Back to Search Results

Description
Details
Sub-Projects
Publications
Patents
Outcomes
Clinical Studies
News and More
History
Similar Projects

Host Targeted Therapy for Drug Resistant Salmonella and Francisella infection

Project Number
5R01AI125147-05

Contact PI/Project Leader
AINSLIE, KRISTY MOther PIs

Awardee Organization
UNIV OF NORTH CAROLINA CHAPEL HILL

Description

Abstract Text

Abstract The formation of antibacterial drug resistance is a public health crisis and has led to increaseing healthcare costs and even death. Drug resistance can occur when an antibiotic directly kills a pathogen or prevents its growth because of selective pressure. This phenomena has generated various multi-drug resistant bacterial species that are a global public health concern. Most antibacterial therapeutics target the pathogen in an attempt to clear infection. However, more recently the concept of antibacterial therapeutics that target host specific pathways has been developed. These pathways can potentially prevent infection, virulence, replication, and proliferation. Therapies that target these pathways could potentially treat traditional antibiotic resistant strains. Additionally, targeting the host instead of the pathogen could prevent the development of drug resistance because the therapy could activate pathways that fight resistance and activate the host's defense mechanisms. Futhermore, because many pathogens take advantage of similar pathways, there is a potential for developing therapies that target a broad-spectrum of pathogens. We were one of the first groups to use a host-targeted therapeutic (HTT) for the treatment of a pathogen that is considered a Threat Level of Serious by the CDC. This HTT does not work directly on intracellular pathogens but instead targets host cell promoting pathways that result in clearance of the pathogen. Additionally, this HTT has broad-spectrum activity against pathogens including a NIAID Category A class pathogen. We have both in vitro and in vivo data showing activity and increase in survival. In order to increase activity we have encapsulated this compound in a novel biomaterial that is acid sensitive. This acid sensitivity allows for the intracellular release of encapsulated cargo. Our preliminary data shows that encapsulation of the HTT drastically enhances the efficacy of the compound compared to non-encapsulated form. In this proposal, we propose on performing medicinial chemistry on our HTT to develop a compound with increased activity. We will formulate this compound in our novel polymeric particles for both in vitro and in vivo testing. We will perform various biological assays to determine activity of optimized compounds. In order to do this, our proposal is a partnership between the University of North Carolina, National Taiwan University, and the Research Triangle Institute (RTI). This partnership will be invaluable in obtaining an optimized HTT compound that has activity against a broad spectrum of pathogens as it incoporates academic researchers in the field and RTI's experience with drug development.

Public Health Relevance Statement

Project Narrative Here we propose the optimization of a host targeted therapeutic for the treatment of infection due to drug resistant bacteria. We will alter the chemical structure and formulate the drug to increase the efficacy of the compound. We will perform experiments that will help enable IND FDA filling of the proposed therapy.

NIH Spending Category

Antimicrobial Resistance Biodefense Bioengineering Digestive Diseases Emerging Infectious Diseases Foodborne Illness Infectious Diseases Nanotechnology Orphan Drug Prevention Rare Diseases Vector-Borne Diseases

Project Terms

ADME Study AKT Signaling Pathway Acetates Acids Anti-Bacterial Agents Antibiotic Resistance Antibiotics Autophagocytosis Bacteria Bacterial Drug Resistance Bacterial Infections Biocompatible Materials Biological Biological Assay Biomedical Engineering Camptothecin Categories Cells Centers for Disease Control and Prevention (U.S.) Cessation of life Chemical Structure Chemistry Clinical assessments Computer software Data Development Dextrans Drug Design Drug resistance Encapsulated Excipients Excretory function Formulation Francisella Francisella tularensis Genes Goals Grant Growth Health Care Costs Host Defense Mechanism Human In Vitro Infection Infection prevention

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Details

Back to Search Results

Description
Details
Sub-Projects
Publications
Patents
Outcomes
Clinical Studies
News and More
History
Similar Projects

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Awardee Organization
UNIV OF NORTH CAROLINA CHAPEL HILL

ainslie.1@osu.edu

Organization

Name
UNIV OF NORTH CAROLINA CHAPEL HILL

City
CHAPEL HILL

Country
UNITED STATES (US)

Department Type
PHARMACOLOGY

Organization Type
SCHOOLS OF PHARMACY

State Code
NC

Congressional District
04

Other Information

FOA
RFA-AI-15-024

Study Section
ZAI1-SM-M(M1)

Fiscal Year
2020

Award Notice Date
19-March-2020

Administering Institutes or Centers
NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

DUNS Number
608195277

CFDA Code
855

Project Start Date **22-April-2016**

Project End Date **31-March-2022**

Budget Start Date **01-April-2020**

Budget End Date **31-March-2022**

Project Funding Information for 2020

Total Funding
$1,043,412

Direct Costs
$901,295

Indirect Costs
$142,117

Year	Funding IC	FY Total Cost by IC
2020	NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES	$1,043,412

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	$1,043,412	Antimicrobial Resistance; Biodefense; Bioengineering; Digestive Diseases; Emerging Infectious Diseases; Foodborne Illness; Infectious Diseases; Nanotechnology; Orphan Drug; Prevention; Rare Diseases; Vector-Borne Diseases;

Sub Projects

No Sub Projects information available for 5R01AI125147-05

Publications

No Publications available for 5R01AI125147-05

Patents

No Patents information available for 5R01AI125147-05

Outcomes

Back to Search Results

Description
Details
Sub-Projects
Publications
Patents
Outcomes
Clinical Studies
News and More
History
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Clinical Studies

No Clinical Studies information available for 5R01AI125147-05

News and More

Related News Releases

No news release information available for 5R01AI125147-05

History

No Historical information available for 5R01AI125147-05

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