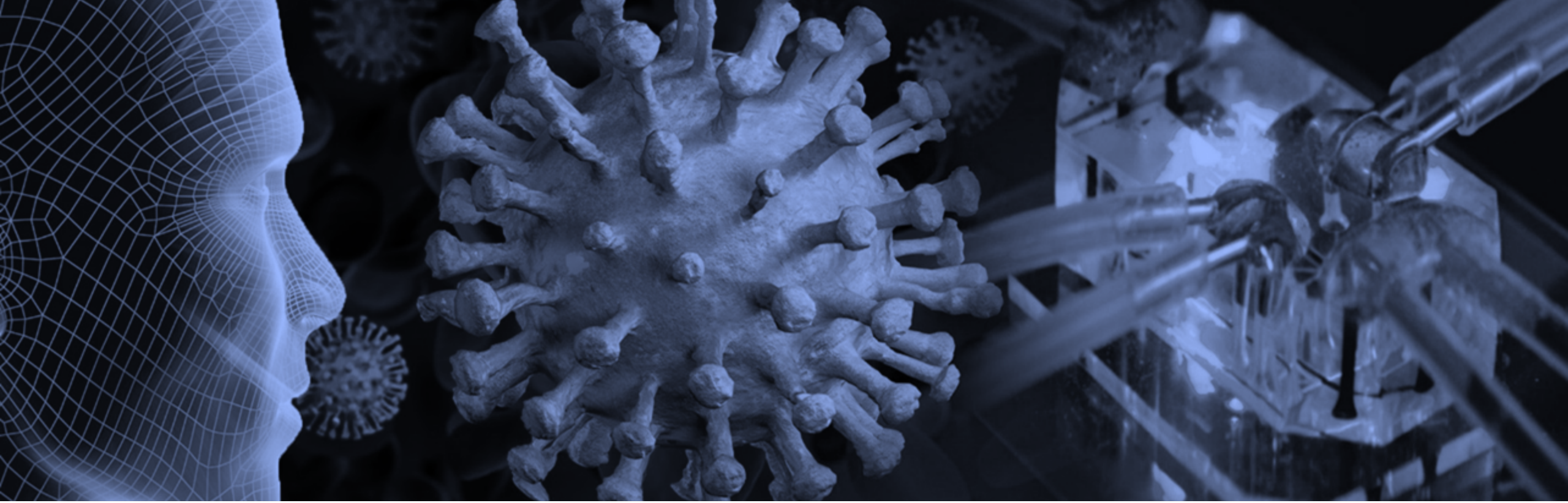


Facilitating Global Connections through the Microphysiological Systems for COVID Research (MPSCoRe) Working Group

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

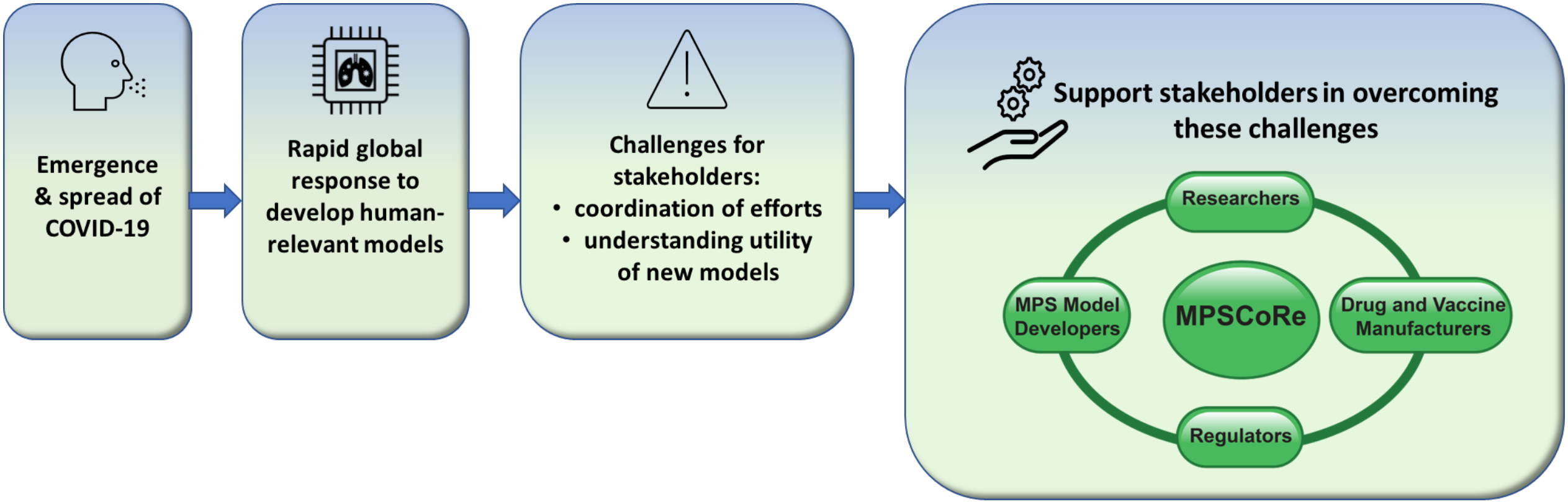
ASCCT Webinar
January 19, 2023

Disclaimer: This project was funded with federal funds from NIEHS, NIH under Contract No. HHSN273201500010C. Any mention of government agencies or use of logos is solely associated with individual scientist participation and expressions of interest and does not represent the official position or involvement of any agency, nor endorsement of any specific activity, platform, or product.

Outline

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

Background


Emergence & spread of COVID-19
Rapid global response to develop human-relevant models
Challenges for stakeholders:
• coordination of efforts
• understanding utility of new models
Support stakeholders in overcoming these challenges
Researchers
MPS Model Developers
MPSCoRe
Drug and Vaccine Manufacturers
Regulators

Founders/Leadership

MPSCoRe Co-Chairs

Anthony Holmes, Ph.D.
NC3Rs

Nicole Kleinstreuer, Ph.D.
NIH/NIEHS/DTT/PTB/NICEATM

Board Members

Kyle Glover, Ph.D.
U.S. Army DEVCOM CBC

Tyler Goralski, Ph.D.
U.S. Army DEVCOM CBC

Candace Kerr, Ph.D.
NIH/NIAID/DMID/OBRRTR

Danilo Tagle, Ph.D.
NIH/NCATS

Mark Williams, Ph.D.
NIH/NIAID/DMID/OBRRTR

NC 3Rs National Centre for the Replacement Refinement & Reduction of Animals in Research

