14th Annual
Miami Center for AIDS
Research Symposium

Curing HIV:
The Next Frontier

Friday, April 6th, 2018
8:30am-4:30pm
Watsco Center - The Fieldhouse
1245 Dauer Drive Coral Gables, FL 33146
The Center for AIDS Research (CFAR) at the University of Miami Leonard M. Miller School of Medicine is the first NIH-funded AIDS research center in Florida, a state with among the highest number of people living with a diagnosis of HIV/AIDS. The Miami CFAR’s mission is to advance HIV/AIDS research by providing scientific leadership and developing an infrastructure that fosters integration of basic and clinical sciences including behavioral/social sciences, promotes education and mentorship, and partners with the community to prevent, treat and cure HIV/AIDS.

This symposium is sponsored by the University of Miami Center for AIDS Research (CFAR) P30AI073961, UM Institute of AIDS and Emerging Infectious Diseases State contract CODMR, and Gilead Sciences, Inc.
Leadership

**Edward Abraham, MD**
Executive Vice President for Health Affairs
CEO, Uhealth
Dean and Chief Academic Officer, Miller School of Medicine

**Carl Schulman, MD**
Executive Dean for Research
Professor of Surgery

**Savita Pahwa, MD**
Director, Miami CFAR
Director, Miami CFAR Laboratory Sciences Core
Professor, Microbiology and Immunology (Pediatrics and Medicine)

**Mario Stevenson, PhD**
Co-Director, Miami CFAR
Co-Director, Miami CFAR Developmental Core
Director, Institute of AIDS and Emerging Infectious Diseases
Chief of Infectious Diseases
Professor of Medicine

**Gwendolyn B. Scott, MD**
Director, Miami CFAR Developmental Core
Director, Division of Pediatric Infectious Disease and Immunology
Professor of Pediatrics

**Maria Alcaide, MD**
Director, Miami CFAR Clinical Sciences Core
Miami CFAR Mentoring Program Leader
Director, Infectious Diseases Research Unit
Assoc. Professor of Clinical Medicine

**Allan Rodriguez, MD**
Director, Miami CFAR Behavioral/Social Sciences & Community Outreach Core
Professor of Clinical Medicine
AGENDA

8:30AM  Breakfast/Registration
9:00AM  Welcome: Savita Pahwa, MD, Miami CFAR Director
9:10AM  Opening Remarks: Carl Shulman, MD
         University of Miami, Executive Dean of Research
9:20AM  Antibodies for HIV Prevention and Treatment
         John Mascola, MD
         Introduction by Jose Martinez-Navio, PhD
10:05AM Broadly Neutralizing Antibodies as an HIV-1 Eradication Strategy
         Dan Barouch, MD, PhD
         Introduction by Mauricio Martins, PhD
10:50AM Break/Coffee
11:10AM Engineering T Cells to Functionally Cure HIV-1 Infection
         James Riley, PhD
         Introduction by Sion Williams, PhD
12:00PM Lunch and Poster Viewing
1:15PM  HIV Reservoirs Exhibit a Resistance to Elimination by CD8+ T-cells that can be Partially Overcome by BCL-2 Inhibition
         Brad Jones, PhD
         Introduction by Lesley de Armas, PhD
2:00PM  HIV Cure Trials: Challenges and Opportunities
         Rajesh Gandhi, MD
         Introduction by Emmanuel Thomas, MD, PhD
2:45PM  Is It Possible an HIV Cure Using Stem Cell Allografts?
         Maria Salgado, PhD
         Introduction by Susanne Doblecki-Lewis, MD
3:30PM  Closing Remarks
3:40PM  Poster Session/Happy Hour
4:30PM  Poster Awards Announcement
Effective vaccines often generate protective antibody responses that are similar to those produced during natural infection. Thus, the isolation of HIV-1 broadly neutralizing monoclonal antibodies (bnAbs) and the elucidation of their maturation pathways has provided insights for a new generation of immunogens and immunization strategies. To stimulate potentially protective neutralizing antibodies, current approaches include the use of near native trimer proteins, recombinant proteins designed to stimulate specific B-cell lineages, and designed to focus the immune response on a known neutralization epitope. However, a highly effective HIV vaccine will likely take years of additional scientific discovery and clinical studies. Thus, passive immunoprophylaxis may provide an interim means of providing protection against HIV-1. Long half-life antibodies may have the potential to maintain protective levels for several months after a single injection. These bnAbs may also have a role in treatment of HIV-1 infection. Several human HIV-1 monoclonal antibodies have entered clinical trials and these data will be discussed.
Notes
Antibodies for HIV Prevention and Treatment

