Mechanisms regulating fetal membrane and neutrophil responses to polymicrobial infection

Project Number	Contact PI/Project Leader	Awardee Organization
5R01AI121183-04	ABRAHAMS, VIKKI M	YALE UNIVERSITY

Description

Abstract Text

Chorioamnionitis is a major risk factor for spontaneous preterm birth and a leading contributor to poor fetal and neonatal outcomes. Chorioamnionitis, defined as inflammation of the fetal membranes (FM), is usually subclinical and diagnosed as histological chorioamnionitis (HCA) after delivery, by evidence of neutrophil infiltration. HCA and preterm birth are thought to be initiated by bacterial infection. However, no single bacterium has been attributed to preterm birth, and antibiotic intervention has proven unsuccessful. Moreover, identifiable bacteria associated with HCA and preterm birth are normally present in the female reproductive tract. Thus, another trigger may be responsible. We postulate that one possible risk factor is a viral infection. In preliminary studies we show that a herpes viral infection of human FMs augments their inflammatory response to low-dose bacterial LPS. Thus, we postulate that a viral infection during pregnancy may change the way FMs respond to bacteria normally present in the genital tract, giving rise to aggravated inflammation; and the mechanisms likely involve innate immune Toll-like receptors (TLRs) and their regulators. In preliminary studies found that FMs express functional TAM tyrosine kinase receptors, a novel family of negative regulators that inhibit TLR-driven immune responses and regulate cell survival. Thus, our central hypothesis is that a polymicrobial viral-bacterial infection of the FMs increases a woman's risk for HCA and preterm birth, and this is mediated by changes in the crosstalk between FM TLRs and TAM receptors. Our goals are to understand the mechanisms by which TLRs and TAM receptors function in FMs and neutrophils in response to a polymicrobial infection, and to characterize their role in HCA and preterm birth. We will address major gaps in our knowledge, such as the impact a viral-bacterial polymicrobial infection has on: 1) FM TLR-mediated responses; 2) FM TAM receptor function; and 3) neutrophil survival and function. Our studies will be translational by determining if TAM receptor agonists can reverse polymicrobial-induced FM inflammation and improve pregnancy outcome, and whether they can serve as biomarkers. Since viral pandemics are likely to become more common, and women are at increasing risk for sexually transmitted infections, our studies are critical for guiding the management of pregnant women under these conditions. Our outcomes have the potential of defining new mechanisms of pathology, predictors of prematurity, and therapeutic targets. We will use herpes and influenza viruses as models that may inform us about how other viruses impact pregnancy. Thus, our specific aims are to determine: 1. The role of TAM receptors and the inflammasome in regulating viral sensitization of FMs to bacteria. 2. The impact a polymicrobial FM infection has on neutrophil survival and function. 3. Whether TAM receptor agonists can predict or prevent polymicrobial infection-induced FM inflammation and preterm birth.

Public Health Relevance Statement

NARRATIVE The major objective of this proposal is to understand the role that Toll-like receptors and the novel regulatory TAM tyrosine kinase receptors play in mediating fetal membrane inflammation in response to a polymicrobial viral-bacterial infection. Our studies will advance our understanding of the mechanisms by which polymicrobial infections cause pregnancy complications, such as chorioamnionitis and preterm birth. Since viral pandemics are likely to become more common, and women are at increasing risk for sexually transmitted infections, our studies are critical for guidin the management of pregnant women under these conditions. Our outcomes have the potential of defining new mechanisms of pathology, predictors of premat

NIH Spending Category

Clinical Research Conditions Affecting the Embryonic and Fetal Periods Emerging Infectious Diseases Health Disparities Infectious Diseases Influenza Maternal Health Minority Health Pediatric Perinatal Period - Conditions Originating in Perinatal Period Pneumonia & Influenza Pregnancy Preterm, Low Birth Weight and Health of the Newborn Prevention Sexually Transmitted Infections Women's Health

Project Terms

Address Agonist Antibiotics Autophagocytosis Bacteria Bacterial Infections Bacterial Model Bacterial Pneumonia Biological Markers Cell Death Process Cell Survival Coculture Techniques Coupled Data Diagnosis Dose Escherichia coli Exposure to Family Female Fetal Membranes Goals Herpesviridae Herpesviridae Infections Histologic Human Immune Immune response In Vitro Infection Inflammasome Inflammation Inflammatory Response Influenza Influenza A Virus, H1N1 Subtype Interferons Interleukin-1 beta Intervention

Read More

Details

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Not Applicable

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NEW HAVEN

Country
UNITED STATES (US)

Department Type
OBSTETRICS & GYNECOLOGY

Organization Type
SCHOOLS OF MEDICINE

State Code
CT

Congressional District
03

Other Information

FOA
PAS-15-055

Study Section
Special Emphasis Panel[ZRG1-EMNR-B(02)M]

Fiscal Year
2019

Award Notice Date
15-May-2019

Administering Institutes or Centers
NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

DUNS Number
043207562

CFDA Code
855

Project Start Date
25-June-2016

Project End Date
31-May-2021

Budget Start Date
01-June-2019

Thank you for your feedback!

Date 2020

Project Funding Information for 2019

Total Funding	Direct Costs	Indirect Costs
$566,647	**$338,297**	**$228,350**

Year	Funding IC	
2019	NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES	$566,647

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	$226,659	Health Disparities; Minority Health;
NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES	$566,647	Clinical Research; Conditions Affecting the Embryonic and Fetal Periods; Emerging Infectious Diseases; Infectious Diseases; Influenza; Maternal Health; Pediatric; Perinatal Period - Conditions Originating in Perinatal Period; Pneumonia & Influenza; Pregnancy; Preterm, Low Birth Weight and Health of the Newborn; Prevention; Sexually Transmitted Infections; Women's Health;

Sub Projects

No Sub Projects information available for 5R01AI121183-04

Publications

Export

American journal of reproductive immunology (New York, N.Y. : 1989) 2018 06; 79 (6) e12440	Romero, Roberto; Xu. Yi: Plazvo.	2018 iCite 7.1

View All

Zika virus infection of Hofbauer cells.

