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The Biology of HIV Infections

Project Number
1ZIAAI001213-05

Contact PI/Project Leader
MARTIN, MALCOLM

Awardee Organization
NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

Description

Abstract Text

BROADLY-ACTING NEUTRALIZING ANTIBODY IMMUNOTHERAPY INITIATED ON DAY 3 OR WEEK 2 AFTER SHIV INFECTION OF RHESUS MACAQUES CAN CONTROL VIREMIA FOR SEVERAL YEARS. We previously reported that combination bNAb immunotherapy initiated on day 3 post infection (PI) maintained durable CD8+ T cell-mediated suppression of SHIVAD8 viremia and pre-inoculation levels of CD4+ T cells in 6 of 13 treated monkeys during 3years of observation, as assessed by successive CD8+ T cell depletion experiments. These initial findings have been extended by monitoring the virologic and CD4+ T cell status of the original Day 3 treated controller monkeys during an additional 2.5 to 3.5 year period; and 2) initiating a new immunotherapy regimen in which the effects of combination bNAb alone, or cART plus bNAb treatment, beginning at week 2 post SHIV infection time point. During the 4th and 5th years after bNAb immunotherapy initiation on day 3 PI, 3 of the 7 original progressor animals) suppressed virus replication and became late controllers. In total, 9 of 13 animals starting combination bNAb immunotherapy on day 3 PI became controller macaques. In an extension of that study, two treatment interventions (bNAbs alone or cART plus bNAbs), beginning at the clinically more relevant week 2 PI, were conducted and conferred controller status to 7 of 12 monkeys that was also dependent on control mediated by CD8+ cells, which developed over a 3-year period. However, the median time to suppression of plasma viremia, following intervention on week 2, was markedly delayed (85 weeks) compared to combination bNAb immunotherapy initiated on day 3 (39 weeks). In both cases, the principal correlate of virus control was the induction of CD8+ T cellular immunity. PREVENTION AND TREATMENT OF SHIVAD8 INFECTION IN RHESUS MACAQUES BY A POTENT D PEPTIDE HIV ENTRY INHIBITOR. Combination anti-retroviral therapy (cART) has greatly improved the length and quality of life of HIV infected individuals with access to treatment and has reduced HIV transmission from treated patients. We have evaluated a potent 16-residue D-peptide (composed of D-amino acids) HIV-1 entry inhibitor, designated CPT31, which targets the highly conserved gp41 N-peptide pocket region, in blocking virus infections both in vitro and in vivo. CPT31 exhibited strong inhibitory breadth against diverse panels of primary virus isolates. In a SHIV macaque model, CPT31 prevented infection from a single high-dose rectal challenge. In chronically infected animals, CPT31 monotherapy rapidly reduced viral load by 2 logs before rebound occurred due to the emergence of drug resistance. In chronically infected animals with viremia initially controlled by combination antiretroviral therapy (cART), CPT31 monotherapy for an additional 13 weeks prevented viral rebound after discontinuation of cART. These data establish CPT31 as a promising new candidate for HIV prevention and treatment. A BROADLY NEUTRALIZING MACAQUE MONOCLONAL ANTIBODY AGAINST THE HIV-1 V3-GLYCAN PATCH. A small fraction of HIV-1 infected humans (Elite Neutralizers) develop potent broadly neutralizing antibodies (bNAbs) against HIV-1 that can protect macaques from infection with simian immunodeficiency HIV **chimeric virus** (SHIV). Similarly, a small number of macaques infected with SHIVs also develop broadly neutralizing serologic activity, but less is known about the nature of these simian antibodies. A monoclonal antibody, Ab1485, has been isolated from a macaque infected with SHIVAD8 that developed broadly neutralizing serologic activity mapping to the V3-glycan region of HIV-1 Env. Ab1485 neutralizes 38.1 % of HIV-1 isolates in a panel of 42 pseudoviruses with a geometric mean IC50 of 0.055 g/ml and SHIVAD8 with an IC50 of 0.028 g/ml. Ab1485 binds to the V3-glycan epitope in a glycan-dependent manner as determined by ELISA and neutralization assays with HIV-1JRCSF mutant viruses. A 3.5 cryo-electron microscopy structure of Ab1485 in complex with a native-like SOSIP Env trimer showed conserved contacts with the N332gp120 glycan and the gp120 GDIR peptide motif, but in a distinct Env-binding orientation relative to human V3/N332gp120 glycan-targeting bNAbs. Finally, intravenous infusion of Ab1485 protected macaques from a high dose intrarectal challenge with SHIVAD8. We conclude that macaques can develop bNAbs against the V3-glycan patch that resemble human V3-glycan bNAbs.

Public Health Relevance Statement

Data not available.

NIH Spending Category

Biotechnology HIV/AIDS Immunization Immunotherapy Infectious Diseases Prevention Vaccine Related Vaccine Related (AIDS)

Project Terms

AIDS prevention AIDS/HIV problem Amino Acids Animals Antibodies Antibody Therapy Binding Biological Assay Biology of HIV Infection CD4 Positive T Lymphocytes CD8-Positive T-Lymphocytes CD8B1 gene Cellular Immunity Chronic Clinical Complex

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Read More

Details

Contact PI/ Project Leader

Name
MARTIN, MALCOLM
Title
Contact
Email not available

Other PIs

Not Applicable

Program Official

Name
Contact
Email not available

Organization

Name
NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES
City
Country

Department Type
Unavailable
Organization Type
Unavailable

State Code
Congressional District

Other Information

FOA
Study Section
Fiscal Year
2020
Award Notice Date

Administering Institutes or Centers
NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES
DUNS Number
CFDA Code

Project Start Date
Project End Date
Budget Start Date
Budget End Date

Project Funding Information for 2020

Total Funding
$2,068,853

Direct Costs
$0

Indirect Costs
$0

Year	Funding IC	FY Total Cost by IC
2020	NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES	$2,068,853

NIH Categorical Spending

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Funding IC	FY Total Cost by IC	NIH Spending Category
NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES	$517,213	Vaccine Related (AIDS)
NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES	$2,068,853	Biotechnology; HIV/AIDS; Immunization; Immunotherapy; Infectious Diseases; Prevention; Vaccine Related;

Sub Projects

No Sub Projects information available for 1ZIAAI001213-05

Publications

No Publications available for 1ZIAAI001213-05

Patents

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