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TOWARDS A MORE RELEVANT MODEL OF HIV INFECTION

Project Number
5DP1DA039543-05

Contact PI/Project Leader
OVERBAUGH, JULIE M.

Awardee Organization
FRED HUTCHINSON CANCER RESEARCH CENTER

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Description

Abstract Text

DESCRIPTION: SHIV macaque models provide an important benchmark for pre-clinical HIV-1 research, serving as a gatekeeper for advancing vaccine and other prevention approaches. The ability of such models to predict intervention(s) that will be efficacious in humans depends to a large extent on how faithfully the model recapitulates key features of HIV-1 transmission and pathogenesis in humans, including both sexual and parenteral transmission. To date, SHIVs have largely been selected by trial and error using the most readily available HIV-1 variants, often those that have been adapted to replication in cell culture (lab-adapted HIV-1 variants). As a result, few SHIV models incorporate key features of circulating variants that are the target of vaccine and other prevention methods. Although efforts in this area are increasing, approaches nonetheless generally rely on constructing and testing a series of SHIV chimeras encoding available HIV-1 variants and moving forward the one that replicates best. Of note, this process of generating pathogenic SHIVs includes serial passage of the virus in macaques to further increase replication fitness, and all of the SHIVs in current use have been adapted in this manner (adapted SHIVs). We propose to pioneer a rational design approach to developing relevant SHIVs that better represent circulating HIV-1 variants central to the **pandemic**. We have found several barriers to HIV-1 replication in macaque cells that are specific to transmitted/founder (T/F) viruses circulating in humans. These restrictions do not appear to be the result of known restriction factors, which are generally not specific to select HIV-1 variants. In our preliminary studies, we found that IFN-stimulated responses have a pronounced effect on the replication of SHIVs encoding circulating T/F envelope variants in macaque T cells, but not on adapted SHIVs. Another critical species-specific barrier of HIV-1s circulating in humans is the macaque CD4 receptor, which is generally a poor receptor for T/F variants, but a functional receptor for lab-adapted variants, potentially explaining the bias towards developing SHIVs based on lab-adapted HIV-1 variants. While T/F variants can be adapted to use the macaque CD4 receptor, adaptation leads to antigenic changes that alter recognition of several broad NAbs that are currently the centerpiece of HIV-1 vaccine efforts. Here, we propose to exploit these preliminary findings to define the mechanisms underlying the envelope-mediated restrictions to HIV-1 replication in macaques, to define the consequences of these changes for the utility of the model and to identify pathways to developing rationally designed SHIVs with enhanced utility for preclinical studies of HIV-1 vaccine and prevention methods.

Public Health Relevance Statement

PUBLIC HEALTH RELEVANCE: Vaccine and other prevention concepts are typically evaluated in preclinical models to identify approaches likely to be efficacious in humans. The preclinical model of choice is SHIV infection of macaques. Unfortunately, current SHIVs do not represent HIV-1 found in humans, including HIV-1 variants found in injecting drug users, limiting information from these studies. Here we propose to develop a more relevant model that will better inform evaluation of HIV-1 vaccines and other interventions.

NIH Spending Category

Biotechnology | Drug Abuse (NIDA only) | HIV/AIDS | Immunization | Infectious Diseases | Prevention | Substance Abuse | Vaccine Related | Vaccine Related (AIDS)

Project Terms

Area | Benchmarking | CD4 Antigens | Cell Culture Techniques | Cells | Chimera organism | Evaluation | Gatekeeping | HIV | HIV Infections | HIV-1 | HIV-1 vaccine | Human | Infection | Injecting drug user | Interferons | Intervention | Macaca | Mediating | Methods | Modeling | Pathogenesis | Pathogenicity | Pathway interactions | Pre-Clinical Model | Prevention | Prevention approach | Process | Research | Serial Passage | Series | T-Lymphocyte | Testing | Vaccines | Variant | Virus | base | design | fitness | **pandemic** disease | pre-clinical | preclinical study | public health relevance | receptor | response | simian human immunodeficiency virus | transmission process

Details

Contact PI/ Project Leader

Other PIs

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Contact PI/Project Leader
OVERBAUGH, JULIE M.