NIH National Institute of Environmental Health Sciences

NIH National Center for Advancing Translational Sciences

NIH National Institute of Allergy and Infectious Diseases

DEVCOM CHEMICAL BIOLOGICAL CENTER

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

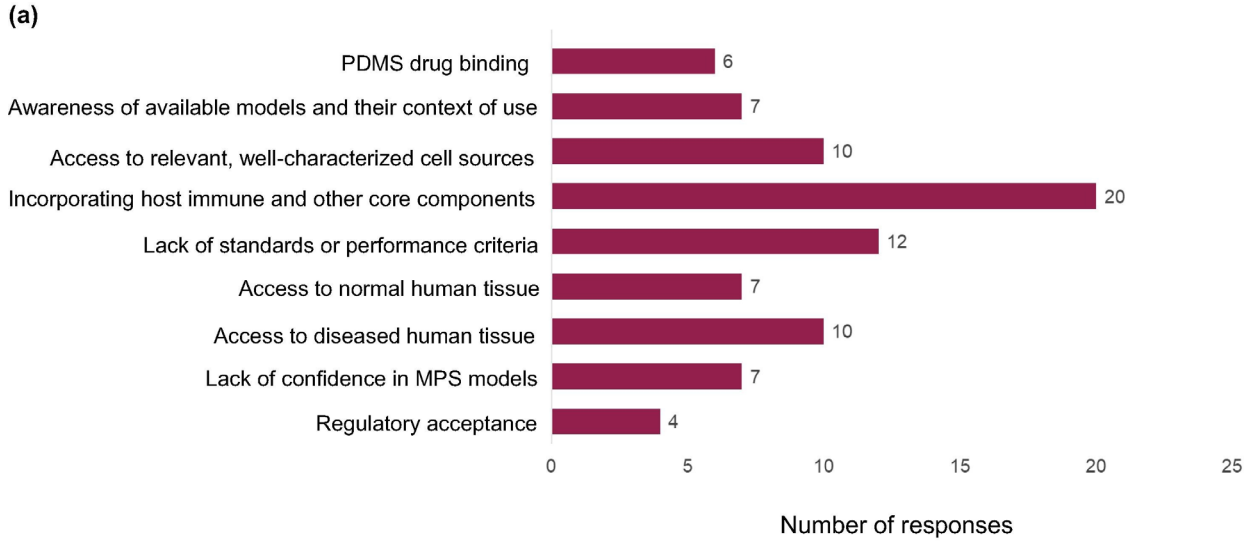
Identifying Scientific and Practical Challenges Affecting the Use of MPS for COVID Research and Drug Development

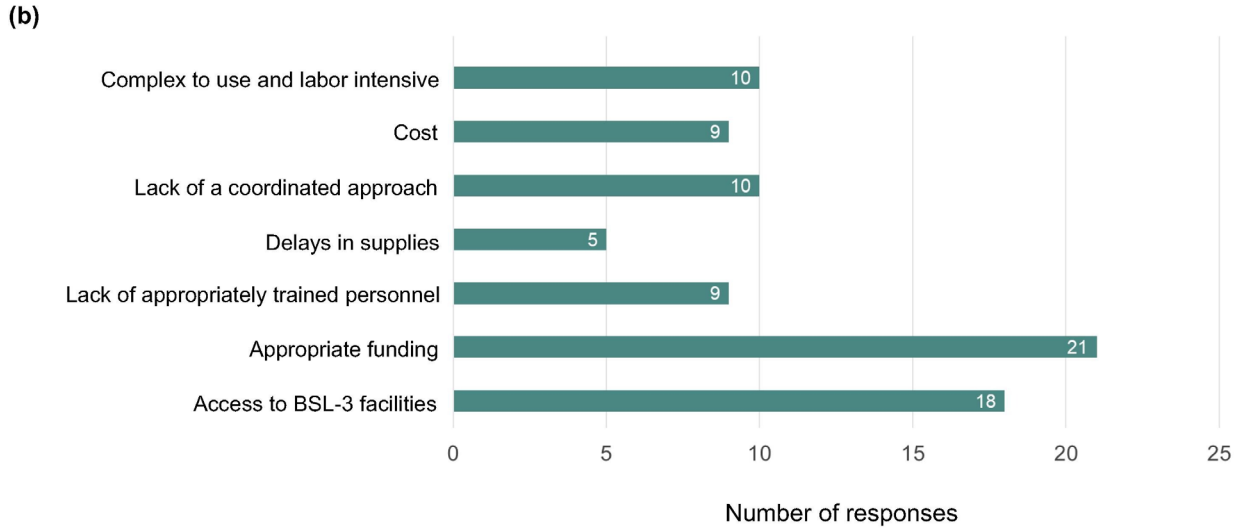
Drug Discovery Today • Volume 26, Number 11 • November 2021

Feature

Harnessing the power of microphysiological systems for COVID-19 research

Nicole Kleinstreuer[a], Anthony Holmes[b,*]

