

**SUMMARY STATEMENT**  
( Privileged Communication )

Release Date: 06/23/2010

PROGRAM CONTACT:  
Suman Mukhopadhyay

Application Number: 1 R21 AI091991-01

Principal Investigator

DOW, STEVEN W. DVM, PHD

Applicant Organization: COLORADO STATE UNIVERSITY-FORT COLLINS

Review Group: ZRG1 IDM-A (80)

Center for Scientific Review Special Emphasis Panel  
Special Topics: Bacterial Pathogenesis

Meeting Date: 06/10/2010

RFA/PA: PA10-069

Council: OCT 2010

PCC: M46B B

Requested Start: 08/01/2010

Project Title: Mechanisms of Enteric Burkholderia psuedomallei infection

SRG Action: Impact/Priority Score: [REDACTED]

Human Subjects: 10-No human subjects involved

Animal Subjects: 30-Vertebrate animals involved - no SRG concerns noted

Project Year	Direct Costs Requested	Estimated Cost
1	[REDACTED]	[REDACTED]
2	[REDACTED]	[REDACTED]
<b>TOTAL</b>	[REDACTED]	[REDACTED]

**ADMINISTRATIVE BUDGET NOTE:** The budget shown is the requested budget and has not been adjusted to reflect any recommendations made by reviewers. If an award is planned, the costs will be calculated by Institute grants management staff based on the recommendations outlined below in the COMMITTEE BUDGET RECOMMENDATIONS section.

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**1R21AI091991-01 Dow, Steven**

**RESUME AND SUMMARY OF DISCUSSION:** The investigator has previously shown that mice can readily sustain an enteric infection with *Burkholderia pseudomallei* (Bp) and cites a body of epidemiological evidence suggesting the likelihood of an enteric route of infection in humans; and in the present application will examine the ability of a set of (human) clinical isolates to cause enteric murine infections, use fluorescently labeled Bp to assess cell type infectivity, and study dissemination to distal sites (following enteric infection). This well reasoned and supported application has the potential to change the way we think about the melioidosis (the diseases caused by Bp) an emerging tropical disease and recognized bioterror threat previously viewed as a primarily respiratory and skin infectious agent. Strengths of the application include the accomplished investigator and research team, strong preliminary data, the direct doable and logical set of experiments, and the likelihood of paradigm shifting insights into melioidosis. The panel is genuinely excited by the work proposed and there is a very high level of enthusiasm.

**DESCRIPTION (provided by applicant):** *Burkholderia pseudomallei* (Bp) is a Gram-negative bacterial pathogen that can cause a variety of difficult-to-treat infections in humans ranging from acute sepsis to chronic abscesses. While Bp is endemic in Southeast Asia and northern Australia, infections are now being diagnosed with increasing frequency around the world, including in Central and South America. Therefore, it is likely that Bp infections will soon be identified in the U.S. *Though infection with Bp was previously thought to occur by inhalation or skin inoculation, our new studies indicate that Bp is actually a primary enteric pathogen, which can readily establish acute or persistent GI tract infection following oral inoculation in mouse models.* However, at present essentially nothing is known regarding the pathogenesis of enteric infection with Bp. Therefore, the studies proposed here are intended to fill a critical void in our understanding of pathogenesis of infection with this important and emerging bacterial pathogen. First, we will use the mouse infection model of Bp infection to determine whether most or all strains of Bp can establish enteric infection and to identify virulent and avirulent isolates. Second, we will use the model to define the role of the intestine as a reservoir for Bp infection and to identify cells in the GI tract where the organism is maintained during chronic infection. Last, we will investigate how Bp is disseminated to other organs during chronic enteric infection. The information generated in these studies will substantially alter our view of Bp as a pathogen and also lead to a reassessment of the risks posed by oral Bp infection.

**PUBLIC HEALTH RELEVANCE:** *Burkholderia pseudomallei* is an important and dangerous bacterial pathogen that appears in recent years to be spreading around the world, including Central and South America. This organism is particularly dangerous because it is able to survive for years in soil and water, is very resistant to most antibiotics, and can cause rapidly fatal infections in humans. Previously it was assumed that the organism was contracted only by inhalation or skin injury, but our new data indicate that *B. pseudomallei* is also very infectious orally and causes chronic intestinal infection with fecal shedding. We will therefore study the mechanisms that allow *B. pseudomallei* to infect the intestinal tract, using mouse models of infection.

**CRITIQUE 1:**

Significance: 2  
Investigator(s): 2  
Innovation: 2  
Approach: 2  
Environment: 1

**Overall Impact:**

**Strengths**

- *Burkholderia pseudomallei* is a poorly understood emerging pathogen, potentially a bioterror weapon - this study provides a straightforward analysis of its pathogenesis

### **1. Significance:**

#### **Strengths**

- Enteric infection seems a likely route of pathogenesis
- Logical methodology, nice methods which are likely to succeed

#### **Weaknesses**

- How much of the pathology due to inhalation is due to ingestion?

