AWARD NUMBER: W81XWH-18-1-0765

TITLE: Aerosol Delivery of CPZEN-45 for Treatment of Nontuberculous Mycobacterial (NTMs) Infections

PRINCIPAL INVESTIGATOR: Dr. Gail Cassell

CONTRACTING ORGANIZATION: Infectious Disease Research Institute, Seattle, WA

REPORT DATE: October 2020

TYPE OF REPORT: Annual Report

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	**2. REPORT TYPE**	**3. DATES COVERED**
October 2020	Annual	30Sep2019 – 29Sep2020

4. TITLE AND SUBTITLE

Aerosol Delivery of CPZEN-45 for Treatment of Nontuberculous Mycobacterial (NTMs) Infections

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-18-1-0765

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
Gail Cassell, PhD; Darrick Carter, PhD;

E-Mail: gail.cassell@pailifesciences.com; Grant@IDRI.org

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

Infectious Disease Research Institute
1616 Eastlake Ave E, Ste 400
Seattle WA 98102-3797

8. PERFORMING ORGANIZATION REPORT

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

This DOD Therapeutic Development Award is focused on a new antibiotic, CPZEN-45, discovered by our team for treatment of non-tuberculous mycobacterial infections (NTM) in patients with chronic obstructive pulmonary disease (COPD). We have two major objectives: **Objective 1**-To optimize fermentation and scale-up of manufacturing processes for high yield of CPZEN-45, including spray dried CPZEN-45. We have optimized fermentation and scale-up of CPZEN-45 and the processes have been successfully transferred to our manufacturing partner. **Objective 2**- To further define and characterize *in vitro* efficacy of CPZEN-45 against additional species of NTMs recently isolated from VA patients with COPD. We have obtained 26 recent NTM isolates from COPD patients (VA) Aurora, CO), phenotype and titers were determined, and DNA extracted for whole genome sequencing to evaluate phenotypic and genotypic correlation with resistance. Our objective to develop an efficacious regimen for COPD patients has started by screening multiple CPZEN-45 combinations with standard NTM compounds in human THP-1 cells using a checkerboard assay. **Synergy measurement by checkerboard analysis** will be used to determine the impact on potency of the combination of antibiotics in comparison to their individual activities. The optimized synergistic regimens will then be tested in COPD mouse and guinea pig efficacy models.

15. SUBJECT TERMS

Chronic Obstructive Pulmonary Disease, Veterans, CPZEN-45, Non-tuberculosis mycobacteria (NTM), NTM New Antibiotic Therapy, animal infection models, *M. avium*, *M. abscessus*.

16. SECURITY CLASSIFICATION OF:			**17. LIMITATION OF ABSTRACT**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON**
					USAMRMC
a. REPORT	**b. ABSTRACT**	**c. THIS PAGE**	UU	10	**19b. TELEPHONE NUMBER** *(include area code)*
U	U	U			

TABLE OF CONTENTS

	Page
1. Introduction	5
2. Keywords	5
3. Accomplishments	5
4. Impact	6
5. Changes/Problems	6
6. Products	7
7. Participants & Other Collaborating Organizations	8
8. Special Reporting Requirements	9
9. Appendices	10

1. INTRODUCTION:

Non-tuberculous mycobacteria (NTM) are environmental bacteria found commonly in soil, water, and biofilms. Chronic lung disease is the most frequent disorder caused by NTM; moreover, NTM lung infections not uncommonly complicate individuals with chronic obstructive pulmonary disease (COPD, aka emphysema). The incidence and prevalence of NTM lung disease (NTM-LD) in the U.S. is increasing yearly and now surpasses that of tuberculosis (TB). Veterans are three times more likely to develop COPD and NTM infection than the general population. NTM-LD is often treated for at least 18-24 months with at least three and sometimes a four or more-drug regimen. Despite this intense regimen – reflecting the high resistance of NTM to available antibiotics – the long-term cure rate is at best ~50% as the relapse rate is high. Thus, new antibiotics are urgently needed. Members of our research team have discovered a new chemical entity, CPZEN-45, which has been shown to have a novel mechanism of action. It is considered highly promising because it has been shown: (i) to directly kill many pathogenic species of NTM (both drug sensitive and drug resistant), (ii) to have efficacy in laboratory animals experimentally infected with NTM, (iii) to possess an acceptable toxicity profile, and (iv) to be able to be delivered directly to the lungs as a dry-powder. Before CPZEN-45 can be studied in patients with NTM-LD, we must do further pre-clinical work by making sure we can produce sufficient quantities of high quality CPZEN-45 as well as supply large amounts of the compound to do further testing in animals to further ensure efficacy and safety.