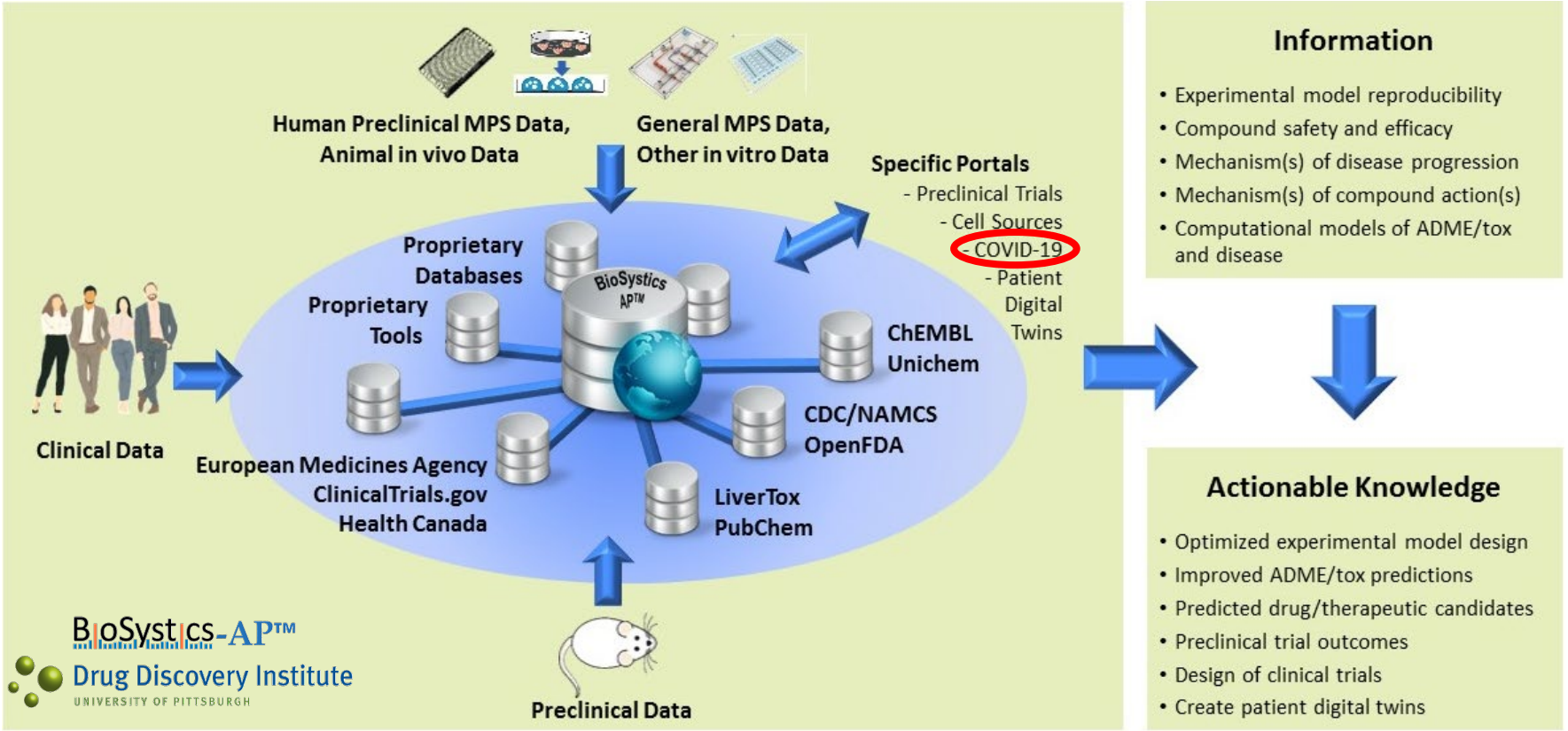




https://doi.org/10.1016/j.drudis.2021.06.020

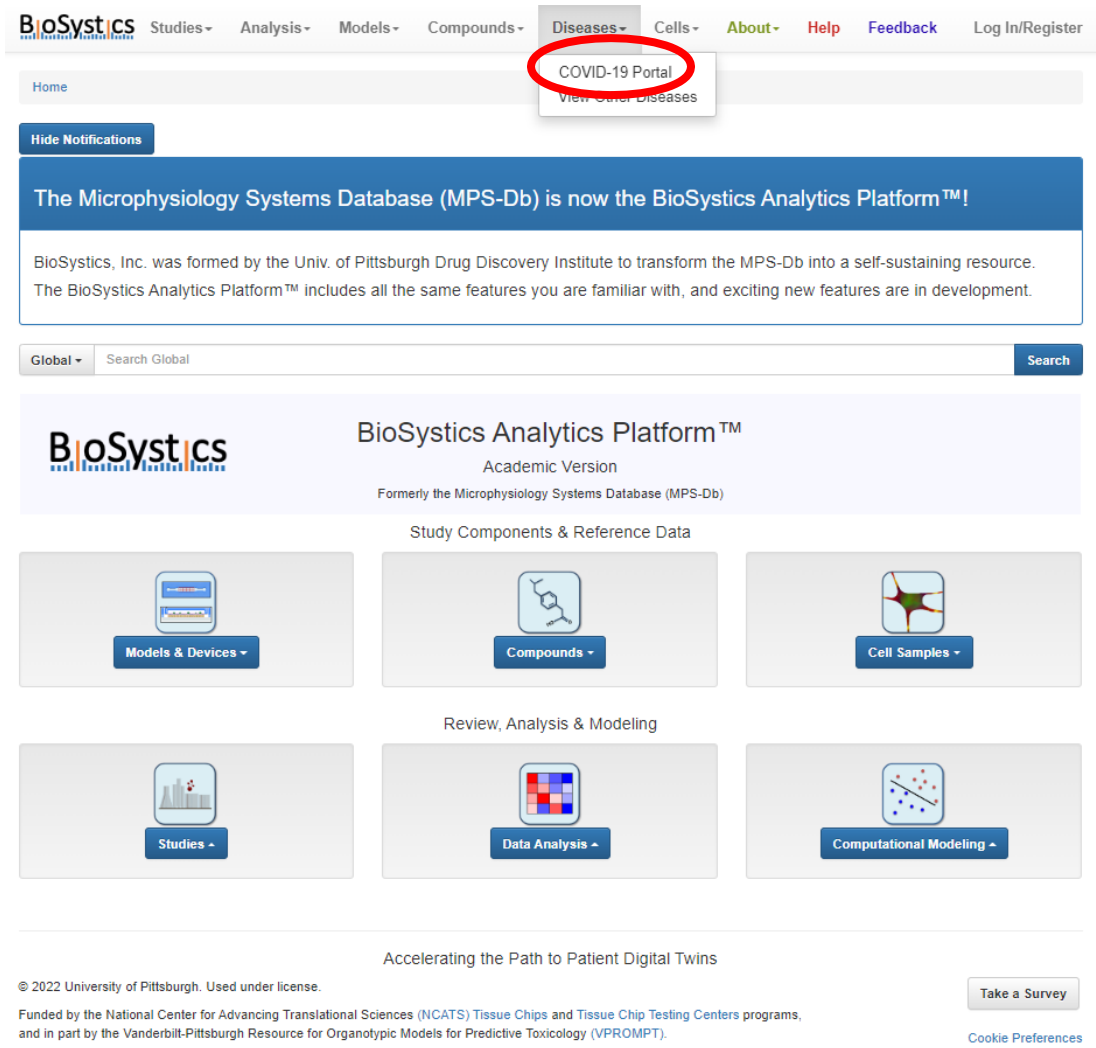
BioSystics Analytics Platform™ COVID-19 Portal

- Facilitate connections between MPS technology developers and potential end users
- Provide cross-discipline and -sector expertise in characterizing criteria for model performance and readiness