Dr. Dan Barouch will discuss new data exploring the therapeutic efficacy of the broadly neutralizing antibody (bNAb) PGT121 in ART-suppressed, SHIV-infected rhesus monkeys, both alone and with a TLR7 agonist as an innate immune stimulant. PGT121 with the TLR7 agonist led to a substantial delay in viral rebound following ART discontinuation, suggesting the potential of bNAbs as components of HIV cure strategies.
HIV is adept at avoiding naturally generated T cell responses; therefore, there is a need to develop HIV-specific T cells with greater potency for use in HIV cure strategies. Starting with a CD4-based chimeric antigen receptor (CAR) that was previously used without toxicity in clinical trials, we optimized the vector backbone, promoter, HIV targeting moiety, and transmembrane and signaling domains to determine which components augmented the ability of T cells to control HIV replication. This re-engineered CAR was at least 50-fold more potent in vitro at controlling HIV replication than the original CD4 CAR, or a TCR-based approach, and substantially better than broadly neutralizing antibody-based CARs. In a humanized mouse model of HIV treatment, CD4 CAR T cells containing the 4-1BB costimulatory domain controlled HIV spread after ART removal better than analogous CAR T cells containing the CD28 costimulatory domain. Together, these data indicate that potent HIV-specific T cells can be generated using improved CAR design and that CAR T cells could be important components of an HIV cure strategy.
HIV Reservoirs Exhibit a Resistance to Elimination by CD8+ T-cells that can be Partially Overcome by BCL-2 Inhibition

Persistent latent HIV reservoirs in CD4+ T-cells obstruct current cure efforts. The ‘kick and kill’ approach proposes to purge these reservoirs by combining latency reversing agents with immune effectors, such as cytotoxic T-lymphocytes. However, prospects for this approach are largely based on success in in vitro latency models, which do not fully reflect the makeup of latent reservoirs in individuals on long-term antiretroviral therapy. We recently reported the unexpected observation that combinations of latency reversing agents (LRAs) and HIV-specific CD8+ T-cells failed to drive reductions in infectious viral reservoirs from ex vivo patient CD4+ T-cells, as measured by quantitative viral outgrowth assays (QVOAs) (Huang et al, JCI, 2018). We have since been exploring the potential for small molecule modulators of cell survival to prime infected cells in these ex vivo samples for elimination by CD8+ T-cells. We have observed that the addition of the BCL-2 inhibitor ‘ABT-199’ facilities partial ex vivo reductions in infectious HIV reservoirs when used in combination with CD8+ T-cells and LRAs. Our findings suggest that ‘prime, kick, and kill’ therapeutic approaches hold promise for achieving reductions viral reservoirs.
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HIV cure trials face enormous challenges but also bring tremendous opportunities. In this talk, we will review some of the main issues confronting ongoing and upcoming HIV cure trials. We will discuss how to measure the HIV reservoir, focusing on limitations of current assays and progress that is being made to more accurately assess HIV persistence, including how we might identify biomarkers to predict antiretroviral therapy (ART)-free remission. We will discuss selected clinical trials that are aiming to reduce or control HIV reservoirs, with a focus on current efforts in the AIDS Clinical Trials Group. We will highlight a recent study on the relationship between HIV reservoirs and persistent immune activation, and its implications for how cure might affect activation. And finally, we will discuss how we might assess the impact of interventions on achieving ART-free remission, including new information on the effect of treatment interruptions on HIV reservoirs. Throughout the talk, the challenges we face will be discussed along-side potential opportunities to move the field forward towards an HIV cure.
Is It Possible an HIV Cure Using Stem Cell Allotransplants?

To date, the only evidence of a medical intervention capable of curing HIV-1 infection (the “Berlin patient”), involved an allogeneic hematopoietic stem cell transplantation (allo-HSCT) with a CCR5-mutated donor. The multifactorial transplantation-associated mechanisms that led to such unique outcome are not fully understood. The IciStem Consortium has compiled the largest cohort of HIV+ individuals that have gone through an allo-HSCT with a comprehensive clinical, virological and immunological follow-up.

An extensive work has been done in six HIV+ treated long-term survivors after receiving an allo-HSCT with CCR5wt donor cells. After extensive analysis within the consortium, we postulate that that alloreactivity under allo-HSCT with episodes of graft-versus-host reactions may facilitate a “graft-vs.-HIV reservoir” effect, contributing to dramatic reductions on the HIV reservoir under cART. By understanding the mechanism that allo-HSCT succeed to eradicate HIV infection, new cure strategies can be designed by mimicking the graft-vs.-HIV effect observed in this study.
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