Awardee Organization
FRED HUTCHINSON CANCER RESEARCH CENTER

Organization

Name
FRED HUTCHINSON CANCER RESEARCH CENTER

City
SEATTLE

Country
UNITED STATES (US)

Department Type
Unavailable

Organization Type
Research Institutes

State Code
WA

Congressional District
07

Other Information

FOA
RFA-DA-15-004

Study Section
ZDA1-GXM-A(07)R

Fiscal Year
2019

Award Notice Date
19-July-2019

Administering Institutes or Centers
NATIONAL INSTITUTE ON DRUG ABUSE

DUNS Number
078200995

CFDA Code
279

Project Start Date
30-September-2015

Project End Date
31-July-2021

Budget Start Date
01-August-2019

Budget End Date
31-July-2021

Project Funding Information for 2019

Total Funding
$880,000

Direct Costs
$500,000

Indirect Costs
$380,000

Year	Funding IC	FY Total Cost by IC
2019	NATIONAL INSTITUTE ON DRUG ABUSE	$880,000

NIH Categorical Spending

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Funding IC	FY Total Cost by IC	NIH Spending Category
NATIONAL INSTITUTE ON DRUG ABUSE	$880,000	Biotechnology; Drug Abuse (NIDA only); HIV/AIDS; Immunization; Infectious Diseases; Prevention; Substance Abuse; Vaccine Related; Vaccine Related (AIDS);

Sub Projects

No Sub Projects information available for 5DP1DA039543-05

Publications

Export

Journal (Link to PubMed abstract)	Authors	Publication Year	Similar Publications	CitedBy	iC
The TOP vector: a new high-titer lentiviral construct for delivery of sgRNAs and transgenes to primary T cells.					
Molecular therapy. Methods & clinical development 2021 Mar 12; 20 30-38	Humes, Daryl; Rainwater, Stephanie; Overbaugh, Julie	2021			
Identification of HIV-1 Envelope Mutations that Enhance Entry Using Macaque CD4 and CCR5.					
Viruses 2020 02 21; 12 (2)	Roop, Jeremy I; Cassidy, Noah A; Dingens, Adam S; Bloom, Jesse D; Overbaugh, Julie	2020			
An Antigenic Atlas of HIV-1 Escape from Broadly Neutralizing Antibodies Distinguishes Functional and Structural Epitopes.					
Immunity 2019 02 19; 50 (2) 520-532.e3	Dingens, Adam S; Arenz, Dana; Weight, Haidyn; Overbaugh, Julie; Bloom, Jesse D	2019		iCite 2.77	
Antibody Lineages with Vaccine-Induced Antigen-Binding Hotspots Develop Broad HIV Neutralization.					

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Project Number	Contact PI/Project Leader	Awardee Organization
5DP1DA039543-05	OVERBAUGH, JULIE M.	FRED HUTCHINSON CANCER RESEARCH CENTER

Macaque interferon-induced transmembrane proteins limit replication of SHIV strains in an Envelope-dependent manner.

PLoS pathogens 2019 07; 15 (7) e1007925 — Sharma, Amit; McLaughlin Jr, Richard N; Basom, Ryan S; Kikawa, Caroline; OhAinle, Molly; Yount, Jacob S; Emerman, Michael; Overbaugh, Julie — 2019 — iCite 0.53

A virus-packageable CRISPR screen identifies host factors mediating interferon inhibition of HIV.

eLife 2018 12 06; 7 — OhAinle, Molly; Helms, Louisa; Vermeire, Jolien; Roesch, Ferdinand; Humes, Daryl; Basom, Ryan; Delrow, Jeffrey J; Overbaugh, Julie; Emerman, Michael — 2018 — iCite 2.47

Patents

No Patents information available for 5DP1DA039543-05

Outcomes

The Project Outcomes shown here are displayed verbatim as submitted by the Principal Investigator (PI) for this award. Any opinions, findings, and conclusions or recommendations expressed are those of the PI and do not necessarily reflect the views of the National Institutes of Health. NIH has not endorsed the content below.

No Outcomes available for 5DP1DA039543-05

Clinical Studies

No Clinical Studies information available for 5DP1DA039543-05

News and More

Related News Releases

No news release information available for 5DP1DA039543-05

History

No Historical information available for 5DP1DA039543-05

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