THE FORUM FOR COLLABORATIVE RESEARCH

BROADLY NEUTRALIZING ANTIBODIES FOR HIV TREATMENT: CLINICAL RESEARCH CONSIDERATIONS

October 30, 2023
Washington, DC

1608 Rhode Island Avenue NW
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www.forumresearch.org

THE FORUM
For Collaborative Research℠

Berkeley Public Health

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MEETING SUMMARY

Introduction

There has been considerable improvement in treatment for HIV with antiretroviral drugs (ARVs), leading to significant reductions in HIV-associated mortality and morbidity globally. However, there were still 630,000 HIV-related deaths globally in 2022 and only 76% of the 39 million people living with HIV were on antiretroviral therapy (ART). Therefore, there continues to be a need for new therapeutic interventions that address some of the challenges with currently available options. Broadly neutralizing antibodies (bnAbs)[1] are a promising new strategy against HIV as they can directly inhibit HIV replication by targeting viral epitopes and indirectly by enhancing the host's immune system. As biologics, they could have a favorable side effects profile, and their long-acting nature may be desirable for many potential users.

The Forum for Collaborative Research (henceforth the Forum) is a public-private partnership based at the University of California, Berkeley, that aims to address pressing regulatory and scientific issues in global health through multi-stakeholder dialogue and consensus-building. It has extensive experience in facilitating collaboration to identify barriers, prioritize research, and identify solutions to accelerate therapeutic development for HIV. The Forum has been approached by stakeholders to facilitate consensus around diagnostic, regulatory, and pharmacokinetic issues in bnAb development for HIV treatment. On October 30, 2023, the Forum convened the first workshop of a series in Washington, DC, USA, with the objective to discuss specific clinical research considerations for bnAbs for HIV treatment. Considerations during the workshop were limited to bnAbs for adult HIV treatment and the US regulatory context. A list of participants is provided in the appendix. The workshop planning was informed by a scientific advisory committee (see appendix). This report summarizes the key discussion points of that workshop, highlighted in Box 1.

Box 1: Key discussion points of the workshop

- Challenges for bnAb development have been similarly encountered in ARV development, including the complexity of the HIV envelope for genotypic and phenotypic testing, developing viable susceptibility assays, and defining drug resistance.
- A range of bnAbs are at different stages of clinical development, with studies ongoing on safety, pharmacodynamics, pharmacokinetics, and efficacy.
- Susceptibility assays to prescreen patients and monitor viral phenotype changes during therapy are being developed and tested. The use and correlation of genotypic and phenotypic assays are critical for developing diagnostic approaches.
- Future work in bnAbs for HIV treatment includes the need for more susceptibility assays and validation testing on these assays. Additionally, long-term monitoring in cohort studies and further work on tailoring bnAbs to fit a certain population niche is needed.

[1] Different ways to spell "bnAbs" exist in scientific discourse. One of the discussion points of this meeting was the need to standardize the spelling, with the recommendation to use "bnAbs". This has been adopted in this report.

Lessons from ARVs

Presenter: Joe Eron, Dan Kuritzkes, Jackie Reeves

Lessons learned from measuring ARV activity through genotypic and phenotypic assays can inform the development of bnAbs. Genotypic testing with Sanger or next-generation sequencing determines the presence or absence of specific changes in HIV genes encoding drug targets, while phenotypic testing measures the inhibition of a drug by assaying the susceptibility of recombinant or pseudo-typed viruses. Defining drug resistance in ART requires the observation of a specific mutation associated with virologic failure and that the mutation reduces drug susceptibility. The cutoffs for resistance-associated mutations in ARV susceptibility are especially complex due to HIV viral envelope complexity, which has been a barrier to developing genotypic and phenotypic assays along with CCR5 antagonists. Algorithms measuring ARV activity require regular updates and a flow of samples to adjust these cutoff values. Past experience with novel ARVs highlights the need for collaboration between stakeholders to improve clinical utility and develop a viable screening assays for bnAbs to be a competitive option.

Examples of bnAbs development programs

Presenter: Peter Leone, Marina Caskey, Ripley Ballou

The workshop reviewed several bnAb development programs, with different bnAbs at different stages of clinical development. Additional bnAbs under development are reviewed elsewhere.[2]

- ViiV Healthcare is developing VH3810109 (N6LS), a bnAb targeting the CD4 binding site, that has been introduced through the BANNER phase 2a proof-of-concept study and the EMBRACE phase 2b study combining N6LS with the ARV cabotegravir. BANNER was a multicenter study to assess the safety, pharmacodynamics, pharmacokinetics, and antiviral activity of N6LS in ART-naive adults. Results showed virological suppression in 13/14 participants, few non-serious adverse events, and baseline viral sensitivity moderately correlated with the magnitude and duration of antiviral response. The EMBRACE study aims to determine the maintenance of virological suppression and pharmacokinetics, frequency, and route of administration for future phase 3 studies.
- Rockefeller University is developing 3BNC117-LS, another CD4 binding site targeting Ab, in combination with 10-1074-LS, a v3 loop bnAb. These bnAbs have been tested in combination in small phase I studies that show patients tolerated subcutaneous and intravenous administration well and there is antiviral activity in individuals with sensitive viruses.
- IAVI is actively involved in discovery and optimization of bnAbs with a neonatal target population. The second generation antibody, ePGT121, shows improved antibody-dependent cellular cytotoxicity compared to parental generations.