https://mps.csb.pitt.edu/

BioSystics Analytics Platform™ COVID-19 Portal



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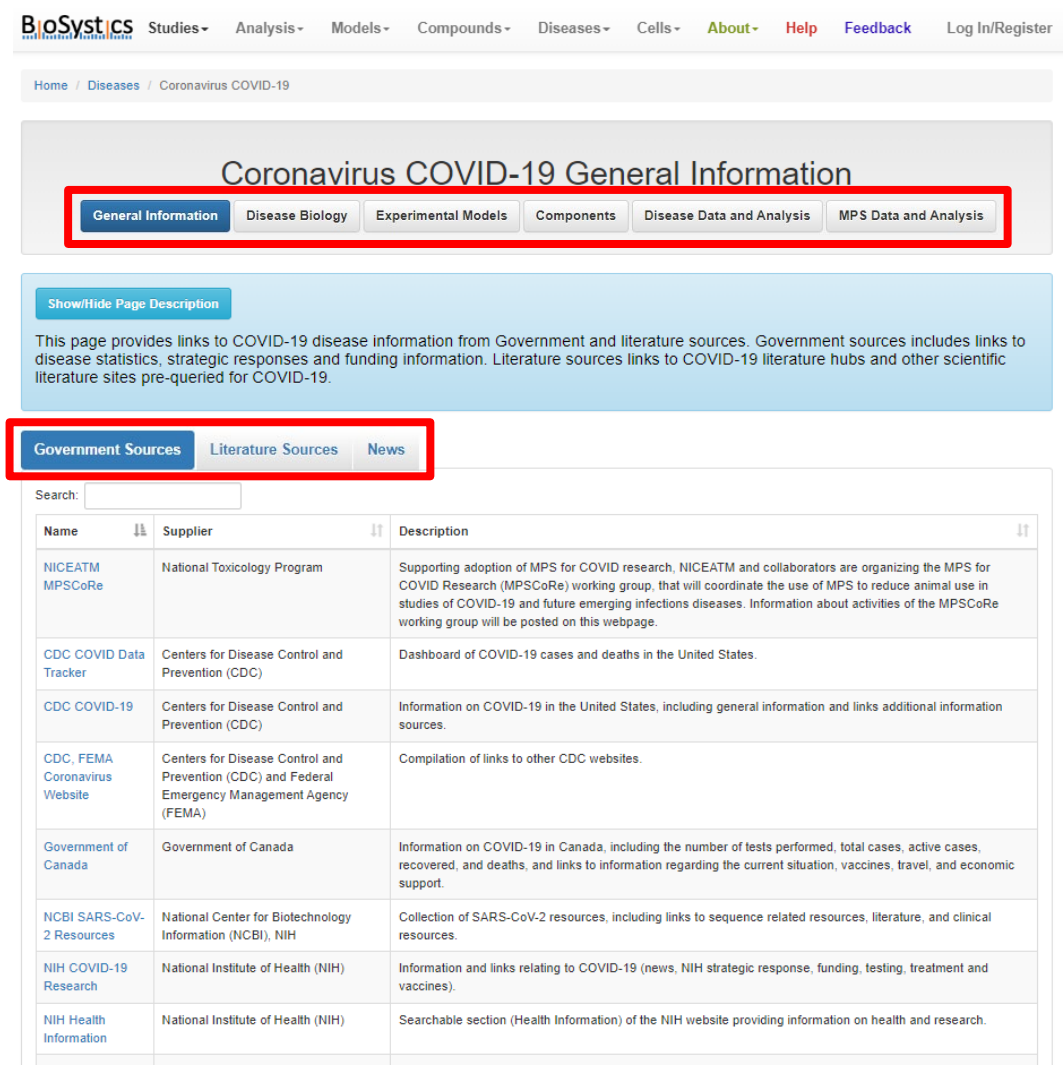

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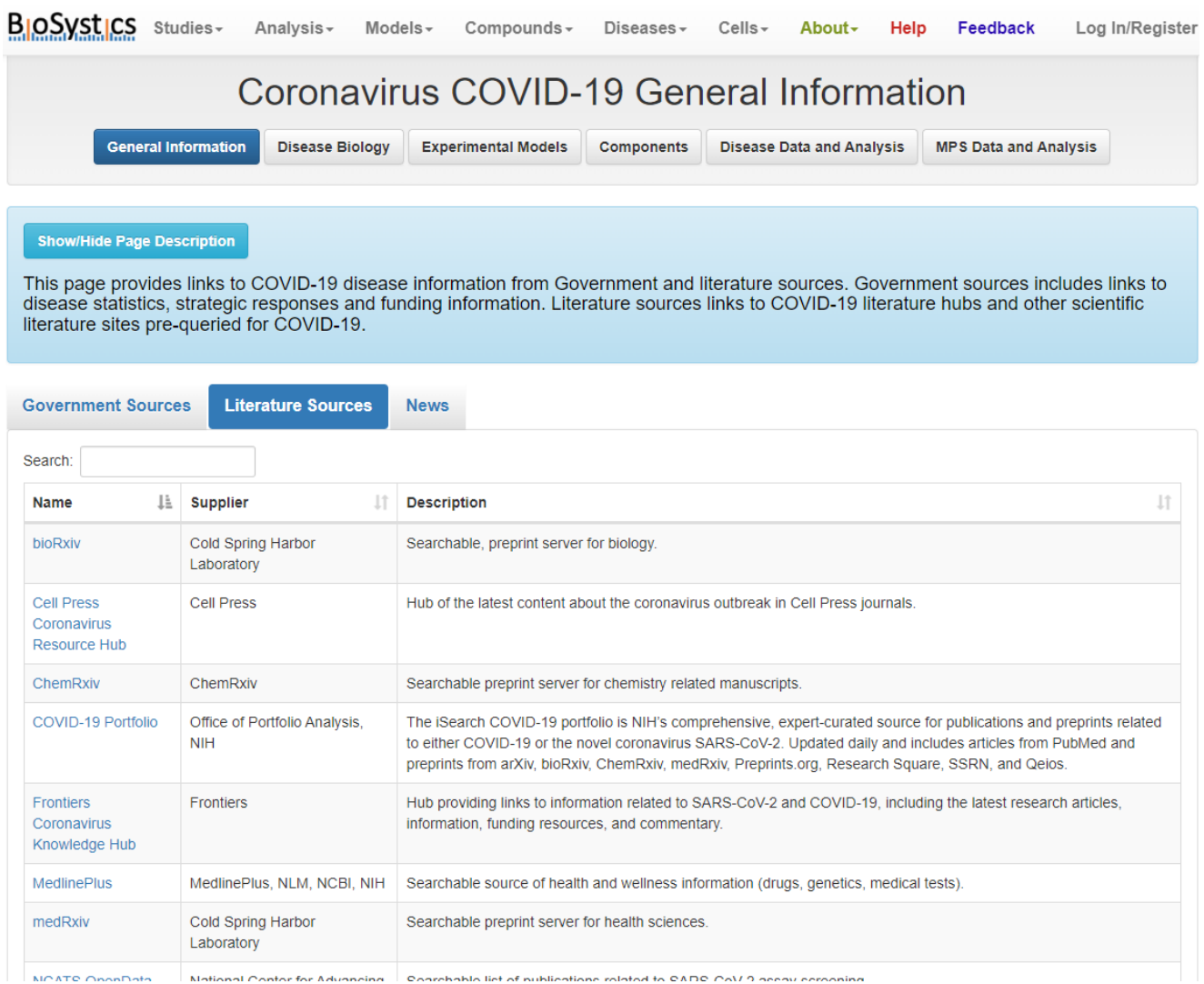

