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Engineering a human brain organoid-based platform to study neurotropic viruses

Project Number
5U19AI131130-03

Contact PI/Project Leader
MING, GUO-LI Other PIs

Awardee Organization
UNIVERSITY OF PENNSYLVANIA

Description

Abstract Text

SUMMARY – Overview Modeling of **infectious** diseases that affect the human central nervous system (CNS), such as those associated with Zika virus (ZIKV) and West Nile virus (WNV), has been challenging due to the inaccessibility of the relevant cell types. Reprogramming human somatic cells, such as skin fibroblasts, into induced pluripotent stem cells (iPSCs) provides a genetically tractable and renewable source of human neural cell populations. We can differentiate these iPSCs into many of the cell types critical for the study of neurotropic viruses, but typically this is performed in monolayer cultures to allow for more control and to generate more homogeneous cell populations, but this methodology lacks the self-organizing properties and interactive dynamics among different cell populations observed during organ development. Recently, more complex structures resembling whole developing organs, named organoids, have been generated from human iPSCs via 3D culturing methods. This **emerging** new technology has the potential to significantly advance our understanding of **infectious** diseases and for future therapeutic development. The success of this approach, however, critically depends on how well organoids mimic biological structures, recapitulate human physiology and **disease** pathology, and incorporate components critical to **disease** and human host responses. We propose to develop a robust platform for organoid development to model brain development that can be adopted by single labs for basic research, and is amenable to translational studies and drug development and testing. Our Research Center is comprised of three Research Projects, a Scientific Core, and an Administrative Core led by experts in virology, stem cell biology, neural development, and bioengineering. We will focus on ZIKV and WNV, two neurotropic flaviviruses, to develop our organoid platform, which can then be used by the scientific community to investigate other **infectious** diseases that affect the nervous system. Importantly, ZIKV and WNV are thought to impact the CNS at different stages of development, with ZIKV having been recently implicated as being causal for microcephaly in some pregnant women. This affords us the opportunity to develop an organoid platform with proof-of-principle testing with viruses suspected to have cell type- and stage-specific tropism. Project 1 will focus on technology development to generate more mature organoids and the scaling up of robust assays to perform medium-throughput compound testing. Project 2 will focus on ZIKV infections in early stage organoids and Project 3 will evaluate co-culture organoid systems to model WNV infections in later stage organoids. The projects will be supported by a Scientific Core that will provide cells and on-site training to Projects 2 & 3, as well as optimization of differentiation protocols and bioinformatics analyses. Finally, the Administrative Core will provide logistical support to facilitate collaborations among investigators and to coordinate the timely release of results and resources to the scientific community.

Public Health Relevance Statement

NARRATIVE - Overview Harnessing the power of human induced pluripotent stem cells to differentiate and self-organize into 3D brain- like structures could lead a new translational platform for infectious disease modeling. This Center is designed to standardize protocols for low-cost and efficient generation of highly consistent cerebral organoids that capture key features of human brain development. Zika virus and West Nile virus, two neurotropic flaviviruses, will be the focus of the current research program to illustrate the utility of this platform for biological discovery and testing of therapeutic compounds.

Project Terms

3-Dimensional Ache Address Adherent Culture Adopted Adult

Affect Americas Animals Arthralgia Basic Science Bioinformatics

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Data Decision Making Development Diagnostic Diarrhea **Disease**

Read More

Details

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Country
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Department Type
NEUROSCIENCES

Organization Type
SCHOOLS OF MEDICINE

State Code
PA

Congressional District
03

Other Information

FOA
RFA-AI-16-022

Study Section
ZAI1-BLG-M(J2)

Fiscal Year	Award Notice Date
2019	11-April-2019

Administering Institutes or Centers
NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

DUNS Number **042250712**
CFDA Code **855**

Project Start Date **01-April-2017**
Project End Date **31-March-2022**
Budget Start Date **01-April-2019**
Budget End Date **31-March-2020**

Project Funding Information for 2019

Total Funding
$1,524,227

Direct Costs
$1,617,300

Indirect Costs
$257,654

Year	Funding IC	
2019	NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES	$1,524,227

Sub Projects

No Sub Projects information available for 5U19AI131130-03

Thank you for your feedback!

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Patents

No Patents information available for 5U19AI131130-03

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 5U19AI131130-03

Clinical Studies

No Clinical Studies information available for 5U19AI131130-03

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Related News Releases

No news release information available for 5U19AI131130-03

History

No Historical information available for 5U19AI131130-03

Similar Projects

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