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Human Organ Chip-enabled discovery of therapeutics and prophylactics for viral pandemics

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Professor of Bioengineering, Harvard School of Engineering and Applied Sciences

Hansjörg Wyss Institute for Biologically Inspired Engineering at Harvard University

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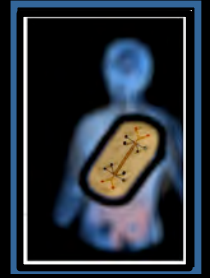
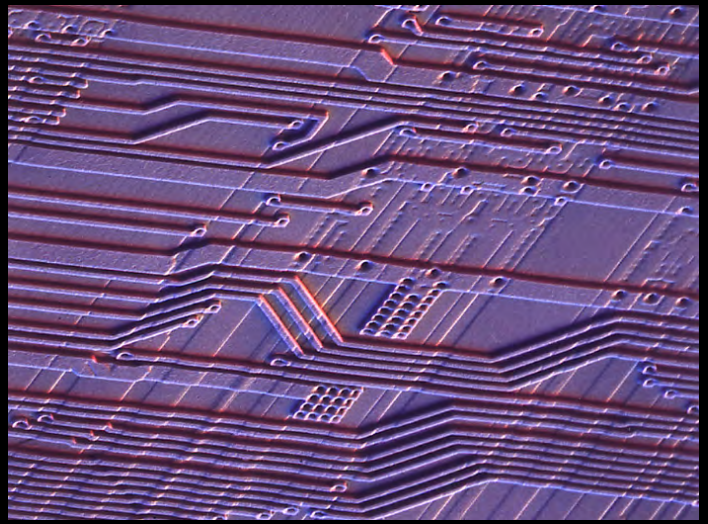
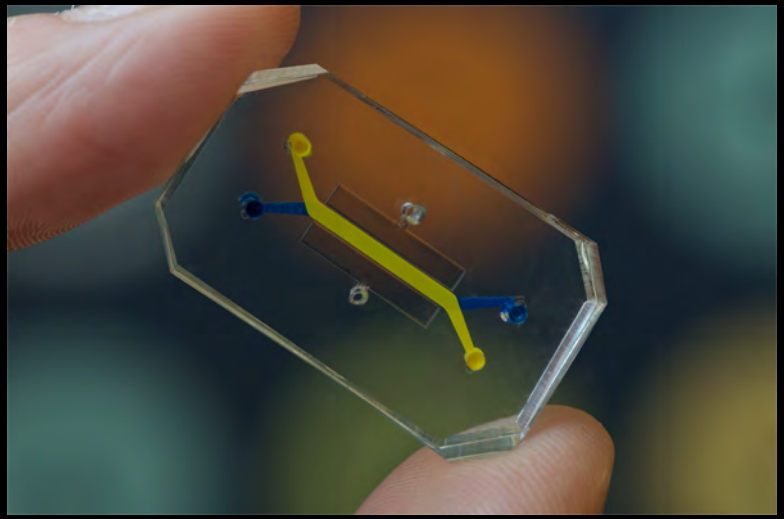


Human Organs-on-Chips

- Engineered microchips containing living human cells that reconstitute organ-level functions

- ***ACCELERATE drug development, REPLACE animal testing, and ADVANCE personalized medicine***