[2] Frattari, G. S., Caskey, M., & Søgaard, O. S. (2023). Broadly neutralizing antibodies for HIV treatment and cure approaches. *Current Opinion in HIV and AIDS*, *18*(4), 157–163. https://doi.org/10.1097/coh.0000000000000802 Schriek, A. I., Aldon, Y. L. T., van Gils, M. J., & de Taeye, S. W. (2024). Next-generation bNAbs for HIV-1 cure strategies. *Antiviral Research*, *222*, 105788. https://doi.org/10.1016/j.antiviral.2023.105788

Measures of susceptibility and diagnostic approaches

Presenter: Nicole Doria-Rose, Yunda Huang, Laurie VanderVeen

Susceptibility assays are critical for selecting clinical candidates in bnAbs research and could be used in bnAb therapy to prescreen patients and monitor viral phenotype changes during therapy. Measuring in vitro susceptibility to bnAbs is accomplished by utilizing neutralization assays that observe the prevention of target cell infection by free viruses to measure inhibition. Neutralization is typically measured with pseudoviruses on cell lines. These neutralization titers correlate with in vivo protection. The correlation with in vivo protection has also been shown in non-human primate models with antibody challenges at a lower dose and higher potency. When interpreting neutralization assay data, it is important to consider HIV clades, geography, and coverage complementarity to determine sensitivity cutoff values. PT80 titers are a novel proxy of the experimentally measured ID80 used in studies on bnAbs for HIV prevention. This measure may be an important tool to consider in the design of future bnAb trials, although higher PT80 is likely needed for viral suppression compared to prevention.

The use and correlation of genotypic and phenotypic assays is important to overcome the challenges posed by HIV envelope diversity. The CATNAP database (https://www.hiv.lanl.gov/components/sequence/HIV/neutralization/) correlates viral sequencing data with bnAb in vitro neutralization data. Assessing viral susceptibility to bnAbs involves understanding patient characteristics, identifying the correct sample type, and analyzing the presence of genotypic and phenotypic signatures. The workshop reviewed work by Gilead Sciences that has identified proviral genotypic signatures, largely based on clade B, that predict phenotypic susceptibility of proviruses with a high positive predictive value and specificity but a low sensitivity. Plasma HIV RNA is determined to be a desirable substrate to predict susceptibility. Additional data are needed on the correlation between susceptibility testing and clinical outcomes.

Future directions

Workshop participants highlighted an imminent need for more validated susceptibility assays for bnAbs. Multiple centers should collaborate to test and validate the same samples with newly developed assays. A collaborative database including data on genotypes, phenotypes, and viral rebounds was highlighted as an approach to improve the efficiency of bnAb development. A key factor in safety and clinical viability is the use of long-term monitoring of bnAb activity, and a time horizon of at least 5 years post-administration was discussed. Novel studies may also delve into the specific niches for bnAbs, for example neonatal populations, and how to better tailor the development of therapeutics to these populations.

APPENDIX

Meeting attendees

Forum for Collaborative Research Veronica Miller Logan Donaldson Nicholas Murdock Margot Yann Christopher Berry Donnice Butler Chris Hoffman	**US Food & Drug Administration** Damon Deming Julia Lathrop Benjamin Lorenz Charu Mullick Lisa Naeger Jules O'Rear Viswanath Ragupathy Kimberly Struble
Treatment Action Group Cheriko Boone Richard Jefferys	**Merck & Co.** Rafael Campo Kalyan Pande
Rockefeller University Marina Caskey	**NIAID/National Institutes of Health** Tae-Wook Chun Nicole Doria-Rose Richard Koup Lucio Gama
Gilead Sciences Sean Collins Laurie VanderVeen	**HIV i-Base** Simon Collins
University of North Carolina, Chapel Hill Joseph Eron	**Imperial College London** Sarah Fidler
ViiV Healthcare Margaret Gartland Christine Lampkin Peter Leone Jan Losos Armstrong Murira Kimberly Smith Allan Tenorio Vani Vannappagari Andrew Zolopa	**University of British Colombia** Richard Harrigan
IAVI Rip Ballou Jon Heinrichs	**Fred Hutchinson Cancer Center** Yunda Huang
British HIV Association / UK Community Advisory Board Jo Josh	**Ragon Institute, Massachusetts General Hospital / Harvard University** Boris Juelg
O'Neill Institute Sharonann Lynch	**Quest Diagnostics** Bill Meyer
Labcorp-Monogram Biosciences Chris Petropoulos Jacqueline Reeves	**Aarhus University** Ole Schmeltz Søgaard
Weill Cornell Medicine Timothy Wilkin	**SisterLove, Inc.** Dazon Dixon Diallo

Scientific Advisory Committee

Dan Barouch Harvard University	**Tim Wilkin** Weill Cornell
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Kalyan Pande Merck & Co.	**Mike Robertson** Merck & Co.
Viswanath Ragupathy US Food & Drug Administration/CBER	**Ole Schmeltz Søgaard** Aurhus University
Laurie VanderVeen Gilead Sciences	**Vani Vannappagari** ViiV Healthcare