

Facilitating Global Connections through the Microphysiological Systems for COVID Research (MPSCoRe) Working Group

Amber Daniel, MTox

Inotiv, contractor supporting the National Toxicology Program
Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM)

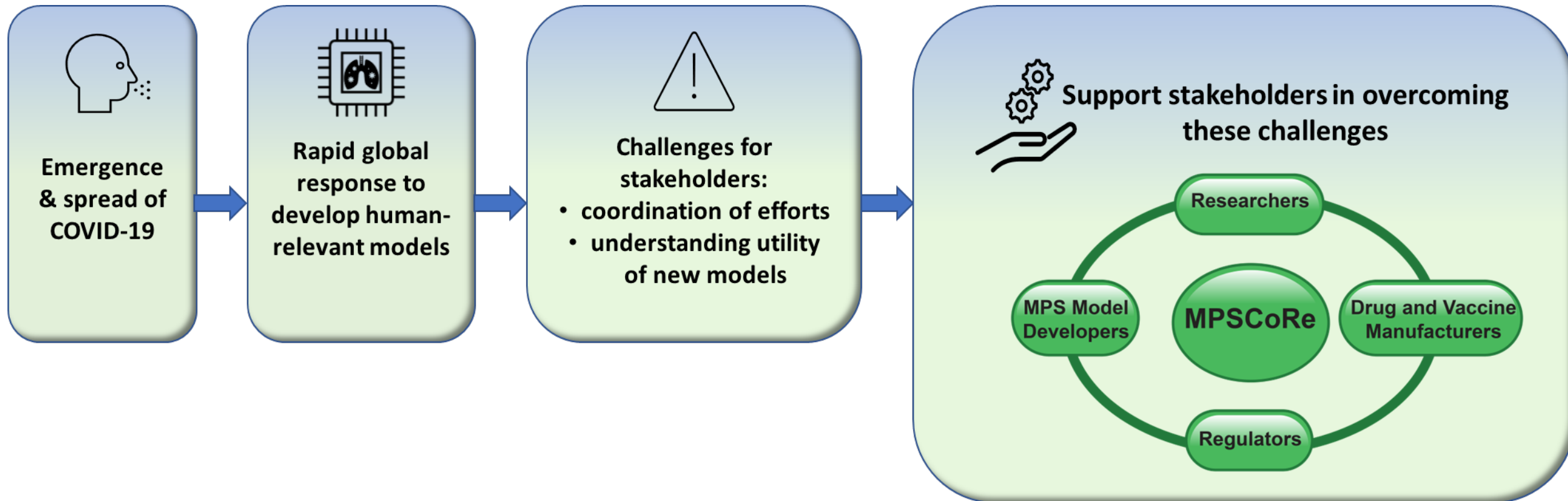
ASCCT Webinar
January 19, 2023

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Outline

- Background
- Objectives
- Activity highlights
- Future directions
- Impact

Background



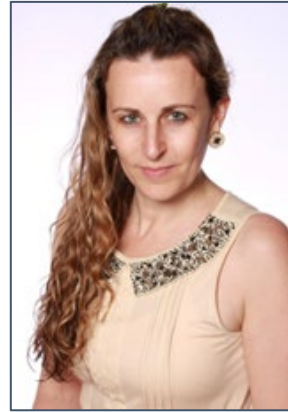
Founders/Leadership

MPSCoRe Co-Chairs



Anthony Holmes, Ph.D.

NC3Rs



Nicole Kleinstreuer, Ph.D.

NIH/NIEHS/DTT/PTB/NICEATM

Board Members

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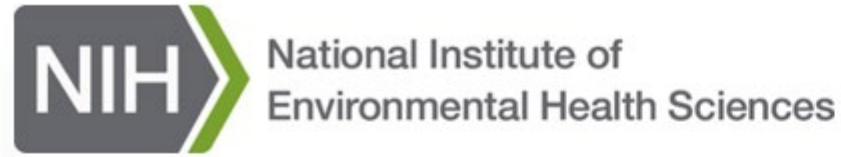
NIH/NCATS

Mark Williams, Ph.D.

NIH/NIAID/DMID/OBRTR

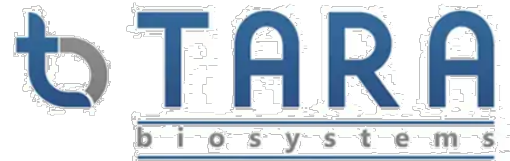
Current Membership:

Regulators,
Government Agencies
& Contractors



Disclaimer: Participation by individual scientists does not represent the official viewpoint of any government agency.