### **2. Investigator(s):**

#### **Strengths**

- Strong investigator with substantial publications dealing with this and similar organisms
- Has appropriate collaborators to make labeled organisms

### **3. Innovation:**

#### **Strengths**

- Enteric infection has not been studied with this organism -
- Investigator make a nice analogy to other enteric infections

### **4. Approach:**

#### **Strengths**

- Entirely straightforward analysis of the mode of pathogenesis on an enteric infection
- RFP labeled organisms - should be useful to follow - alternative methods
- Use of CD18 null mice may (or may not) provide real insights into the mechanism of dispersion

#### **Weaknesses**

- Uses lots of different genetic backgrounds - may be more useful to figure out what is going on in the C57Bl6 - so mutants can be exploited

### **5. Environment:**

#### **Strengths**

- Outstanding group at Ft. Collins with documented expertise and publications using their BSL3 facility

### **Protections for Human Subjects:**

Not Applicable (No Human Subjects)

### **Vertebrate Animals:**

Acceptable

**Biohazards:**

Acceptable

**Select Agents:**

Acceptable

**Resource Sharing Plans:**

Not Applicable (No Relevant Resources)

**Budget and Period of Support:**

Recommend as Requested

**CRITIQUE 2:**

Significance: 1

Investigator(s): 2

Innovation: 3

Approach: 2

Environment: 1

**Overall Impact:**

**Strengths**

- The proposed research is a descriptive study that follows up on the discovery that *B. pseudomallei* establish a persistent enteric infection in mice. The discovery indicates that there is a significant oral route of infection, and has the potential to significantly expand our understanding of many aspects of melioidosis. The work will provide a general characterization of oral route of infection, which should help set the stage for studies to evaluate the impact of this route in humans.

**1. Significance:**

**Strengths**

- The work has the potential to transform our understanding of the pathogenesis of melioidosis, a poorly understood disease of biodefense importance.
- Epidemiological work suggests that oral infection investigated here in mice may be very important in humans. The support letter from Sharon Peacock is quite compelling on this point.

**2. Investigator(s):**

**Strengths**

- The investigator and his collaborators are highly experienced in working with *B. pseudomallei* animal models and are perfectly positioned to carry out the proposed work.

**3. Innovation:**

### **Strengths**

- The research topic is quite novel. Although the experimental attack is straightforward, the relatively descriptive studies are quite appropriate at this early point.

### **4. Approach:**

#### **Strengths**

- A first experiment to screen different *B. pseudomallei* clinical isolates for oral infectivity is feasible and should help define how universal this route of infection is.
- The analysis of the infection of different enteric cell types using GFP tagged bacteria is an appropriate way to help define the cellular course of the infection.

#### **Weaknesses**

- Including the avirulent *B. pseudomallei* relative *B. thailandensis* in the set of strains assayed for oral infection could provide a valuable negative control.

### **5. Environment:**

#### **Strengths**

- The RBL facilities are exceptionally good for BSL3 work of the sort described here.
- The investigator has a close collaborator Herb Schweizer who should provide bacterial expertise where necessary.

#### **Protections for Human Subjects:**

Not Applicable (No Human Subjects)

#### **Vertebrate Animals:**

Acceptable

- Mice will be used as the host and handled humanely.

#### **Biohazards:**

Not Applicable (No Biohazards)

#### **Budget and Period of Support:**

Recommend as Requested

#### **Select Agents:**

Acceptable

#### **Applications from Foreign Organizations:**

Not Applicable (No Foreign Organizations)

#### **Resource Sharing Plans:**

Acceptable

### **CRITIQUE 3:**

Significance: 1  
Investigator(s): 1  
Innovation: 2  
Approach: 1  
Environment: 1

#### **Overall Impact:**

##### **Strengths**

- Proposal for novel route of infection by *Burkholderia pseudomallei*.
- The reasoning behind this hypothesis is sound and supported by preliminary field studies.
- The study proposes directed and well-controlled experiments.

#### **1. Significance:**

##### **Strengths**

- Analysis of an emerging pathogen.

#### **2. Investigator(s):**

##### **Strengths**

- Extremely well qualified scientists to carry out this study.

#### **3. Innovation:**

##### **Strengths**

- Looking at an emerging pathogen thru a new lens.

##### **Weaknesses**

- Although the enteric link could be coincidental, studies should be done to detect where the reservoir of bacterial is in infected host.

#### **4. Approach:**

##### **Strengths**

- Very straightforward and based on previous successful studies.

#### **5. Environment:**

##### **Strengths**

- Satisfactory.

#### **Vertebrate Animals:**

- Acceptable

**THE FOLLOWING RESUME SECTIONS WERE PREPARED BY THE SCIENTIFIC REVIEW OFFICER TO SUMMARIZE THE OUTCOME OF DISCUSSIONS OF THE REVIEW COMMITTEE ON THE FOLLOWING ISSUES:**

**VERTEBRATE ANIMAL (Resume): ACCEPTABLE**

**COMMITTEE BUDGET RECOMMENDATIONS: The budget was recommended as requested.**

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NOTICE: In 2008 NIH modified its policy regarding the receipt of resubmission (formerly termed amended) applications. Detailed information can be found by accessing the following URL address: <http://grants.nih.gov/grants/policy/amendedapps.htm>