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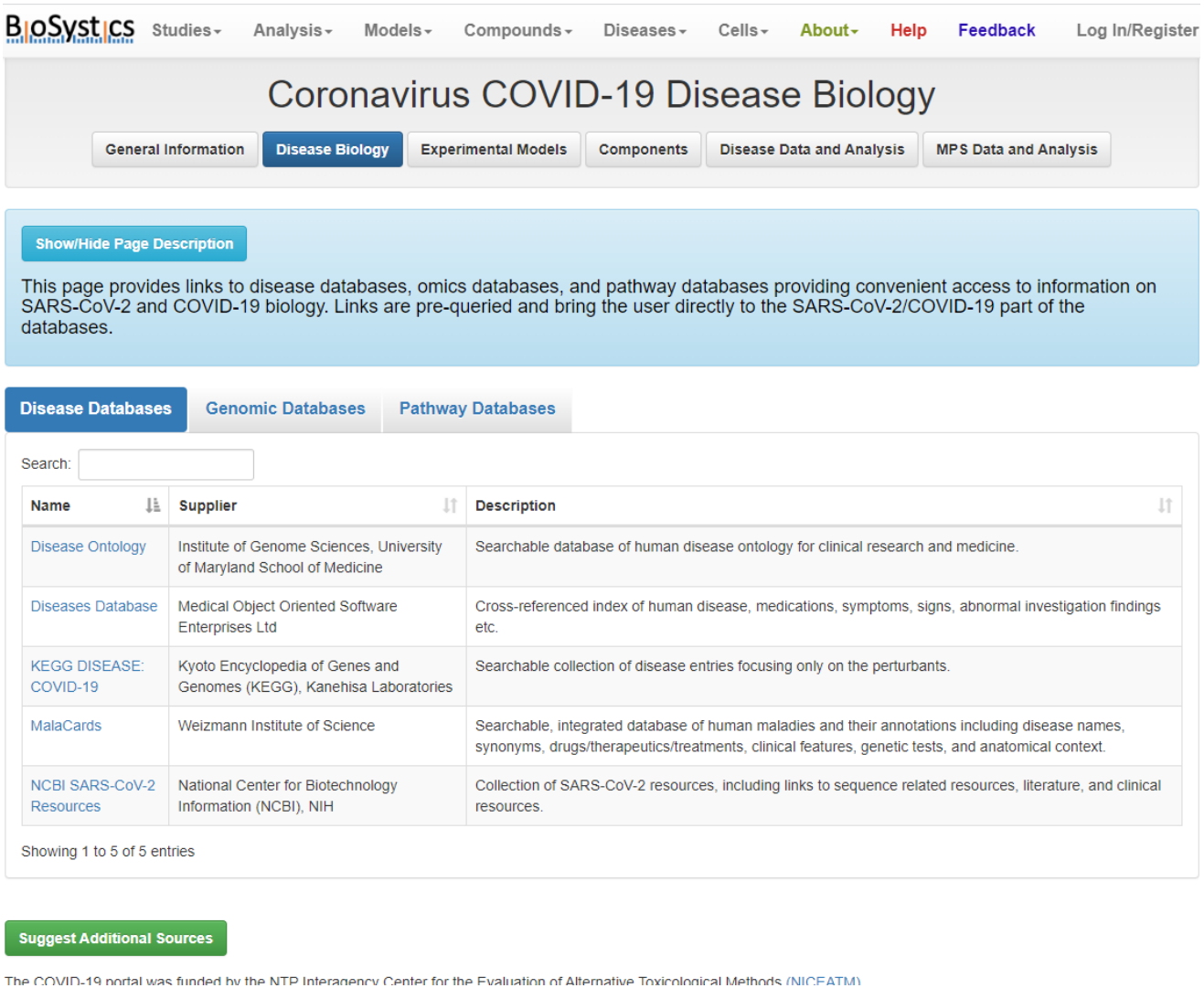