Current Membership:
Biotechnology



Current Membership:
Pharmaceuticals




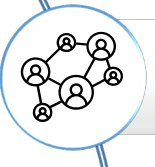


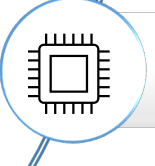

Current Membership:
Academics
& MPS Networks



Current Membership:
Academics
& MPS Networks



MPSCoRe Objectives

-  Provide a neutral forum to facilitate **engagement** among international research efforts
-  Facilitate **connections** between MPS technology developers and potential end users
-  Work with global regulatory authorities to improve understanding of **regulatory needs and decision contexts**
-  Provide **cross-discipline and -sector expertise** in characterizing criteria for model performance and readiness
-  Support the **assessment of novel MPS models** against concurrently generated preclinical and clinical data
-  Ensure that the **animal reduction and replacement opportunities** these model platforms offer are recognized

Identifying Scientific and Practical Challenges Affecting the Use of MPS for COVID Research and Drug Development

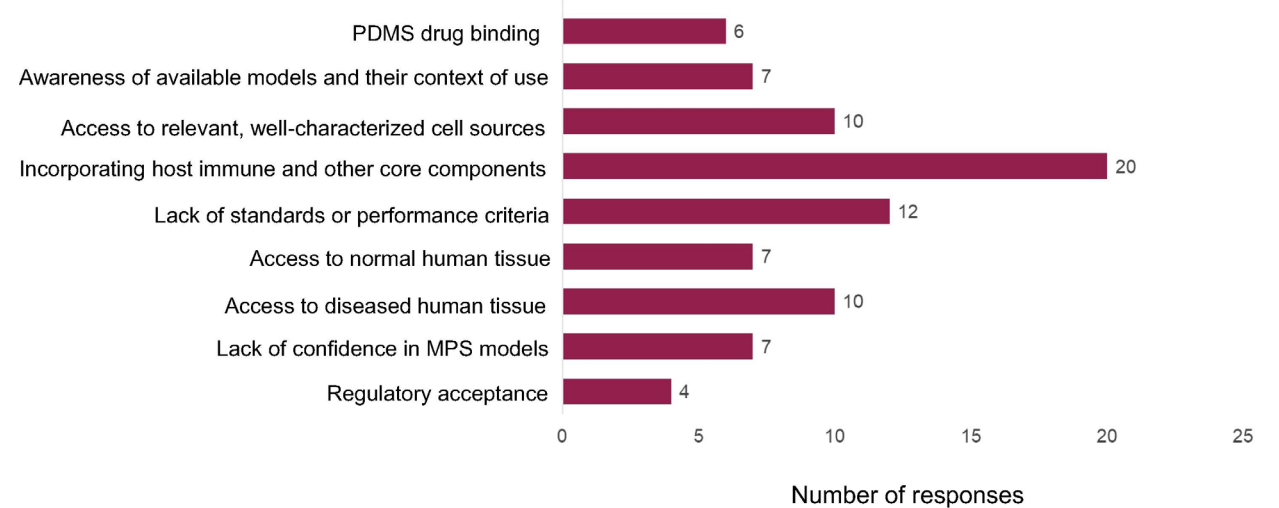
Drug Discovery Today • Volume 26, Number 11 • November 2021

Feature

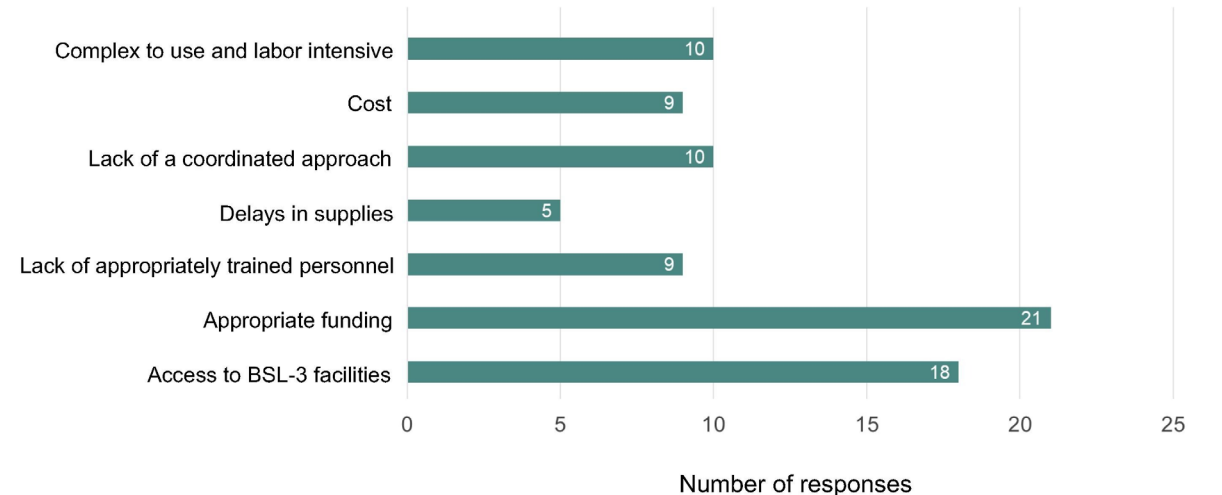
Harnessing the power of microphysiological systems for COVID-19 research

Nicole Kleinstreuer^a, Anthony Holmes^{b,*}

(a)



(b)