2. KEYWORDS:

Chronic Obstructive Pulmonary Disease, Veterans, CPZEN-45, Non-tuberculosis mycobacteria (NTM), animal infection models, NTM New Therapy, *M. avium, M. abscessus.*

3. ACCOMPLISHMENTS:

What were the major goals of the project?

Goal 1: Optimize fermentation and scale-up of manufacturing processes for CPZEN-45, including spray dried CPZEN-45.

Goal 2: Define and characterize in vitro and in vivo efficacy of CPZEN-45 against NTM recently isolated from VA patients with COPD using our well characterized COPD mouse models and to evaluate CPZEN-45 inhaled therapy using a chronic NTM model in guinea pigs.

What was accomplished under these goals?

IDRI entered receivership at the end of 2019 which led to no work being completed during the period of this report. The initial process of transferring both the Principal Investigator, Dr. Gail Cassell, and this project to another institution began in November 2019. Formal relinquishment of the award began in December 2020. No work has taken place on this project since then.

What opportunities for training and professional development has the project provided?

Nothing to report

How were the results disseminated to communities of interest?

None.

What do you plan to do during the next reporting period to accomplish the goals?

This award is in the process of being relinquished by IDRI so that it can be officially transferred to Dr. Gail Cassell's new institution, PAI Life Sciences. Once transferred, the work originally outlined for years 2-3 will begin immediately.

4. **IMPACT:**
What was the impact on the development of the principal discipline(s) of the project?

Nothing to report

What was the impact on other disciplines?

Nothing to report

What was the impact on technology transfer?

Nothing to report

What was the impact on society beyond science and technology?

Nothing to report.

5. **CHANGES/PROBLEMS: Changes in approach and reasons for change**

The project is in the process of being relinquished by IDRI so that it can be transferred to PAI Life Sciences.

Actual or anticipated problems or delays and actions or plans to resolve them

Problem: As IDRI entered receivership in 2019 and Dr. Gail Cassell left IDRI as a result of restructuring, the award is currently in the process of being relinquished by IDRI so that it can be officially transferred to PAI Life Sciences. The nature of receivership has delayed this process longer than was anticipated.

Actions to resolve: IDRI is finalizing the steps necessary to relinquish the award in accordance with Washington State receivership court procedures and the guidance provided by the Contract Officer and Scientific Officer associated with this award.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Nothing to report.

Significant changes in use or care of human subjects

Nothing to report.

Significant changes in use or care of vertebrate animals

Nothing to report.

Significant changes in use of biohazards and/or select agents

Nothing to report.

6. PRODUCTS:

- **Publications, conference papers, and presentations**

Journal publications.

Nothing to report.

Books or other non-periodical, one-time publications.

Nothing to report.

Other publications, conference papers and presentations.

Nothing to report.

- **Website(s) or other Internet site(s)**

Nothing to report.

- **Technologies or techniques**

Nothing to report.

- **Inventions, patent applications, and/or licenses**

Nothing to report.

- **Other Products**

Nothing to report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name:	Dr. Gail Cassell
Project Role:	PD/PI
Researcher Identifier:	N/A
Nearest person month worked:	1.05 Calendar Months
Contribution to Project:	Dr. Cassell coordinates all work with participating organizations, participates in experimental design, and reviews the results.

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

None.

What other organizations were involved as partners?

The subawards that were active for this year of the project include RTI International, Colorado State University, and Denver Research Institute. Each of these subawards were terminated in December 2019 as part of the relinquishment process.

8. SPECIAL REPORTING REQUIREMENTS

QUAD CHARTS:

Aerosol Delivery of CPZEN-45 for Treatment of Non-Tuberculous Mycobacterial (NTMs) Infections

Log Number: PR171209
Award Number: W81XWH1810765

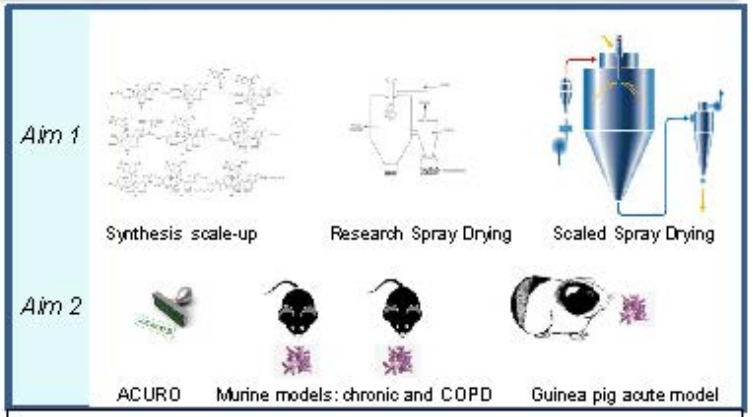
PI: Dr. Gail Cassell **Org:** Infectious Disease Research Institute **Award Amount:** $ 3,273,025