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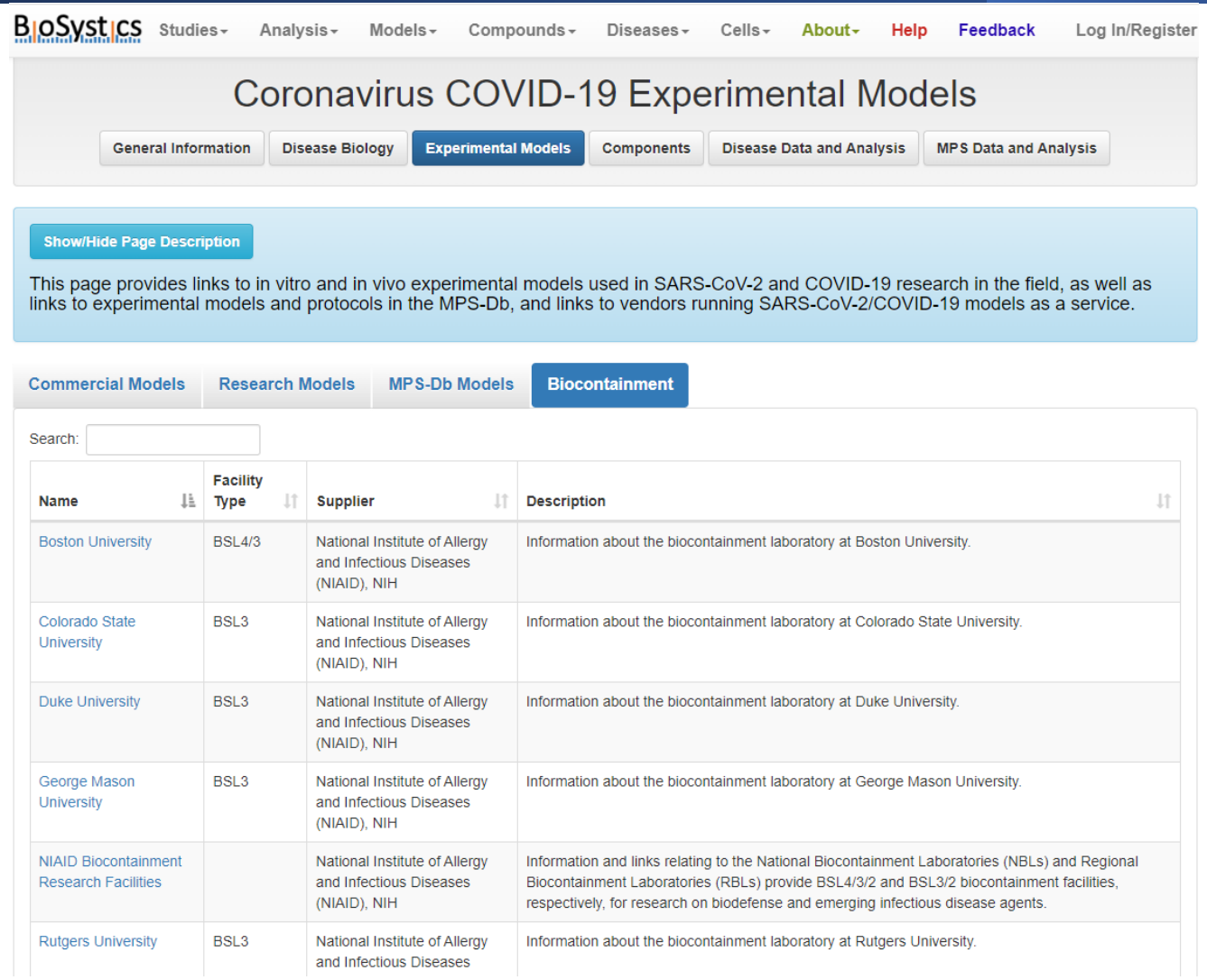
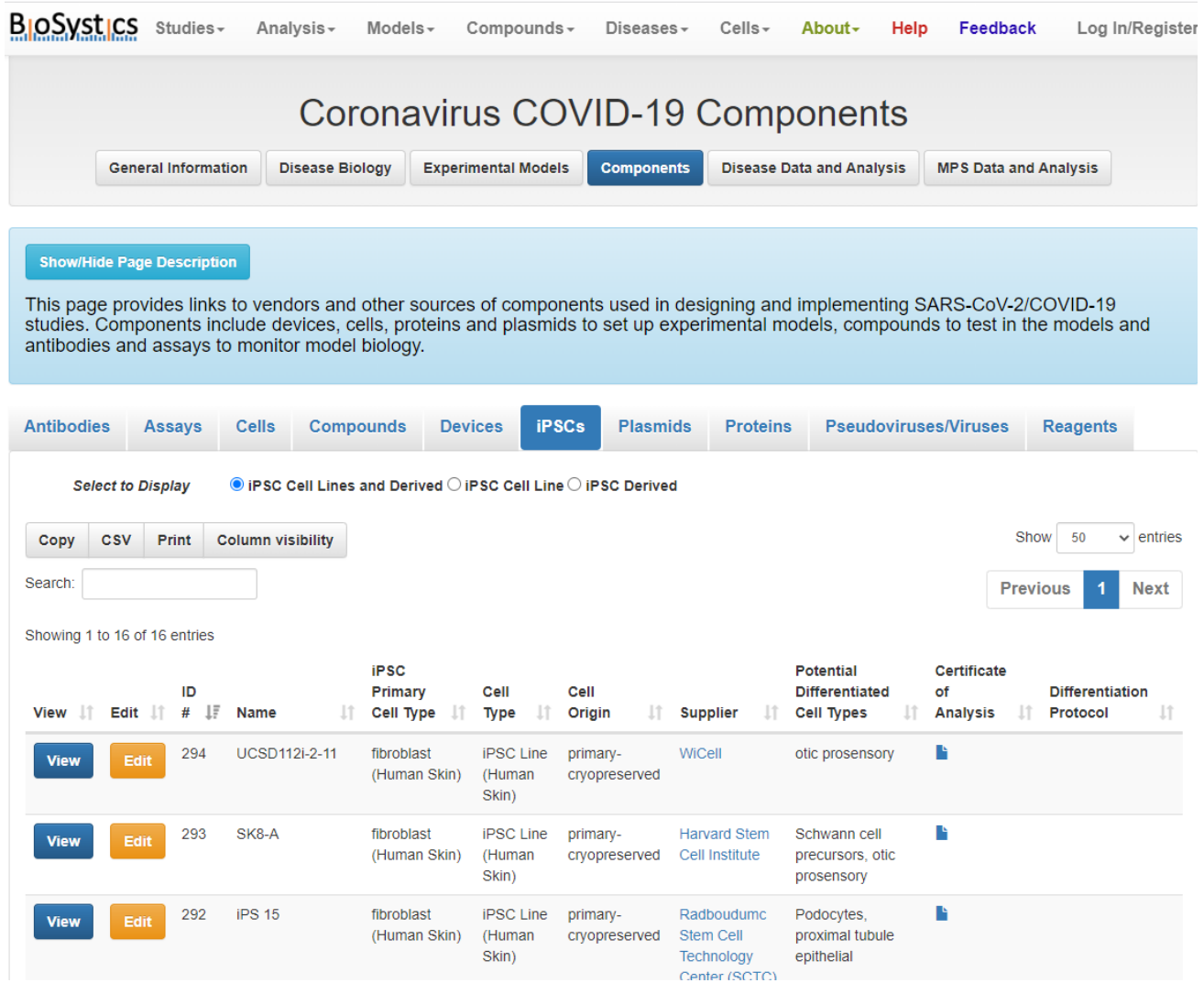


Name	Facility Type	Supplier	Description
Boston University	BSL4/3	National Institute of Allergy and Infectious Diseases (NIAID), NIH	Information about the biocontainment laboratory at Boston University.
Colorado State University	BSL3	National Institute of Allergy and Infectious Diseases (NIAID), NIH	Information 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.

https://mps.csb.pitt.edu/

BioSystics Analytics Platform™ COVID-19 Portal



Characteristics of the iPSCs
- Differentiated cell type(s)
- Differentiated phenotypes
- Differentiated maturity level
- Functional profiles