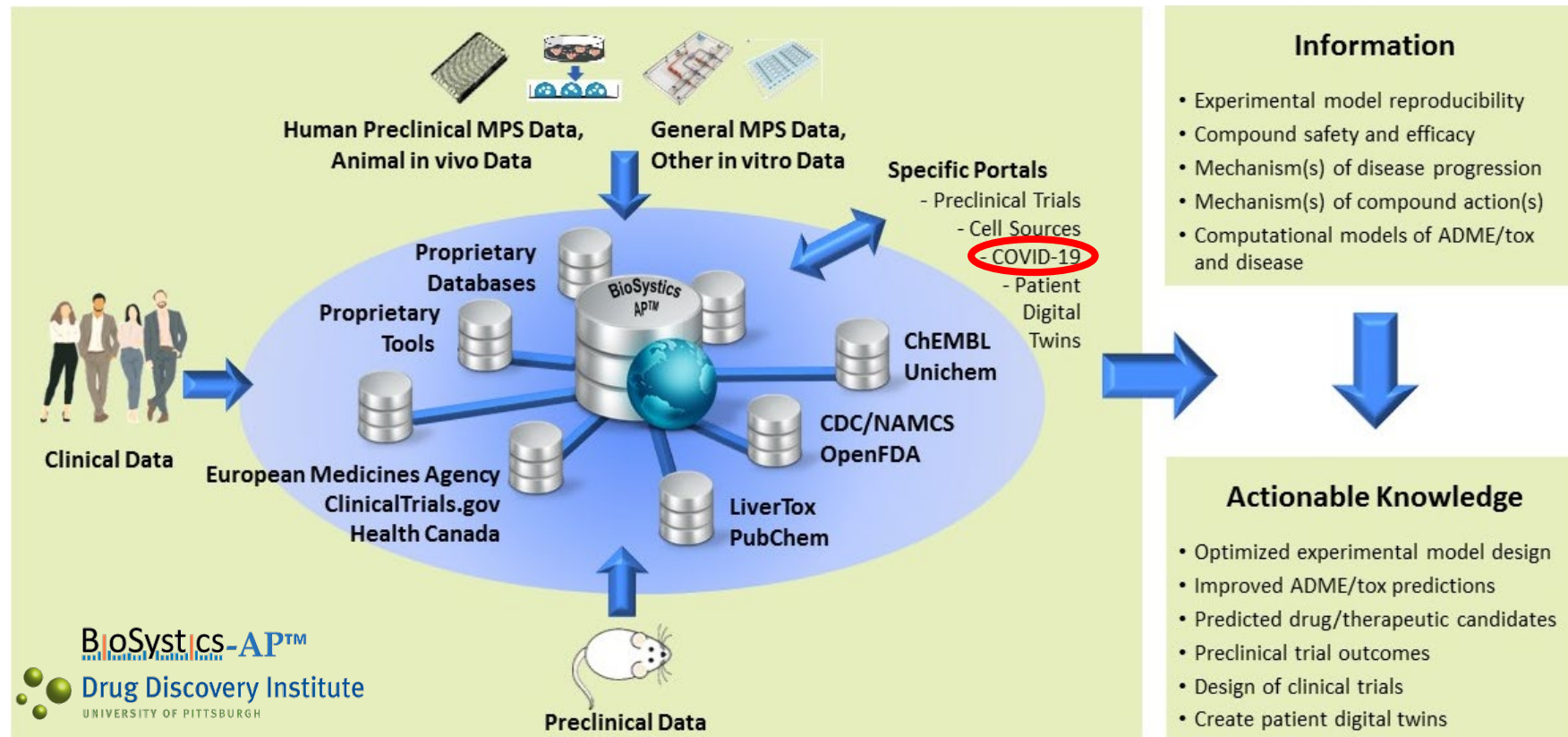


BioSystics Analytics Platform™ COVID-19 Portal



Facilitate connections between MPS technology developers and potential end users

Provide cross-discipline and -sector expertise in characterizing criteria for model performance and readiness



BioSystics Analytics Platform™ COVID-19 Portal

BioSystics Studies - Analysis - Models - Compounds - **Diseases -** Cells - About - Help Feedback Log In/Register

Home

COVID-19 Portal
View Other Diseases

Hide Notifications

The Microphysiology Systems Database (MPS-Db) is now the BioSystics Analytics Platform™!

BioSystics, Inc. was formed by the Univ. of Pittsburgh Drug Discovery Institute to transform the MPS-Db into a self-sustaining resource. The BioSystics Analytics Platform™ includes all the same features you are familiar with, and exciting new features are in development.

Global Search Global Search

BioSystics BioSystics Analytics Platform™
Academic Version
Formerly the Microphysiology Systems Database (MPS-Db)

Study Components & Reference Data

- Models & Devices
- Compounds
- Cell Samples

Review, Analysis & Modeling

- Studies
- Data Analysis
- Computational Modeling

Accelerating the Path to Patient Digital Twins

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Funded by the National Center for Advancing Translational Sciences (NCATS) Tissue Chips and Tissue Chip Testing Centers programs, and in part by the Vanderbilt-Pittsburgh Resource for Organotypic Models for Predictive Toxicology (VPROMPT).

Take a Survey

Cookie Preferences

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Home / Diseases / Coronavirus COVID-19

Coronavirus COVID-19 General Information

General Information Disease Biology Experimental Models Components Disease Data and Analysis MPS Data and Analysis

Show/Hide Page Description

This page provides links to COVID-19 disease information from Government and literature sources. Government sources includes links to disease statistics, strategic responses and funding information. Literature sources links to COVID-19 literature hubs and other scientific literature sites pre-queried for COVID-19.

