, A. R. Crowley *et al.*, IgG Binding Characteristics of Rhesus Macaque FcγγR. *Journal of immunology (Baltimore, Md. : 1950)* **197**, 2936-2947 (2016).

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M. Tian, C. Cheng, X. Chen, H. Duan, H. L. Cheng *et al.*, Induction of HIV Neutralizing Antibody Lineages in Mice with Diverse Precursor Repertoires. *Cell* **166**, 1471-1484 e1418 (2016).

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Recent Publications

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- P. Borrow, M. A. Moody,** Immunologic characteristics of HIV-infected individuals who make broadly neutralizing antibodies. *Immunological reviews* **275**, 62-78 (2017).
- T. Bradley, J. Pollara, S. Santra, N. Vandergrift, S. Pittala *et al.*,** Pentavalent HIV-1 vaccine protects against simian-human immunodeficiency virus challenge. *Nature communications* **8**, 15711 (2017).
- Y. Cai, S. Karaca-Griffin, J. Chen, S. Tian, N. Fredette *et al.*,** Antigenicity-defined conformations of an extremely neutralization-resistant HIV-1 envelope spike. *Proceedings of the National Academy of Sciences of the United States of America* **114**, 4477-4482 (2017).
- H. M. Cheeseman, N. J. Olejniczak, P. M. Rogers, A. B. Evans, D. F. King *et al.*,** Broadly Neutralizing Antibodies Display Potential for Prevention of HIV-1 Infection of Mucosal Tissue Superior to That of Nonneutralizing Antibodies. *Journal of virology* **91**, (2017).
- N. Espy, B. Pacheco, J. Sodroski,** Adaptation of HIV-1 to cells with low expression of the CCR5 coreceptor. *Virology* **508**, 90-107 (2017).
- E. P. Go, H. Ding, S. Zhang, R. P. Ringe, N. Nicely *et al.*,** Glycosylation Benchmark Profile for HIV-1 Envelope Glycoprotein Production Based on Eleven Env Trimers. *Journal of virology* **91**, (2017).
- Herschhorn, X. Ma, C. Gu, J. D. Ventura, L. Castillo-Menendez *et al.*,** Release of gp120 Restraints Leads to an Entry-Competent Intermediate State of the HIV-1 Envelope Glycoproteins. *mBio* **7**, (2016).
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- G. Kelsoe, B. F. Haynes,** What Are the Primary Limitations in B-Cell Affinity Maturation, and How Much Affinity Maturation Can We Drive with Vaccination? Breaking through Immunity's Glass Ceiling. *Cold Spring Harbor perspectives in biology*, (2017).
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Recent Publications

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Upcoming Events

Pre-Scientific Advisory Board Meeting

March 23 - 24, 2018

March 22 - 23, 2019

CHAVI-ID Scientific Advisory Board Meeting

April 16 - 17, 2018

April 15 - 16, 2019

SLG Summer Planning

June 22 - 23, 2018

June 21 - 22, 2019

Annual Retreat

September 30 - October 3, 2018

SLG Fall Planning

October 27 - 28, 2017

October 26 - 27, 2018

Winter Call

January 26 - 27, 2018

January 25 - 26, 2019



CHAVI-ID
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Any updates made to CHAVI-ID events can be found on the CHAVI-ID News and Events webpage:

<https://chavi-id-duke.org/news-events>

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