











[Back to Search Results](#)

-  [Description](#)
-  [Details](#)
-  [Sub-Projects](#)
-  [Publications](#)
-  [Patents](#)
-  [Outcomes](#)
-  [Clinical Studies](#)
-  [News and More](#)
-  [History](#)
-  [Similar Projects](#)

# Mechanisms of MERS-CoV Entry, Cross-species Transmission and Pathogenesis

Project Number	Contact PI/Project Leader	Awardee Organization
5R01AI110700-05	BARIC, RALPH S <a href="#">Other PIs</a>	UNIV OF NORTH CAROLINA CHAPEL HILL

## Description

### Abstract Text

DESCRIPTION (provided by applicant): Recently, a novel and highly virulent Middle Eastern Respiratory Syndrome Coronavirus (MERS-CoV) emerged, causing ~40% mortality rates. MERS-CoV replicates efficiently in humans, camels and **bats**, but not mouse cells demonstrating a broad yet rodent-restricted host range. Ominously, person-to-person transmission and subclinical infections endanger global populations and economies. Importantly, we have demonstrated that closely related bat coronaviruses (Bt CoV), like HKU4, uses the same bat and human receptor for entry as MERS-CoV, raising the specter of further zoonotic introductions of antigenically distinct coronaviruses into human populations. Consequently, we develop a multidisciplinary program that includes X- Ray crystallography, electron microscopy, protein biochemistry, molecular virology, reverse genetics and animal model development to address fundamental questions regulating key BtCoV HKU4 and MERS-CoV-host structure-function relationships in: i) receptor mediated binding, fusion and entry, ii) cross species transmission, and iii) in vivo pathogenesis. MERS-CoV and BtCoV HKU4 encode an envelope-anchored spike glycoprotein (S) that binds to its host receptor dipeptidyl peptidase 4 (DPP4) through its S1 subunit, initiating a cascade of host serine protease regulated conformation changes that elicit S2-mediated membrane fusion and entry. The major barrier for HKU4 mediated entry into human cells occurs at protease initiated membrane fusion, rather than at the receptor binding interface. Thus, our program identifies a checkpoint associated with bat CoV cross species transmission into other mammals, including humans. In addition to identifying key structural and biochemical interactions that regulate S and DPP4 receptor ortholog-guided binding protease regulated fusion and entry, we apply reverse genetics, structure-guided mutations, and experimental evolution to study HKU4 and MERS-CoV host adaptation and pathogenesis, using recently developed transgenic animal models. In Aim 1, we study the biochemistry and structure of MERS-CoV and HKU4 bound to various species receptor-binding domains (RBD). In Aim 2, we study S processing by bat and human entry proteases. In Aim 3, we study HKU4 and MERS-CoV pathogenesis using transgenic mice and experimental evolution. The overall goal is to build a comprehensive understanding of the molecular mechanisms guiding group 2c CoV receptor recognition, entry and pathogenesis. In parallel, we produce key deliverables that are crucial for developing effective antivirals and vaccines, thereby improving rapid response and the overall global health.

### Public Health Relevance Statement

PUBLIC HEALTH RELEVANCE: MERS-CoV is an emerging respiratory virus associated with ~40% mortality rates in humans. Virus receptor interactions and S glycoprotein-protease processing events are key regulators of entry, tissue tropism, species specificity and disease emergence. Our studies identify genetic pathways regulating CoV cross species transmission and receptor ortholog usage, resulting in robust animal models of human disease; critical reagents for therapeutic and vaccine testing.

### NIH Spending Category

Biodefense    Emerging Infectious Diseases    Genetics    Infectious Diseases

### Project Terms

Address    Animal Model    Animals    Antiviral Agents    Binding

Binding Proteins    Biochemical    Biochemistry    Biological Availability    Camels

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[◀ Back to Search Results](#)

## Mechanisms of MERS-CoV Entry, Cross-species Transmission and Pathogenesis

**Project Number**  
**5R01AI110700-05**

**Contact PI/Project Leader**  
**BARIC, RALPH S**Other PIs

**Awardee Organization**  
**UNIV OF NORTH**  
**CAROLINA CHAPEL HILL**

## Read More

 Details

### Contact PI/ Project Leader

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**UNIV OF NORTH CAROLINA  
CHAPEL HILL**

City  
CHAPEL HILL

Country  
**UNITED STATES (US)**

Department Type  
**PUBLIC HEALTH & PREV  
MEDICINE**

Organization Type  
**SCHOOLS OF PUBLIC  
HEALTH**

State Code  
**NC**

Congressional District  
**04**

## Other Information

FOA  
[PA-13-302](#)

Study Section  
**Virology - A Study Section[VIRA]**

Fiscal Year	Award Notice
2019	Date
	13-March-
	2019

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

DUNS Number CFDA Code  
**608195277 855**

Project Start Date	<b>20-April-2015</b>
Project End Date	<b>24-September-2020</b>

Budget Start Date	01-April-2019
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Budget End Date **24-September-2020**

## Project Funding Information for 2019

Total Funding  
**\$721,207**

Direct Costs  
**\$601,878**

Indirect Costs  
**\$119,329**

Year	Funding IC
2019	NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES \$721,207

## NIH Categorical Spending











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Funding IC	FY Total Cost by IC	NIH Spending Category
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[Back to Search Results](#)

-  [Description](#)
-  [Details](#)
-  [Sub-Projects](#)
-  [Publications](#)
-  [Patents](#)
-  [Outcomes](#)
-  [Clinical Studies](#)
-  [News and More](#)
-  [History](#)
-  [Similar Projects](#)

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5R01AI110700-05	BARIC, RALPH S <a href="#">Other PIs</a>	UNIV OF NORTH CAROLINA CHAPEL HILL
		Diseases;

## Sub Projects

No Sub Projects information available for 5R01AI110700-05

## Publications

No Publications available for 5R01AI110700-05

## Patents

No Patents information available for 5R01AI110700-05

## 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 5R01AI110700-05

## Clinical Studies

No Clinical Studies information available for 5R01AI110700-05

## News and More

### Related News Releases

No news release information available for 5R01AI110700-05











## History

No Historical information available for 5R01AI110700-05

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[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  
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