Government Sources Literature Sources News

Search:

Name	Supplier	Description
NICEATM MPSCoRe	National Toxicology Program	Supporting adoption of MPS for COVID research, NICEATM and collaborators are organizing the MPS for COVID Research (MPSCoRe) working group, that will coordinate the use of MPS to reduce animal use in studies of COVID-19 and future emerging infections diseases. Information about activities of the MPSCoRe working group will be posted on this webpage.
CDC COVID Data Tracker	Centers for Disease Control and Prevention (CDC)	Dashboard of COVID-19 cases and deaths in the United States.
CDC COVID-19	Centers for Disease Control and Prevention (CDC)	Information on COVID-19 in the United States, including general information and links additional information sources.
CDC, FEMA Coronavirus Website	Centers for Disease Control and Prevention (CDC) and Federal Emergency Management Agency (FEMA)	Compilation of links to other CDC websites.
Government of Canada	Government of Canada	Information on COVID-19 in Canada, including the number of tests performed, total cases, active cases, recovered, and deaths, and links to information regarding the current situation, vaccines, travel, and economic support.
NCBI SARS-CoV-2 Resources	National Center for Biotechnology Information (NCBI), NIH	Collection of SARS-CoV-2 resources, including links to sequence related resources, literature, and clinical resources.
NIH COVID-19 Research	National Institute of Health (NIH)	Information and links relating to COVID-19 (news, NIH strategic response, funding, testing, treatment and vaccines).
NIH Health Information	National Institute of Health (NIH)	Searchable section (Health Information) of the NIH website providing information on health and research.

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Government Sources Literature Sources News

Search:

Name	Supplier	Description
bioRxiv	Cold Spring Harbor Laboratory	Searchable, preprint server for biology.
Cell Press Coronavirus Resource Hub	Cell Press	Hub of the latest content about the coronavirus outbreak in Cell Press journals.
ChemRxiv	ChemRxiv	Searchable preprint server for chemistry related manuscripts.
COVID-19 Portfolio	Office of Portfolio Analysis, NIH	The iSearch COVID-19 portfolio is NIH's comprehensive, expert-curated source for publications and preprints related to either COVID-19 or the novel coronavirus SARS-CoV-2. Updated daily and includes articles from PubMed and preprints from arXiv, bioRxiv, ChemRxiv, medRxiv, Preprints.org, Research Square, SSRN, and Qeios.
Frontiers Coronavirus Knowledge Hub	Frontiers	Hub providing links to information related to SARS-CoV-2 and COVID-19, including the latest research articles, information, funding resources, and commentary.
MedlinePlus	MedlinePlus, NLM, NCBI, NIH	Searchable source of health and wellness information (drugs, genetics, medical tests).
medRxiv	Cold Spring Harbor Laboratory	Searchable preprint server for health sciences.
NCATS OpenData	National Center for Advancing	Searchable list of publications related to SARS-CoV-2 assay screening

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Coronavirus COVID-19 Disease Biology

General Information **Disease Biology** Experimental Models Components Disease Data and Analysis MPS Data and Analysis

Show/Hide Page Description

This page provides links to disease databases, omics databases, and pathway databases providing convenient access to information on SARS-CoV-2 and COVID-19 biology. Links are pre-queried and bring the user directly to the SARS-CoV-2/COVID-19 part of the databases.

Disease Databases **Genomic Databases** Pathway Databases

Search:

Name	Supplier	Description
Disease Ontology	Institute of Genome Sciences, University of Maryland School of Medicine	Searchable database of human disease ontology for clinical research and medicine.
Diseases Database	Medical Object Oriented Software Enterprises Ltd	Cross-referenced index of human disease, medications, symptoms, signs, abnormal investigation findings etc.
KEGG DISEASE: COVID-19	Kyoto Encyclopedia of Genes and Genomes (KEGG), Kanehisa Laboratories	Searchable collection of disease entries focusing only on the perturbants.
MalaCards	Weizmann Institute of Science	Searchable, integrated database of human maladies and their annotations including disease names, synonyms, drugs/therapeutics/treatments, clinical features, genetic tests, and anatomical context.
NCBI SARS-CoV-2 Resources	National Center for Biotechnology Information (NCBI), NIH	Collection of SARS-CoV-2 resources, including links to sequence related resources, literature, and clinical resources.

Showing 1 to 5 of 5 entries

[Suggest Additional Sources](#)

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Coronavirus COVID-19 Experimental Models

General Information Disease Biology **Experimental Models** Components Disease Data and Analysis MPS Data and Analysis

Show/Hide Page Description

This page provides links to in vitro and in vivo experimental models used in SARS-CoV-2 and COVID-19 research in the field, as well as links to experimental models and protocols in the MPS-Db, and links to vendors running SARS-CoV-2/COVID-19 models as a service.

Commercial Models Research Models MPS-Db Models **Biocontainment**

Search:

Name	Facility Type	Supplier	Description
Boston University	BSL4/3	National Institute of Allergy and Infectious Diseases (NIAID), NIH	Information about the biocontainment laboratory at Boston University.
Colorado State University	BSL3	National Institute of Allergy and Infectious Diseases (NIAID), NIH	Information about the biocontainment laboratory at Colorado State University.
Duke University	BSL3	National Institute of Allergy and Infectious Diseases (NIAID), NIH	Information about the biocontainment laboratory at Duke University.
George Mason University	BSL3	National Institute of Allergy and Infectious Diseases (NIAID), NIH	Information about the biocontainment laboratory at George Mason University.
NIAID Biocontainment Research Facilities		National Institute of Allergy and Infectious Diseases (NIAID), NIH	Information and links relating to the National Biocontainment Laboratories (NBLs) and Regional Biocontainment Laboratories (RBLs) provide BSL4/3/2 and BSL3/2 biocontainment facilities, respectively, for research on biodefense and emerging infectious disease agents.
Rutgers University	BSL3	National Institute of Allergy and Infectious Diseases	Information about the biocontainment laboratory at Rutgers University.

