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MMRRC COVID-19 variant testing in humanized mouse models

Project Number	Former Number	Contact PI/Project Leader	Awardee Organization
3U42OD012210-22S1	5U42OD012210-22	LLOYD, KC KENT	UNIVERSITY OF CALIFORNIA AT DAVIS

Description

Abstract Text

ABSTRACT & SCOPE OF WORK The Mutant Mouse Resource and Research Center at the University of California, Davis (MMRRC-UC Davis) is pleased to submit this administrative supplement for up to 1 year of support in response to ORIP's participation in PA-20-272, "Administrative Supplements to Existing NIH Grants and Cooperative Agreements" specifically related to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) disease (COVID-19). This application addresses a number of the stated objectives of the call to support COVID-19 related research, including to develop and characterize animal models for post-acute sequelae of COVID-19 (PASC) and to study the susceptibility of existing COVID-19 animal models to emerging viral genomic variants. Specifically, this application will generate polygenic humanized mouse models for virus challenge, validation, and post- acute sequellae of COVID-19 (PASC) in both young and aging mice using well-established testing and screening platforms in an ABSL3 environment. This project will build upon our successful efforts to generate monogenic humanized knockin/murine knockout mouse lines for several genes (ACE2, TMPRSS2, and FURIN) involved in SARS-CoV-2 binding, entry, and activation. With this prior experience in hand, we now propose to determine infectivity and transmission in new polygenic humanized mice to assess the extent to which they can be used as suitable models of PASC in humans. Specifically in this project we will 1) use in vitro fertilization (IVF) expansion and intercrossing of our extant monogenic models to rapidly generate polygenic humanized mouse models of hACE2/hTMPRSS2 and hACE2/hTMPRSS2/hFURIN, 2) validate the pathophysiological effects and assess PASC after challenge with currently dominant circulating (B.1.1.7; strain: USA/CA_CDC_5574/2020) in young and aging male and female cohorts of polygenic humanized mice under ABSL3 conditions, and 3) establish breeding colonies and cryopreserved germplasm of humanized mouse models for archiving and distribution to the biomedical research community. Validation studies will involve systematic characterization of viral load and clearance, body weight kinetics, and lung inflammation after SARS-CoV-2 challenge of male and female cohorts of mice; positive results will be communicated to the ACTIV-Preclinical Working Group and others at NIH. In addition, observational and pathological screening of surviving aging mice will be conducted to screen for evidence of PASC; promising findings will be communicated with members of the PASC Initiative and Investigator Consortium (OTA-21-015A and B) and other NIH staff to ensure rapid translation of findings for human studies and functional studies in animal models. Further, we will ensure that our mouse models and testing platform will be made readily available for use by other researchers to swiftly assess the in vivo consequences of not only newly appearing SARS-CoV-2 variants that escape current therapeutic and vaccine strategies but also of future viruses with similarly high- impact **pandemic potential**. This study is essential to overcome genetic discrepancies between mouse and human and to fill crucial gaps in existing small animal models of COVID-19 that hinder translation of research findings to improvements in human health, including understanding the development, treatment, and prevention of PASC, the effectiveness of antiviral therapies, and the reliability of disease-prevention vaccine strategies.

Public Health Relevance Statement

PROJECT NARRATIVE This proposal from the Mutant Mouse Resource and Research Center at UC Davis (MMRRC-UC Davis) seeks to use an established screening and testing platform in an ABSL3 environment for rapid and reliable determination of viral susceptibility, pathogenesis, and pathophysiological consequences of infection after challenge with SARS-CoV-2 variants in polygenic humanized mouse models of COVID-19 in response to NIH PA-20-272, Administrative Supplements to Existing NIH Grants and Cooperative Agreements. This project will build upon our previous successful efforts to produce, validate, and distribute monogenic humanized COVID- 19 relevant mouse models. We will conduct studies to validate the models as human surrogates for the study of SARS-CoV-2 infection (e.g., viral load and clearance, body weight kinetics, lung inflammation) and to assess their suitability as models for the evaluation of post-acute sequelae of COVID-19 (PASC) in humans. We will also establish breeding colonies of mouse models for distribution by the MMRRC and ensure that the testing platform will be available to researchers to assess the in vivo consequences of SARS-CoV-2 variants and of future viruses with similar high-impact (e.g., pandemic) potential. Promising results will be communicated with the ACTIV-Preclinical Working Group, the PASC Initiative and Investigator Consortium, and other NIH program scientists and staff.

