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#### **Engineered Antimicrobial Platform to Target Pulmonary Intracellular Infections**

**Project Number Contact PI/Project Leader** 5R01Al134729-03

**Awardee Organization** STAYTON, PATRICK S.Other Pls **UNIVERSITY OF WASHINGTON** 



#### **Abstract Text**

PROJECT SUMMARY/ABSTRACT Intracellular infections based in the lung alveolar macrophage population remain one of the most challenging anti-infective settings and unmet medical needs. Diseases such as tuberculosis, legionellosis, tularemia and melioidosis cause high mortality and morbidity costs around the globe. The long-term goal of this project is to develop and validate a new inhalable macromolecular therapeutic platform termed "drugamers" that targets antibiotics and antibiotic drug combinations to the alveolar macrophage to better treat lung-based intracellular infections. A key new property of this platform, that currently does not exist in clinically available therapeutics and delivery systems, is the ability to engineer custom tailored pharmacokinetic (PK) drug release profiles in the alveolar compartment and targeted alveolar macrophages that match the required PK profiles of specific antibiotic classes and specific bacterial infection processes. To achieve this objective, the project brings together a multi-disciplinary team across polymer therapeutics, glycan targeting of alveolar macrophages, and clinical expertise in alveolar-based bacterial pathology and treatment. The initial therapeutic focus is on tularemia and melioidosis, with clinical investigators and access to BSL-3 human pathogen models and facilities. The proposal is structured around 4 specific aims to: (1) Synthetically construct mannose-targeted drugamers of fluoroquinolone, β-lactam, and aminoglycoside drugs and drug combinations with controlled release profiles and architectural morphologies designed to optimize alveolar macrophage uptake. (2) Optimize the biocompatibility, alveolar macrophage targeting, and PK properties - measured by liquid chromatography - mass spectrometry analysis - of the drugamer library in murine models based on known drug dosing profiles of these major classes of antibiotics. Select optimized drugamers based on these in vivo properties to carry forward into the surrogate models of tularemia and melioidosis of the next aim. (3) Evaluate in vivo bactericidal efficacy of the mannose-targeted drugamers selected through their winning properties in Aim 2. Drugamers administered by aerosoloization will be tested for their ability to achieve cures in highly lethal mouse disease models infected by controlled aerosolization of surrogate Francisella and Burholderia bacteria. (4) Highly effective drugamer designs selected in Aim 3 will be assessed in human pathogen mouse models using Francisella tularensis and Burkholderia pseudomallei at the University of Washington BSL3 select agent facility. If successful, this project will identify lead inhalation therapeutics for future clinical pathway development against tularemia and melioidosis. Because the drugamer platform is modular, it could also be developed against other unmet intracellular lung infection therapy needs, where the growing issue of drug resistance provides a compelling need for the tailored and combination dosing profiles of this platform.

## **Public Health Relevance Statement**

PROJECT NARRATIVE Lung infections remain a major public health challenge across the developed and developing world, with diseases such as tuberculosis and melioidosis causing high mortality and morbidity. Effective antibiotic treatment to combat intracellular lung infections remains an unmet need, and the well documented emergence of drug resistance, combined with the different dosing requirements of individual antibiotics, creates a need to target combination drugs to alveolar macrophages with carefully tailored release profiles. The overarching goal of this proposal is to develop a macromolecular therapeutic platform that meets these significant areas of need in global health using advanced polymer chemistry and molecular engineering.!

#### **NIH Spending Category**

**Biodefense Bioengineering Emerging Infectious Diseases Infectious Diseases** Lung **Vector-Borne Diseases Orphan Drug** Nanotechnology **Rare Diseases** 

#### **Project Terms**

**Anti-Infective Agents Aerosols Alveolar Alveolar Macrophages Aminoglycoside Antibiotics Antibiotic Therapy Antibiotics Bacterial Infections Architecture** Area **Bacteria Biodistribution Biological Availability Blood** Burkholderia pseudomallei Carbapenems **Chlamydophila Infections Clinical Investigator** Ciprofloxacin Clinical **Clinical Pathways Clinical Trials Combined Antibiotics** Custom **Disease** Disease model Development Dose

Thank you for your feedback!

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> **Drug Combinations Drug Kinetics Drug resistance Engineering Enzymes Evaluation** Francisella tularensis **Exhibits Family** Fluoroquinolones **Formulation** Francisella **Future** . .. . . .

**Read More** 



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**UNIVERSITY OF WASHINGTON** 

City

**SEATTLE** 

Country **UNITED STATES (US)**  Department Type **BIOMEDICAL ENGINEERING** 

Organization Type

**BIOMED ENGR/COL ENGR/ENGR STA** 

State Code

WA

**Congressional District** 

07

**Other Information** 

FOA PA-16-160

Study Section

<u>Drug Discovery and Mechanisms of</u> <u>Antimicrobial Resistance Study</u>

Section[DDR]

**Award Notice Date** Fiscal Year 05-November-

2020

Administering Institutes or Centers NATIONAL INSTITUTE OF ALLERGY **AND INFECTIOUS DISEASES** 

**DUNS Number** CFDA Code

605799469 855 **Project Start** 

13-November-

2017 Date

**Project End Date** 31-October-

2022

**Budget Start** 01-November-

2019 Date

**Budget End Date** 31-October-

2020

**Project Funding Information for 2020** 

**Total Funding Direct Costs Indirect Costs** \$512,525 \$335,958 \$176,567

**Funding IC FY Total Cost by IC** Year 2020 NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES \$512,525

**NIH Categorical Spending** 

Click here for more information on NIH Categorical Spending

**NIH Spending Category Funding IC** FY Total Cost by IC Biodefense; Bioengineering; Emerging NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES \$512,525 Infectious Diseases; Infectious Diseases; Lung; Nanotechnology; Orphan Drug; Rare Diseases; Vector-Borne Diseases;

**品 Sub Projects** 

No Sub Projects information available for 5R01Al134729-03

**Publications** 

No Publications available for 5R01Al134729-03



No Patents information available for 5R01Al134729-03

#### 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 5R01Al134729-03

## **†** Clinical Studies

No Clinical Studies information available for 5R01Al134729-03

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No news release information available for 5R01Al134729-03

## History

No Historical information available for 5R01Al134729-03

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