BioSystics Analytics Platform™ COVID-19 Portal

The screenshot displays the BioSystics Analytics Platform COVID-19 Portal. The main navigation bar includes links for Studies, Analysis, Models, Compounds, Diseases, Cells, About, Help, Feedback, and Log In/Register. The central heading is 'Coronavirus COVID-19 Components', with sub-tabs for General Information, Disease Biology, Experimental Models, Components (selected), Disease Data and Analysis, and MPS Data and Analysis. A 'Show/Hide Page Description' button is present, followed by a descriptive paragraph. Below this is a secondary navigation bar with tabs for Antibodies, Assays, Cells, Compounds, Devices, iPSCs (selected), Plasmids, Proteins, Pseudoviruses/Viruses, and Reagents. Under the iPSCs tab, there are radio buttons to 'Select to Display' IPSC Cell Lines and Derived, IPSC Cell Line, or IPSC Derived. A search bar and pagination controls are also visible. The main content area shows a table of 16 entries, with the first three rows displayed.

View	Edit	ID #	Name	iPSC Primary Cell Type	Cell Type	Cell Origin	Supplier	Potential Differentiated Cell Types	Certificate of Analysis	Differentiation Protocol
View	Edit	294	UCSD112i-2-11	fibroblast (Human Skin)	iPSC Line (Human Skin)	primary-cryopreserved	WiCell	otic prosensory		
View	Edit	293	SK8-A	fibroblast (Human Skin)	iPSC Line (Human Skin)	primary-cryopreserved	Harvard Stem Cell Institute	Schwann cell precursors, otic prosensory		
View	Edit	292	iPS 15	fibroblast (Human Skin)	iPSC Line (Human Skin)	primary-cryopreserved	Radboudumc Stem Cell Technology Center (SCTC)	Podocytes, proximal tubule epithelial		

Characteristics of the iPSCs

- Differentiated cell type(s)
- Differentiated phenotypes
- Differentiated maturity level
- Functional profiles

Patient profile

- Demographic
- Known disease conditions
- Genomic abnormalities

Source of cells

- Vendor
- Collaborator
- Others

Protocols

- Isolation of patient cells (e.g., skin, blood, other cells)
- Differentiation to target cell type
- Preparation for model

Established applications

- Healthy tissue/organ model(s)
- Disease tissue/organ model(s)

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Coronavirus COVID-19 Disease Data and Analysis

General Information Disease Biology Experimental Models Components **Disease Data and Analysis** MPS Data and Analysis

Show/Hide Page Description

This page provides links to SARS-CoV-2/COVID-19 in vitro and in vivo experimental data, and clinical data in external databases. Links to external computational modeling resources focused on SARS-CoV-2/COVID-19 are also provided here.

Preclinical Data Clinical Data **Computational Modeling**

Search:

Name	Supplier	Description
COVID-19 HPC Consortium	COVID-19 High Performance Computing (HPC) Consortium	Links to the HPC consortium high-performance computing resources in support of COVID-19 research.
MIDAS	MIDAS Coordination Center, University of Pittsburgh	Portal for COVID-19 modeling research.
Molecular Structure and Therapeutics COVID-19 Hub	The Molecular Sciences Software Institute (MolSSI) and Centre of Excellence for Computational Biomolecular Research (BioExcel)	Community-driven data repository and curation service for molecular structures, models, therapeutics, and simulations related to computational research related to therapeutic opportunities for COVID-19.
Wolfram COVID-19 Data & Resources	Wolfram	Information on COVID-19, including links to curated computable data, computational essays, and livestreams on a variety of topics related to COVID-19.

Showing 1 to 4 of 4 entries

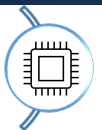
[Suggest Additional Sources](#)

