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Development of synthetic viral circuitry to regulate viruses in mosquito disease vectors

Project Number	Former Number	Contact PI/Project Leader	Awardee Organization
1DP2AI152071-01	1DP2OD027599-01	AKBARI, OMAR SULTAN	UNIVERSITY OF CALIFORNIA, SAN DIEGO

Description

Abstract Text

PROJECT SUMMARY Annually, arboviruses cause morbidity and mortality unparalleled to most other infectious diseases. In fact, billions of people are at risk or arboviral infections creating a large economic burden and imposition on the health systems of many developing countries. With no available vaccine and limited drugs for most arboviral diseases, prevention is essential to disease reduction. Currently, prevention is achieved by sustained vector control; however, with the breakdown or imminent breakdown of many current vector control strategies, we need to develop novel tools to prevent arboviral infection. In this proposal, we aim to improve the technologies available for population replacement strategies, which could be a key tool for the sustainable management of vector-borne disease. While the goal of creating disease, refractory mosquitoes is not novel, we propose to take a novel approach to developing tools for these population replacement strategies. First, we use CRISPR inspired strategies to develop viral sensors that sense and degrade viral RNA. Once these systems are optimized, we will explore using these CRISPR inspired components to create synthetic viral sensors that recognize either viral protein or **virus** essential host factors and subsequently trigger a signal transduction cascade leading to the production of an antiviral effector. These studies will be performed initially in cell culture models and then transitioned into the dengue, Zika, yellow fever and chikungunya vector, Aedes aegypti. In another approach, we will take advantage of advancements in synthetic RNA switch development in prokaryotic organisms to design and test RNA switches as viral sensors. We will also use the natural architecture of viral RNA switches to develop viral RNA sensors to either outcompete natural viral switches for viral synthesis initiators thereby slowing the replication process, or to actually drive the expression of antiviral effectors. The latter effect would create a negative feedback loop that could potentially halt replication. Additionally, we propose to develop other synthetic tools for mosquitoes, which are inspired by CRISPR, RNA biology and **virus** regulatory elements. All of these technologies have great potential to improve the tools available to create robust, versatile and consistent antiviral synthetic circuitry in mosquitoes. If successful, these tools would be the first steps towards creating an adaptive immune system for this species, but many of the elements could be used to manipulate any cellular pathway or be used to build novel regulatory pathways. Moreover, for most of these technologies proof-of-principle has only been achieved in an in vitro, prokaryotic or cell culture system. Therefore, it would be a remarkable, albeit difficult, accomplishment to bring these technologies into such an important whole organism system. The potential impact on human health could be tremendous.

Public Health Relevance Statement

PROJECT NARRATIVE Genetic manipulation of mosquitoes is becoming a feasible approach to combat vector-borne disease, but the tools available for optimizing these strategies is limited. The application of new synthetic biology approaches inspired by CRISPR, RNA regulators and RNA viruses could be key to the improvement of mosquito transgenesis and population replacement strategies. However, most of these technologies are rudimentary, even in simpler systems, so we aim to adapt and optimize these technologies to create viral sensors and other synthetic elements to support the development of novel mosquito population replacement systems.

NIH Spending Category

Biodefense Bioengineering Biotechnology Emerging Infectious Diseases Genetics Infectious Diseases Prevention Rare Diseases Vector-Borne Diseases

Project Terms

Adaptive Immune System Aedes Antiviral Agents Arbovirus Infections Arboviruses Architecture Biology Cell Culture System Cell Culture Techniques Clustered Regularly Interspaced Short Palindromic Repeats Communicable Diseases Culicidae Dengue Developing Countries Development Disease Disease Vectors Economic Burden Elements Feedback Gene Transfer Techniques Goals Health Health system Human In Vitro Integration Host Factors Modeling Morbidity - disease rate Organism Pathway interactions Pharmaceutical Preparations Population Replacements Prevention Production RNA RNA Viruses Refractory Regulatory Element Regulatory Pathway Replication-Associated Process