Study/Product Aim(s)

- Study Aim 1: Optimize fermentation and scale-up of manufacturing processes for CPZEN-45, including spray dried CPZEN-45.
- Study Aim 2: Define and characterize in vitro efficacy of CPZEN-45 against additional species of NTMs recently isolated from VA patients with COPD and to evaluate efficacy in our well characterized acute and chronic COPD mouse models and to evaluate CPZEN-45 Inhaled Therapy Using a Chronic NTM Model in guinea pigs

Approach

New antibiotics for Non-Tuberculosis Mycobacterial Lung Disease (NTM-LD) are urgently needed. We have discovered a new chemical entity, CPZEN-45, which has is highly promising since it: (i) directly kills many pathogenic species of NTM (both drug sensitive and drug resistant), (ii) has *in vivo* efficacy, and (iii) possess an acceptable toxicity profile, and (iv) can be delivered directly to the lungs as a dry-powder. Before CPZEN-45 can be studied in patients with NTM-LD, we must do further pre-clinical work - making sure we can produce sufficient quantities of high quality CPZEN-45 as well as supply large amounts of the compound to do further testing in animals to further ensure efficacy and safety.



Accomplishments: Aim 1: CPZEN-45 drug synthesis scaled to 500 g;
Aim 2: ACURO approvals for both models received

Timeline and Cost*

Activities / CY	18	19	20
Aim1: Scale up / Task 1: Improve drug substance yield			
Aim1: Scale up / Task 2: Transfer spray drying			
Aim2: Define and characterize efficacy of CPZEN-45 / Task 1: ACURO review			
Aim2: Define and characterize efficacy of CPZEN-45 / Task 2: in vivo Models			
Estimated Budget ($K)	**$1,203k**	**$1,270k**	**$798k**

*Updated: 12/1/4/20: Timelines & budget 4Q19 - 4Q20 are estimates only pending transfer of grant to new institution.

Goals/Milestones

CY18 Goals – Synthesis Scale-up and Animal Modeling
- ☑ CPZEN-45 scaled to 500 g
- ☑ ACURO approval received

CY19 Goal – Spray Drying Scale-up and Murine Testing
- ☐ Research spray dried lots for guinea pig and mouse models
- ☑ Begin transfer to spray-dry manufacturer
- ☐ Begin murine testing

CY20 Goal – Manufacturing and Animal Modeling
- ☐ Complete scale-up manufacturing
- ☐ Complete murine testing
- ☐ Complete guinea pig testing

Comments/Challenges/Issues/Concerns

- IDRI's receivership on 12/2019 and the transition of both the project to a new institution caused unforeseen delay in operation.

Budget Expenditure to Date

Projected Expenditure: $ 2,473,906
Actual Expenditure: $ 633,839.66

9. APPENDICES:
AWARD CHART:

PR171209: Aerosol Delivery of CPZEN-45 for Treatment of Nontuberculous Mycobacterial (NTMs) Infections

PI: DR. GAIL CASSELL, INFECTIOUS DISEASE RESEARCH INSTITUTE

Budget: $3,273,025.00 **Topic Area:** Antimicrobial Resistance **Mechanism:** W81XWH-17-PRMRP-TTDA

Research Area: Chemotherapy/Pharmacotherapy (803), Drug Resistance / Multidrug Resistance (804) **Award Status:** 9/30/18 – 9/29/21

Study Goals:

To improve the clinical outcome for patients with nontuberculous mycobacterial (NTM) lung disease by further development of a new antibiotic, CPZEN-45.

Specific Aims:

1) Optimization of fermentation and scaling up manufacturing to support IND enabling activities;
2) Evaluation of efficacy in a more relevant animal model of chronic obstructive pulmonary disease with a chronic NTM lung infection,
3) To identify the most optimal combination of drugs for eradicating NTM in this model, and to prove efficacy by administration of CPZEN- 45 by aerosol.

Key Accomplishments:

Publications: None
Patents: None
Funding Obtained: None