BioSystics Analytics Platform™ COVID-19 Portal

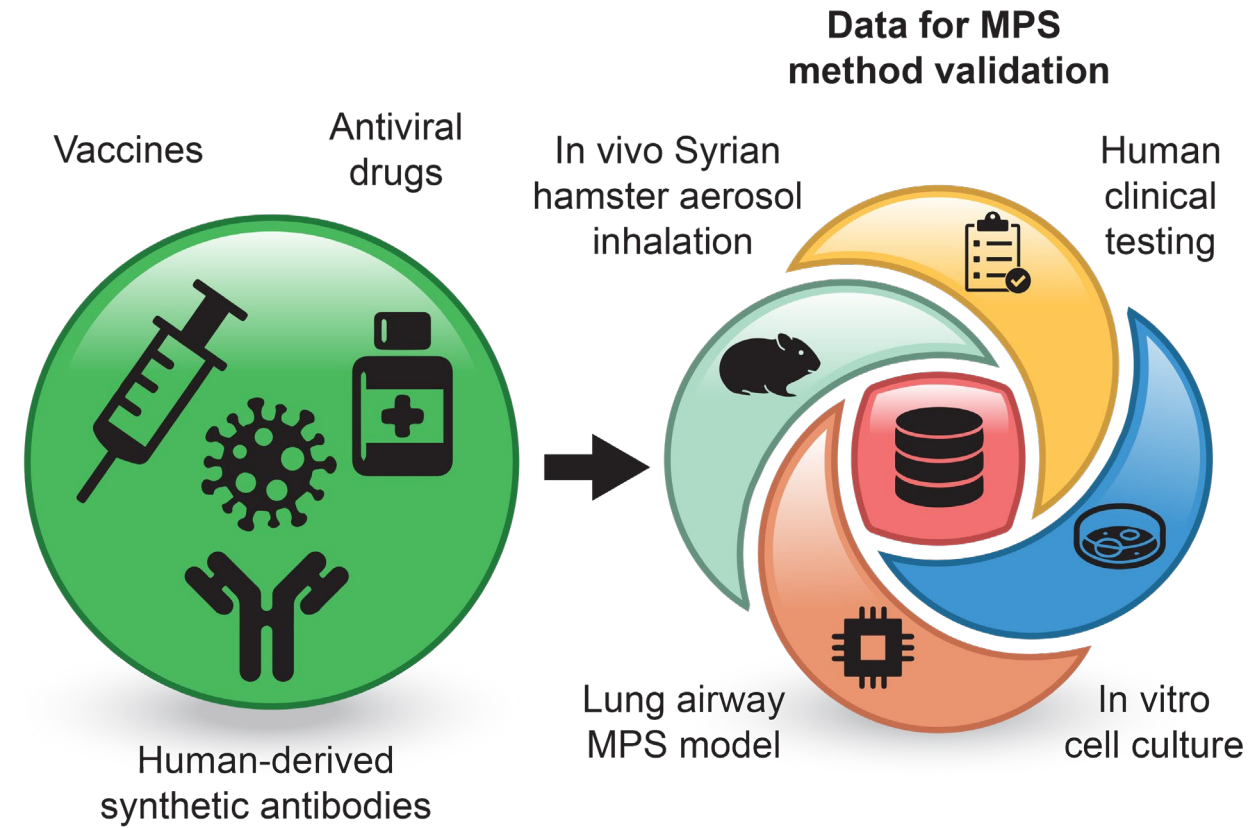
MPSCoRe members may access a **private** list of other member profiles, and share their own information about:

- Organization
- Areas of expertise
- Platforms in use (or of interest)
- Species and tissue types in use (or of interest)
- Applications for the model
- Focus of SARS-CoV-2 and COVID-19 research
- Availability of biosafety levels 3 and 4 facilities

Proof-of-Concept Study



Support the assessment of novel MPS models against concurrently generated preclinical and clinical data



Other Activities

- Regular virtual workshops and webinars
- Engagement with WHO to facilitate rapid response to research capabilities for COVID-19 variants of concern



Provide a neutral forum to facilitate engagement among international research efforts



Facilitate connections between MPS technology developers and potential end users

Future Directions

- Possible expansion of working group scope to include other emerging infectious diseases
- Efforts to advance regulatory acceptance of MPS approaches

Proposed Symposium/Workshop



Work with global regulatory authorities to improve understanding of regulatory needs and decision contexts

Symposium/Workshop

- May 2023
- Virtual event
- Raise awareness of opportunities
- Facilitate discussion/collaboration among international regulators
- Feature presentations on MPS models for infectious disease research
 - Potential for regulatory applications
 - Current regulatory approaches
 - Food and Drug Administration [Innovative Science and Technology Approaches for New Drugs \(ISTAND\) Pilot Program](#)
 - European Medicines Agency [Innovation Task Force](#)

Food for Thought ...

COVID-19 – Prime Time for Microphysiological Systems, as Illustrated for the Brain

Ian Kang¹, Lena Smirnova¹, Jens H. Kuhn², Helena T. Hogberg¹, Nicole C. Kleinstreuer³ and Thomas Hartung^{1,4}

¹Center for Alternatives to Animal Testing (CAAT), Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA; ²Integrated Research Facility at Fort Detrick (IRF-Frederick), National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH), Fort Detrick, Frederick, MD, USA; ³National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM), National Institute of Environmental Health Sciences (NIEHS), National Institutes of Health, RTP, NC, USA; ⁴CAAT-Europe, University of Konstanz, Konstanz, Germany

Impact

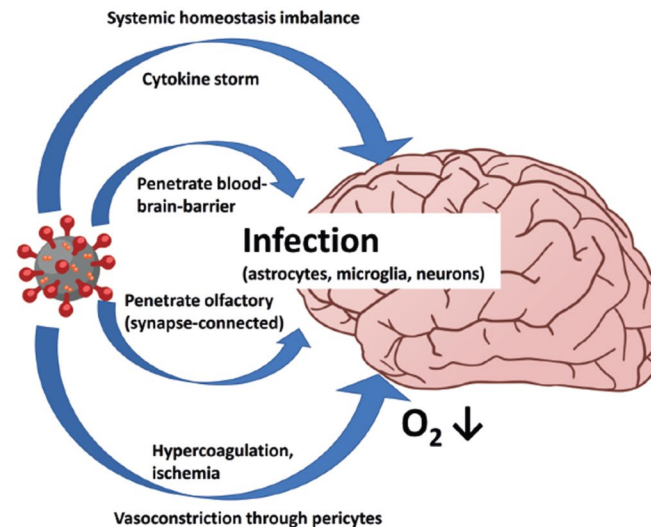
Tab. 2: Symptoms of COVID-19 patients associated with central nervous system (CNS)