Project Terms

2019-nCoV ACE2 Acute Address Administrative Supplement Aging Alleles Animal Model Antiviral Therapy Archives Awareness Binding Biomedical Research Body Weight Breeding C57BL/6 Mouse COVID-19 California Cells Centers for Disease Control and Prevention (U.S.) Communities Cryopreservation Deposition Development Disease Effectiveness Embryo Ensure Environment Evaluation Event FURIN gene Female Fertilization in Vitro Frequencies Future Genes Genetic Genotype Grant Hand Health Heart Human Immune response Inbred BALB C Mice Infection

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Contact PI/Project Leader
LLOYD, KC KENT

Awardee Organization
UNIVERSITY OF CALIFORNIA AT DAVIS

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UNIVERSITY OF CALIFORNIA AT DAVIS

City
DAVIS

Country
UNITED STATES (US)

Department Type
SURGERY

Organization Type
SCHOOLS OF MEDICINE

State Code
CA

Congressional District
03

Other Information

FOA
PA-20-272

Study Section

Fiscal Year
2021

Award Notice Date
01-July-2021

Administering Institutes or Centers
OFFICE OF THE DIRECTOR, NATIONAL INSTITUTES OF HEALTH

DUNS Number
047120084

CFDA Code
351

Project Start Date
01-July-2021

Project End Date
31-January-2025

Budget Start Date
01-July-2021

Budget End Date
31-January-2022

Project Funding Information for 2021

Total Funding
$498,821

Direct Costs
$358,864

Indirect Costs
$139,957

Year	Funding IC	FY Total Cost by IC
2021	OFFICE OF THE DIRECTOR, NATIONAL INSTITUTES OF HEALTH	$498,821

Sub Projects

No Sub Projects information available for 3U42OD012210-22S1

Publications

Export

Journal (Link to PubMed abstract)	Authors	Publication Year	Similar Publications	CitedBy	iC
Biallelic UBE4A loss-of-function variants cause intellectual disability and global developmental delay.					
Genetics in medicine : official journal of the American College of Medical Genetics 2021 04; 23 (4) 661-668	Melo, Uirá Souto; Bonner, Devon: Kent Llovd. Kevin C:	2021			
View All					
Hypoglycemia after Bariatric Surgery in Mice and Optimal Dosage and Efficacy of Glucose Supplementation.					
Comparative medicine 2020 04 01; 70 (2) 111-118	Hsi, Zoe Y; Stewart, Leslie A; Lloyd, K C Kent; Grimsrud, Kristin N	2020		iCite 0.83	
DNA fragmentation index (DFI) as a measure of sperm quality and fertility in mice.					
Scientific reports 2020 03 02; 10 (1) 3833	Li, Ming-Wen; Lloyd, K C Kent	2020		iCite 4.22	

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Generating mouse models for biomedical research: technological advances.

Disease models & mechanisms 2019 01 08; 12 (1) — Gurumurthy, Channabasavaiah B; Lloyd, Kevin C Kent — 2019 — iCite 4.51

Subset of Cortical Layer 6b Neurons Selectively Innervates Higher Order Thalamic Nuclei in Mice.

Cerebral cortex (New York, N.Y. : 1991) 2018 05 01; 28 (5) 1882-1897 — Hoerder-Suabedissen, Anna; Havashi. Shuichi: Upton. — 2018 — iCite 4.27

View All

Secretagogin protects Pdx1 from proteasomal degradation to control a transcriptional program required for β cell specification.

Molecular metabolism 2018 08; 14 108-120 — Malenczyk, Katarzyna; Szodorai, Edit; Schnell, Robert; Lubec, Gert; Szabó, Gábor; Hökfelt, Tomas; Harkany, Tibor — 2018 — iCite 0.69

Itch suppression in mice and dogs by modulation of spinal α2 and α3GABAA receptors

Patents

No Patents information available for 3U42OD012210-22S1

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 3U42OD012210-22S1

Clinical Studies

No Clinical Studies information available for 3U42OD012210-22S1

News and More

Related News Releases

No news release information available for 3U42OD012210-22S1

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No Historical information available for 3U42OD012210-22S1

Similar Projects

No Similar Projects information available for 3U42OD012210-22S1

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