Patient profile
- Demographic
- Known disease conditions
- Genomic abnormalities

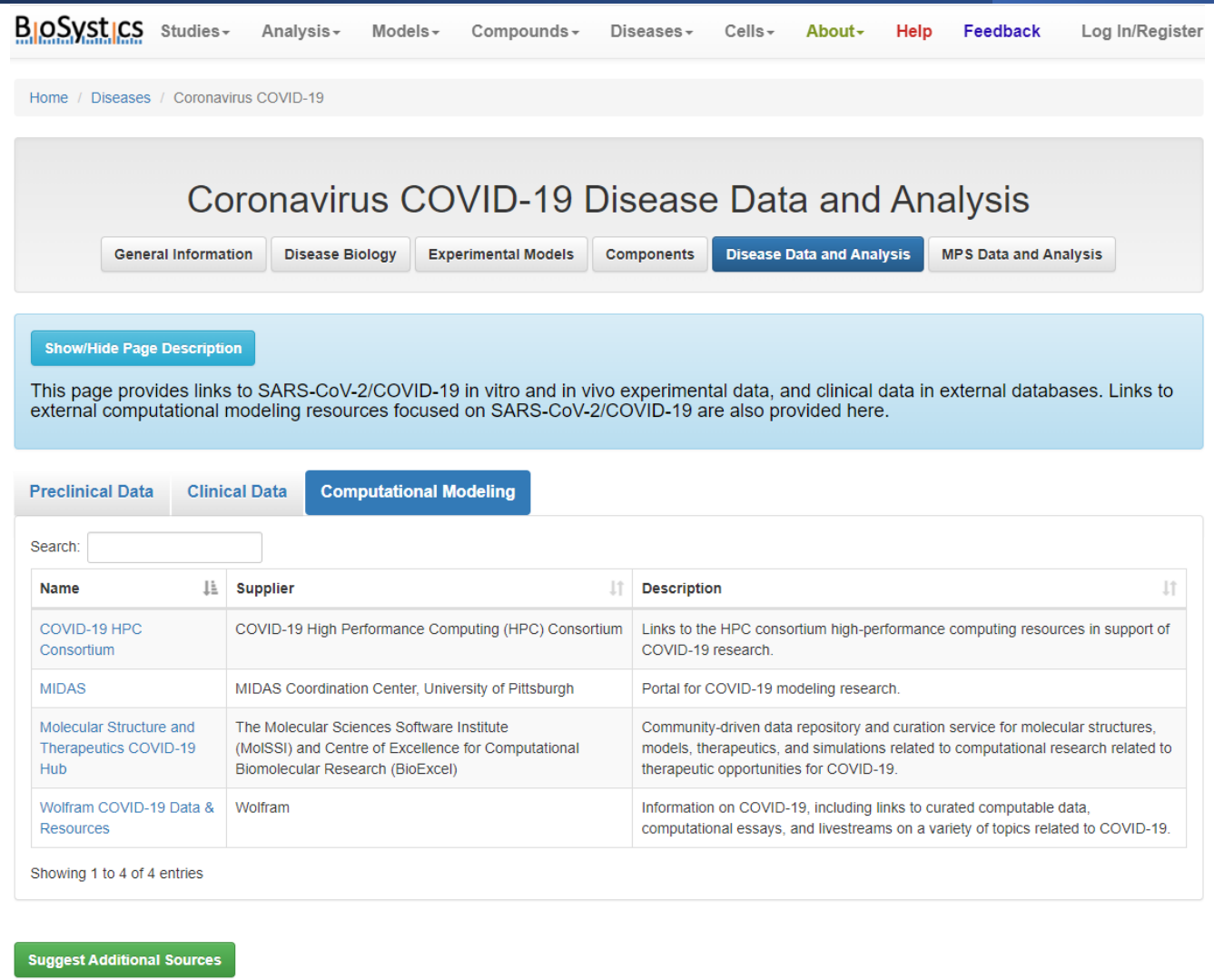
Source of cells
- Vendor
- Collaborator
- Others

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)

https://mps.csb.pitt.edu/

BioSystics Analytics Platform™ COVID-19 Portal



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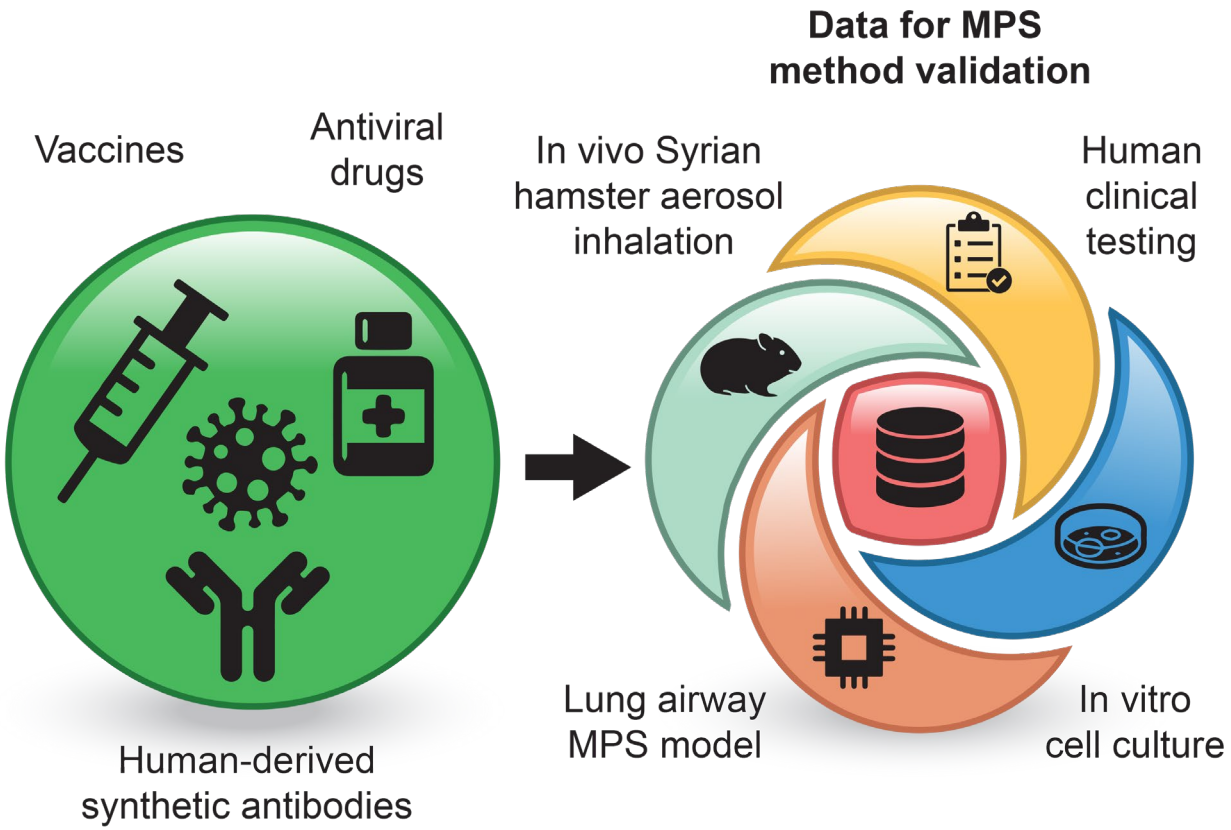
MPSCoRe members may access a **private** list of other member profiles, and share their own information about:

- 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

https://mps.csb.pitt.edu/

Proof-of-Concept Study

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



https://www.niaid.nih.gov/research/covid-19-research-integrated-research-facility

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

https://ntp.niehs.nih.gov/go/mps
https://nc3rs.org.uk/resources/alternatives

Future Directions

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

https://ntp.niehs.nih.gov/go/mps
https://nc3rs.org.uk/resources/alternatives

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

Impact

ALTEX ● Volume 38, Number 4 ● October 2021

Food for Thought ...