	Chou et al., 2021 (n = 3,055)	Sheraton et al., 2020 (n = 3,308)	Rogers et al., 2021 (n = 99,905)	Vitalakumar et al., 2021 (n = 190,785)	Bodnar et al., 2021 (n = div.)
Acute encephalopathy (psychosis, confusion, memory loss, trouble focusing, behavioral changes, fatigue and 'brain fog')	49%	7%		23% encephalopathy; 34% fatigue; 14% confusion	7-32% encephalopathy; 8-30% dizziness; 1-4% confusion
Loss of consciousness, coma	17%	5%			4-9%
Seizures	1%			4%	< 1%
Syncope	5%				
Headaches	37%	20%	21%	15%	7-70%
Loss of taste and smell	26%	51 / 59%	37 / 43%	27 / 26%	5-70%
Stroke	6%				1.4-5%
Paralysis, Guillain-Barré syndrome	3%			7%	
Meningitis or encephalitis	0.5%			0.6%	
Myelopathy	< 2%				
Aphasia (loss of ability to understand or express speech)	5%				
New movement abnormalities	3%				
Abnormal tone, weakness	4%		41%		
Abnormal brainstem reflexes	8%				
Vomiting, nausea			7-11%		
Sensory abnormalities	2%				
Sleep disorder					
Depression			23%		
Anxiety			16%		
Altered mental status			8%		

Bodnar et al. (2021) report on studies with very diverse group sizes indicated as "n"

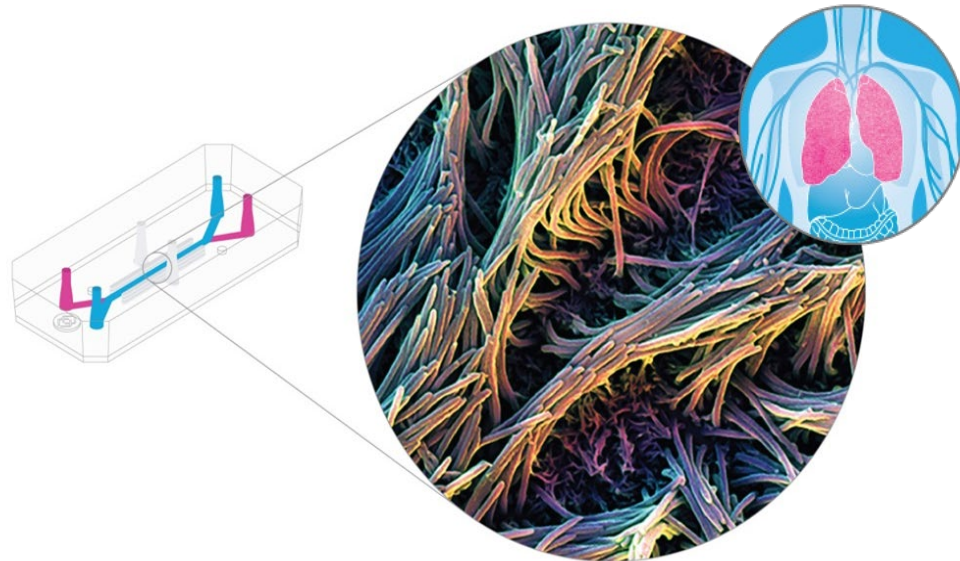
Tab. 1: Original research on SARS-CoV-2 neurotropism using human brain organoids

Date of publication	Article	Main findings (novel findings bold)
Accepted and published online 26 June 2020	Bullen et al., 2020	– ACE2 receptor in all stages of brain organoid development – Infection of a small percentage of brain cells – 500-fold replication within 72 h and virus shedding
Accepted: 24 July 2020; published online 4 August 2020	Zhang et al., 2020	– ACE2, TMPRSS2, cathepsin L, and furin were readily detected in human neural progenitor cells; virus replication and cell death – Brain organoid infection colocalized with neuronal marker TUJ1 and NPC marker NESTIN; replication and shedding
Accepted 31 August 2021; published online 23 September 2021	Ramani et al., 2020	– Virus targets neurons – Altered distribution of tau, hyperphosphorylation and neuronal cell death
Accepted 7 September 2020; published online 8 September 2020	Yi et al., 2020	– Spike-containing SARS-CoV-2 pseudovirus transduced neural layers within brain organoids (10% of neurons) – ACE2 expression was sustained during the development of brain organoids
Accepted 16 September; published online 21 September, 2020	Jacob et al., 2020	– Neurons and astrocytes were sparsely infected, but choroid plexus epithelial cells underwent robust infection
Accepted 7 October 2020;	Pellegrini et al., 2020	– ACE2 expression in mature choroid plexus cells – Tropism of virus for choroid plexus epithelial cells but little to no infection of neurons or glia
	Bong et al., 2021a	– Infection with accompanying metabolic changes in infected and neighboring neurons – No type I interferon response – Blocked with ACE2-antibodies or cerebrospinal fluid from a COVID-19 patient
	Pedrosa et al., 2021	– Non-permissive infection of brainspheres reflecting cortical brain-like tissue – SARS-CoV-2 infection of neural cells triggers an increased pro-inflammatory cytokine response
	Wang, C. et al., 2021	– Low-grade infection of neurons and astrocytes that is boosted in neuron-astrocyte co-cultures and organoids – Increased infection of isogenic ApoE3/3 and ApoE4/4 hiPSCs – Remdesivir treatment inhibits infection
	Tiwari et al., 2021	– Astrocytes, and neurons express low levels of ACE2 and TMPRSS2 and correspondingly are not highly permissive to infection
	McMahon et al., 2021	– Glial cells and cells of the choroid plexus were preferentially targeted in cortical organoids – ACE2 expression in infected cells – No viral replication and cell death involving DNA fragmentation
	Wang, L. et al., 2021	– pericyte-like cells (PLCs) integrated into a cortical organoid enhance infection – virus spreading to astrocytes and mediating inflammatory type I interferon responses