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Former Number
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Contact PI/Project Leader
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Awardee Organization
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UNIVERSITY OF CALIFORNIA, SAN DIEGO

City
LA JOLLA

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UNITED STATES (US)

Department Type
BIOLOGY

Organization Type
SCHOOLS OF ARTS AND SCIENCES

State Code
CA

Congressional District
52

Other Information

FOA
RFA-RM-18-008

Study Section
Special Emphasis Panel[ZRG1 MOSS-R (70)]

Fiscal Year
2019

Award Notice Date
23-August-2019

Administering Institutes or Centers
NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

DUNS Number
804355790

CFDA Code
855

Project Start Date
30-September-2019

Project End Date
31-March-2024

Budget Start Date
30-September-2019

Budget End Date
31-March-2024

Project Funding Information for 2019

Total Funding
$2,367,250

Direct Costs
$1,500,000

Indirect Costs
$867,250

Year	Funding IC	FY Total Cost by IC
2019	OFFICE OF THE DIRECTOR, NATIONAL INSTITUTES OF HEALTH	$2,367,250

NIH Categorical Spending

Click here for more information on NIH Categorical Spending

Funding IC	FY Total Cost by IC	NIH Spending Category
COMMON FUND, OFFICE OF THE DIRECTOR	$2,367,250	Biodefense; Bioengineering; Biotechnology; Emerging Infectious Diseases; Genetics; Infectious Diseases; Prevention; Rare Diseases; Vector-Borne Diseases;

Sub Projects

No Sub Projects information available for 1DP2AI152071-01

Publications

Export

Journal (Link to PubMed abstract)	Authors	Publication Year	Similar Publications	CitedBy	iC
Parasitic nematode fatty acid- and retinol-binding proteins compromise host immunity by interfering with host lipid signaling pathways.					
PLoS pathogens 2021 Oct; 17 (10) e1010027	Parks, Sophia C; Nguyen, Susan; Nasrolahi, Shyon; Bhat,	2021			
View All					
A confinable home-and-rescue gene drive for population modification.					
eLife 2021 Mar 05; 10	Kandul, Nikolay P; Liu, Junru; Bennett, Jared B; Marshall, John M; Akbari, Omar S	2021		iCite 2.51	
A mosquito small RNA genomics resource reveals dynamic evolution and host responses to viruses and transposons.					

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Inherently confinable split-drive systems in Drosophila.

Nature communications 2021 03 05; 12 (1) 1480 — Terradas, Gerard; Buchman, Anna B; Bennett, Jared B; Shriner, Isaiah; Marshall, John M; Akbari, Omar S; Bier, Ethan — 2021 — iCite 4.49

Spatial control of gene expression in flies using bacterially derived binary transactivation systems.

Insect molecular biology 2021 10; 30 (5) 461-471 — Gamez, S; Vesga, L C; Mendez-Sanchez, S C; Akbari, O S — 2021

Ubiquitous and Tissue-specific RNA Targeting in Drosophila Melanogaster using CRISPR/CasRx.

Journal of visualized experiments : JoVE 2021 02 05; (168) — Sun, Ruichen; Brogan, Daniel; Buchman, Anna; Yang, Ting; Akbari, Omar S — 2021

Combating mosquito-borne diseases using genetic control technologies.

Nature communications 2021 07 19; 12 (1) 4388 — Wang, Guan-Hong; Gamez, Stephanie; Raban, Robyn R; Marshall, John M; Alphey, Luke; Li, Ming; Rasgon, Jason L; Akbari, Omar S — 2021

Patents

No Patents information available for 1DP2AI152071-01

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 1DP2AI152071-01

Clinical Studies

No Clinical Studies information available for 1DP2AI152071-01

News and More

Related News Releases

No news release information available for 1DP2AI152071-01

History

No Historical information available for 1DP2AI152071-01

Similar Projects

No Similar Projects information available for 1DP2AI152071-01