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

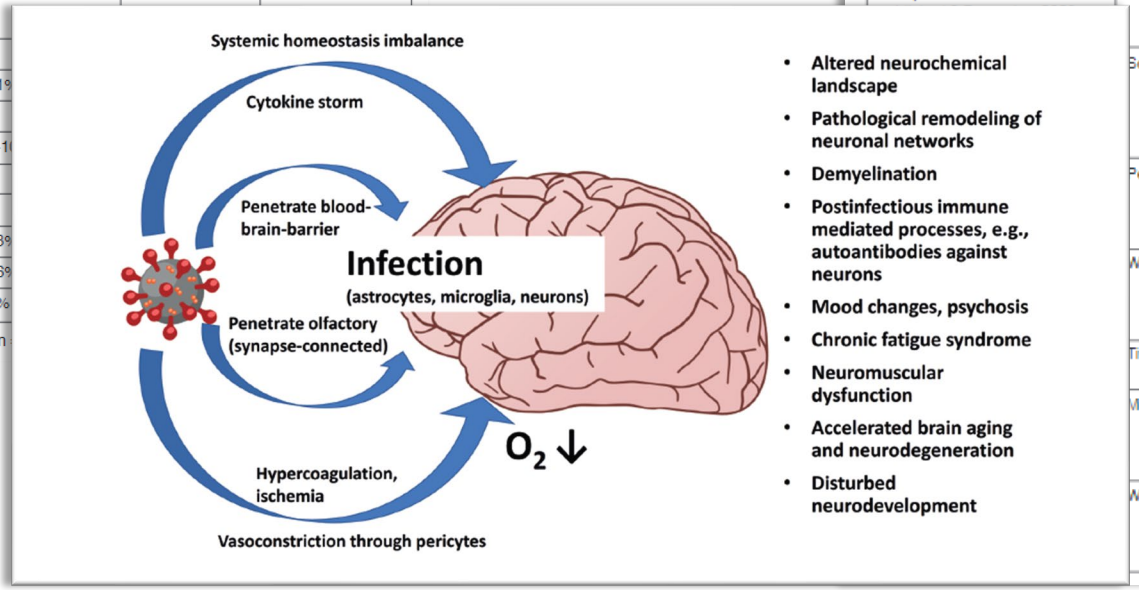
Ian Kang[1], Lena Smirnova[1], Jens H. Kuhn[2], Helena T. Hogberg[1], Nicole C. Kleinstreuer[3] and Thomas Hartung[1,4]

[1]Center for Alternatives to Animal Testing (CAAT), Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA; [2]Integrated 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; [3]National 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; [4]CAAT-Europe, University of Konstanz, Konstanz, Germany

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			7-1		
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

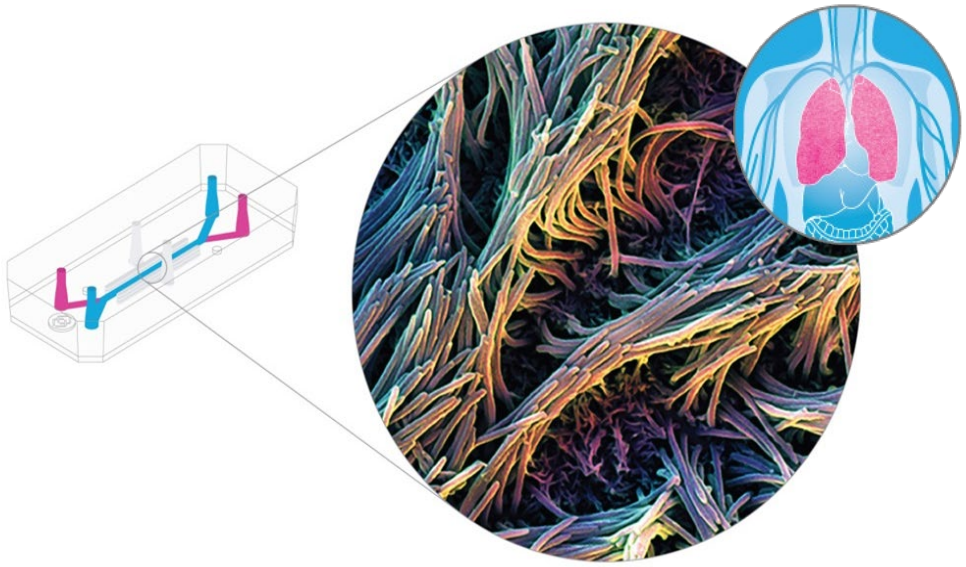


Tab. 1: Original research on SARS-CoV-2 neurotropism using human brain organoids

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
	Song 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 (PLCa) integrated into a cortical organoid enhance infection – **virus spreading to astrocytes and mediating inflammatory type I interferon responses**

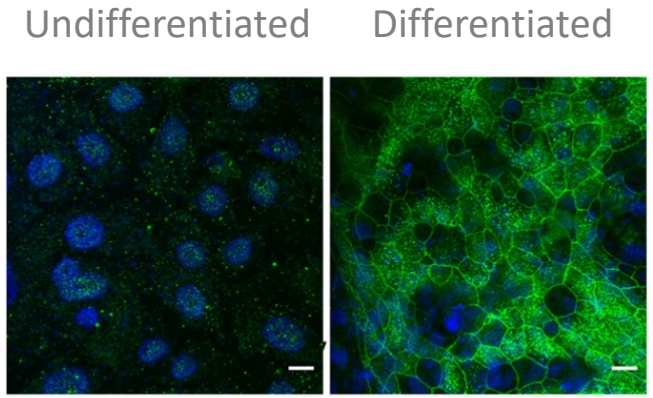
doi.org/10.14573/altex.2110131

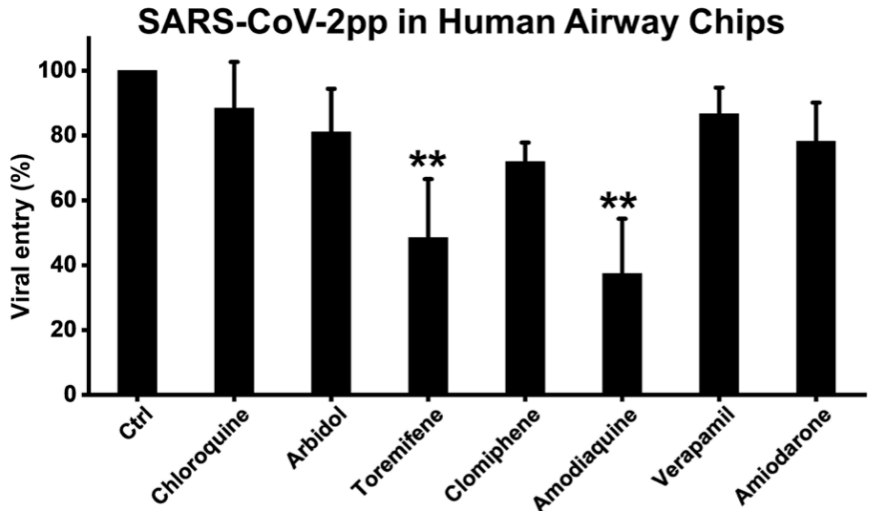
Impact



- 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

Angiotensin Converting Enzyme Receptor 2 (ACE-2) Expression



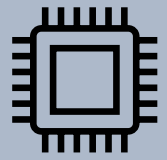


Si et al., 2021 Nat Biomed Eng | doi.org/10.1038/s41551-021-00718-9

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	
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Mark Schurdak	University of Pittsburgh
Proof-of-Concept Study	
Gabriella Worwa	NIAID/IRF
Jens Kuhn	NIAID/IRF

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