- Altered neurochemical landscape
- Pathological remodeling of neuronal networks
- Demyelination
- Postinfectious immune mediated processes, e.g., autoantibodies against neurons
- Mood changes, psychosis
- Chronic fatigue syndrome
- Neuromuscular dysfunction
- Accelerated brain aging and neurodegeneration
- Disturbed neurodevelopment

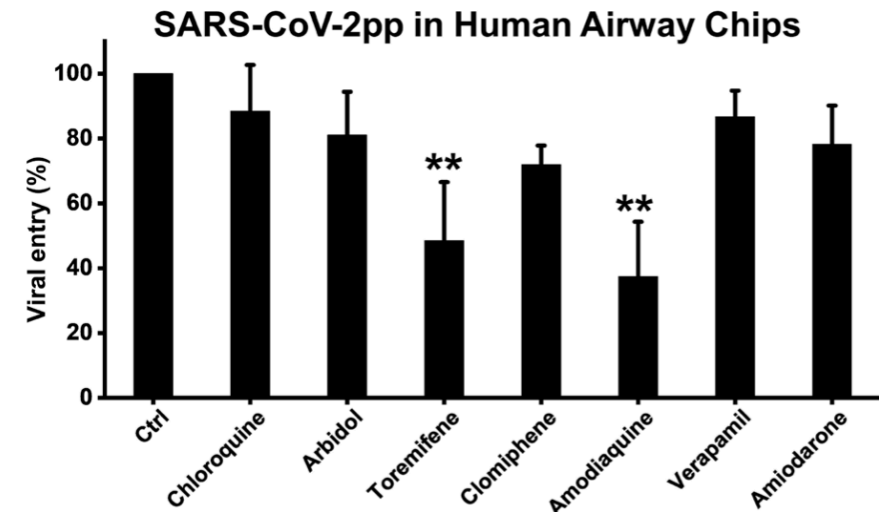
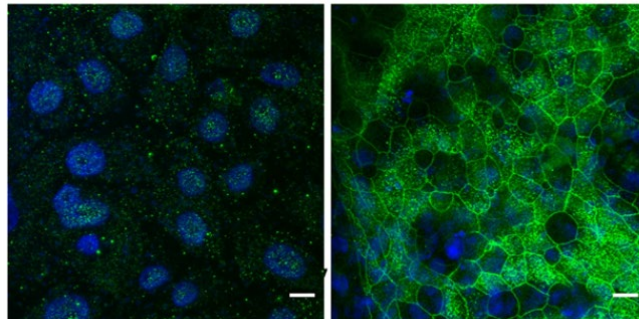
Impact



- Extracellular matrix and cell interactions
- Cell shape and cyto-architecture
- Tissue-tissue interactions
- Mechanical forces
- Dynamic flow system
- Resident or circulating immune cells can be included

Undifferentiated Differentiated

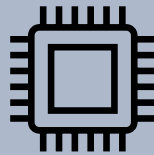
**Angiotensin Converting
Enzyme Receptor 2 (ACE-2)
Expression**



Summary

MPS are human-relevant in vitro platforms to study infectious diseases and develop therapeutics.

- Engagement
- Connections
- Regulatory needs and decision contexts
- Cross-discipline and -sector expertise
- Assessment of novel MPS models
- Ensure animal reduction/replacement opportunities are recognized



Accelerate development and adoption of MPS in infectious disease research



Improve human health



Reduce reliance on animal models

Acknowledgments

MPSCoRe Board

Anthony Holmes (co-chair)	NC3Rs
Nicole Kleinstreuer (co-chair)	NIEHS/NICEATM
Danilo Tagle	NCATS
Candace Kerr	NIAID/DMID
Mark Williams	NIAID/DMID
Kyle Glover	DoD/US Army Devcom CBC
Tyler Goralski	DoD/US Army Devcom CBC

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Cathy Sprankle	Inotiv-NICEATM support staff

BioSystics-AP™

Bert Gough	University of Pittsburgh
Mark Schurdak	University of Pittsburgh

Proof-of-Concept Study

Gabriella Worwa	NIAID/IRF
Jens Kuhn	NIAID/IRF



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