Thank you for your feedback!

Journal (Link to PubMed abstract)	Authors	Publication Year	Similar Publications	CitedBy	iCite RC
American journal of reproductive immunology (New York, N.Y. : 1989) 2017 02; 77 (2)	Simoni, Michael K; Jurado, Kellie Ann; Abrahams, Vikki M; Fikrig, Erol; Guller, Seth	2017			4.2

Inflammasome assembly in the chorioamniotic membranes during spontaneous labor at term.

American journal of reproductive immunology (New York, N.Y. : 1989) 2017 05; 77 (5)	Gomez-Lopez, Nardhv: Romero.	2017			2.1

View All

Viral Infection Sensitizes Human Fetal Membranes to Bacterial Lipopolysaccharide by MERTK Inhibition and Inflammasome Activation.

Journal of immunology (Baltimore, Md. : 1950) 2017 10 15; 199 (8) 2885-2895	Cross, Sarah N; Potter, Julie A:	2017			2.2

View All

A Role for the Inflammasome in Spontaneous Labor at Term with Acute Histologic Chorioamnionitis.

Reproductive sciences (Thousand Oaks, Calif.) 2017 06; 24 (6) 934-953	Gomez-Lopez, Nardhv: Romero.	2017			2.5

View All

A Role for the Inflammasome in Spontaneous Preterm Labor With Acute Histologic Chorioamnionitis.

Reproductive sciences (Thousand Oaks, Calif.) 2017 10; 24 (10) 1382-1401	Gomez-Lopez, Nardhv: Romero.	2017			5.1

View All

Patents

No Patents information available for 5R01AI121183-04

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 5R01AI121183-04

Clinical Studies

No Clinical Studies information available for 5R01AI121183-04

News and More

Thank you for your feedback!

Related News Releases

No news release information available for 5R01AI121183-04

History

Total project funding amount for 5 projects is $2,832,954*

** Only NIH, CDC and FDA funding data*

Export

Project Number	Sub	Principal Investigator(s)/ Project Leader(s)	Organization	Fiscal Year	Admin IC
Mechanisms regulating fetal membrane and neutrophil responses to polymicrobial infection					
5R01AI121183-05		ABRAHAMS, VIKKI M	YALE UNIVERSITY	2020	NIAID NIAID $566,647
Mechanisms regulating fetal membrane and neutrophil responses to polymicrobial infection					
5R01AI121183-04		ABRAHAMS, VIKKI M	YALE UNIVERSITY	2019	NIAID NIAID $566,647
Mechanisms regulating fetal membrane and neutrophil responses to polymicrobial infection					
5R01AI121183-03		ABRAHAMS, VIKKI M	YALE UNIVERSITY	2018	NIAID NIAID $566,647
Mechanisms regulating fetal membrane and neutrophil responses to polymicrobial infection					
5R01AI121183-02		ABRAHAMS, VIKKI M	YALE UNIVERSITY	2017	NIAID NIAID $566,647
Mechanisms regulating fetal membrane and neutrophil responses to polymicrobial infection					
1R01AI121183-01A1		ABRAHAMS, VIKKI M	YALE UNIVERSITY	2016	NIAID NIAID $566,366

Similar Projects

Match Score	Project Number	Sub	Principal Investigator(s)/ Project Leader(s)	Organization	Fiscal Year		
Alcohol and Lung Immunity in the Aged							
370	5R21AA026295-02		KOVACS, ELIZABETH J.	UNIVERSITY OF COLORADO DENVER	2019	NIAAA	NIAAA
Elucidating the Mechanisms of the Neutrophilic Behavior and Hyperinflammatory Respons Influenza Infection							
439	1R15AI131202-01A1		KING, BENJAMIN L	UNIVERSITY OF MAINE ORONO	2018	NIAID	NIAID
Probing the physiological function of oxo-eicosanoid signaling by intravital imaging in a ze infection model							
314	5R21AI139986-02		NIETHAMMER, PHILIPP MICHAEL	SLOAN-KETTERING INST CAN RESEARCH	2019	NIAID	NIAID
Anaplasma regulation of host granulocyte function							
350	5R01AI044102-19		DUMLER, JOHN STEPHEN	HENRY M. JACKSON FDN FOR THE ADV MIL/MED	2019	NIAID	NIAID

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Match Score	Project Number	Sub	Principal Investigator(s)/ Project Leader(s)	Organization	Fiscal Year	Admin IC	Funding IC	F C
Early HIV Effects on Gut Immunity and Inflammation for Seeding Viral Reservoirs								
315	5R01AI123105-05		DANDEKAR, SATYA	UNIVERSITY OF CALIFORNIA AT DAVIS	2020	NIAID	NIAID	
Neutrophil IFN-gamma in host defense and inflammation								
312	5R01AI121090-05		YAROVINSKY, FELIX	UNIVERSITY OF ROCHESTER	2020	NIAID	NIAID	
Innate Immunity in Lung Infection-induced Sepsis								
412	5R01AI140500-03		JEYASEELAN, SAMITHAMBY	LOUISIANA STATE UNIV A&M COL BATON ROUGE	2020	NIAID	NIAID	

Thank you for your feedback!