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Inhibition of Resistant Variants of HIV Protease

Project Number	Former Number	Contact PI/Project Leader	Awardee Organization
8U01AI150461-21	5U01GM062920-21	WEBER, IRENE TOther PIs	GEORGIA STATE UNIVERSITY

Description

Abstract Text

Inhibition of Resistant Variants of HIV Protease HIV/AIDS is a serious **pandemic** with over 36 million infected people. Antiviral drug therapy has decreased the mortality, although the number of new infections remains about 2 million per year. However, the genetic diversity and high mutability of HIV pose a critical challenge for continued efficacy of drugs and development of effective vaccines. Hence, there is urgent need for new therapies to overcome the problem of drug-resistance. We are tackling this challenge by studying the important drug target of HIV protease. Clinical resistance arises even for the potent antiviral inhibitor darunavir. Our structural analyses have identified distinct molecular mechanisms for resistance including mutations that: 1) decrease protease interactions with inhibitors; 2) decrease the enzyme stability; or 3) influence the dynamics. In the last project period, our X-ray structures have guided the design of novel inhibitors 10-fold more effective than darunavir against highly resistant proteases. We have developed algorithms to predict resistance from genotype sequences and have identified representative mutants with high level resistance. We propose to identify common mechanism for resistance and apply these insights to design and assess new inhibitors. These multidisciplinary studies leverage the expertise, unique resources and novel approaches developed in the PIs groups together with an established set of collaborators to integrate computational, X-ray crystallographic, biochemical and biophysical techniques with inhibitor design, chemical synthesis, and virology studies. The expected outcomes will be 1) accurate predictions for resistance, 2) discovery of novel and conserved molecular mechanisms for resistance, and 3) new antiviral inhibitors for resistant HIV infections.

Public Health Relevance Statement

A major challenge limiting success of HIV/AIDS therapy is the rapid development of viral strains with resistance to drugs. Knowledge of the relationships between sequence, structure and activities of HIV protease variants with drug resistant mutations will be applied to predict resistance and develop new antiviral agents.

NIH Spending Category

Antimicrobial Resistance HIV/AIDS Infectious Diseases

Project Terms

AIDS therapy AIDS/HIV problem Address Affinity Algorithms Antiviral Agents Binding Binding Sites Biochemical Characteristics Chemistry Clinical Data Data Set Development Drug Targeting Drug resistance Enzyme Stability Evolution Genetic Variation Genotype HIV HIV Infections HIV Protease HIV Protease Inhibitors HIV resistance Infection Knowledge Molecular Mutation Outcome Peptide Hydrolases Pharmaceutical Preparations Pharmacotherapy Property Proteins Resistance Resources Roentgen Rays Structure Surgical Flaps Vaccines Variant Viral base biophysical techniques chemical synthesis design drug development drug efficacy

Read More

Details

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Organization

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5U01GM062920-21

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WEBER, IRENE TOther PIs

Awardee Organization
GEORGIA STATE UNIVERSITY

Other Information

FOA
PA-16-160

Study Section
AIDS Discovery and Development of Therapeutics Study Section[ADDT]

Fiscal Year
2019

Award Notice Date
17-June-2019

Administering Institutes or Centers
NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

DUNS Number
837322494

CFDA Code
859

Project Start Date
01-July-1997

Project End Date
30-June-2021

Budget Start Date
01-July-2019

Budget End Date
30-June-2020

Project Funding Information for 2019

Total Funding
$345,420

Direct Costs
$228,000

Indirect Costs
$117,420

Year	Funding IC	FY Total Cost by IC
2019	NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES	$345,420

NIH Categorical Spending

Click here for more information on NIH Categorical Spending

Funding IC	FY Total Cost by IC	NIH Spending Category
NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES	$345,420	Antimicrobial Resistance; HIV/AIDS; Infectious Diseases;

Sub Projects

No Sub Projects information available for 8U01AI150461-21

Publications

No Publications available for 8U01AI150461-21

Patents

No Patents information available for 8U01AI150461-21

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 8U01AI150461-21

Clinical Studies

No Clinical Studies information available for 8U01AI150461-21

News and More

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History

No Historical information available for 8U01AI150461-21

Similar Projects

No Similar Projects information available for 8U01AI150461-21

Thank you for your feedback!