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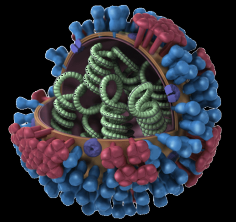
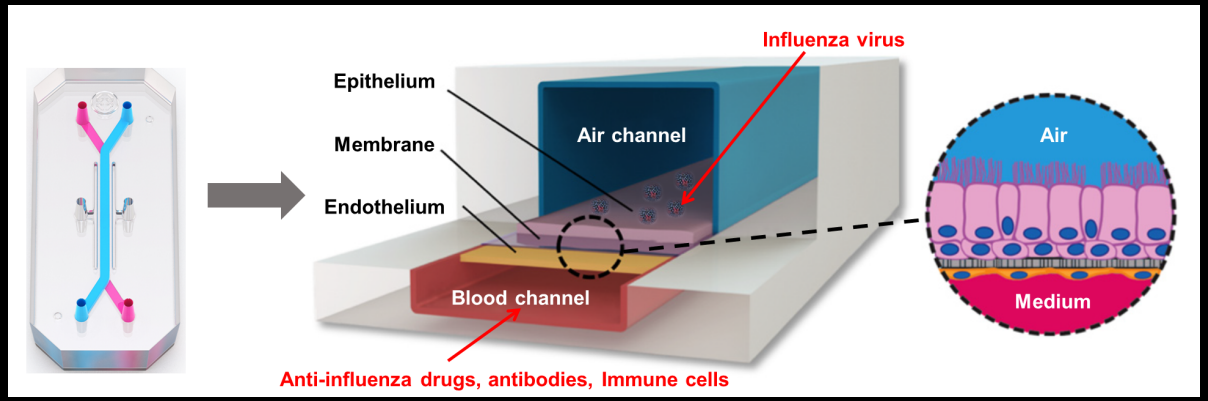
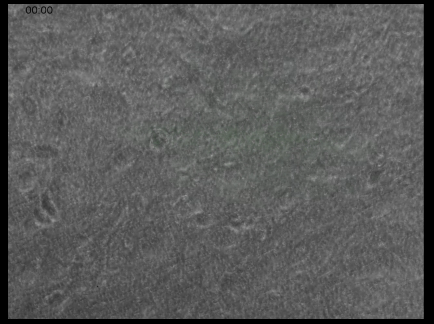
Human Airway Chip Viral Infection Model

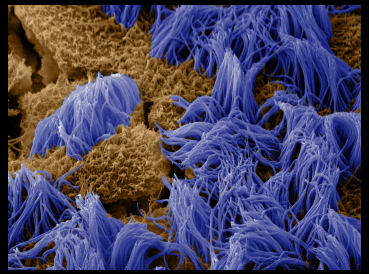


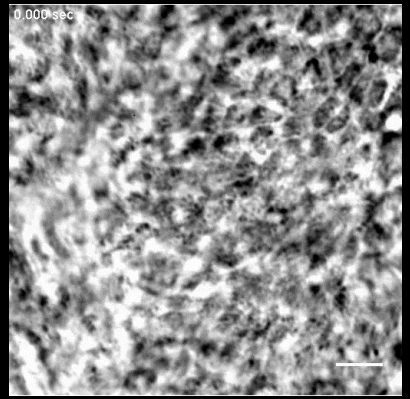
(Benam et al., *Nature Methods* 2015 & *Cell Systems* 2016' Si et al., *bioRxiv* 2019,2020)

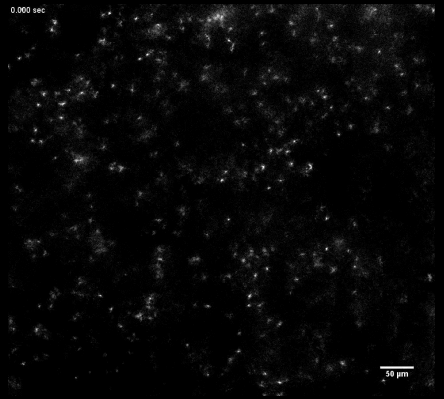


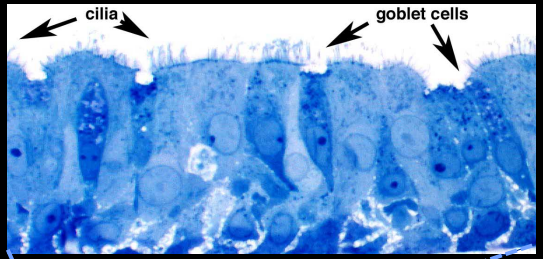
Live Infection
(GFP-Influenza H1N1)











Small Airway:
Diameter < 2 mm

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Funded by DARPA & NIH

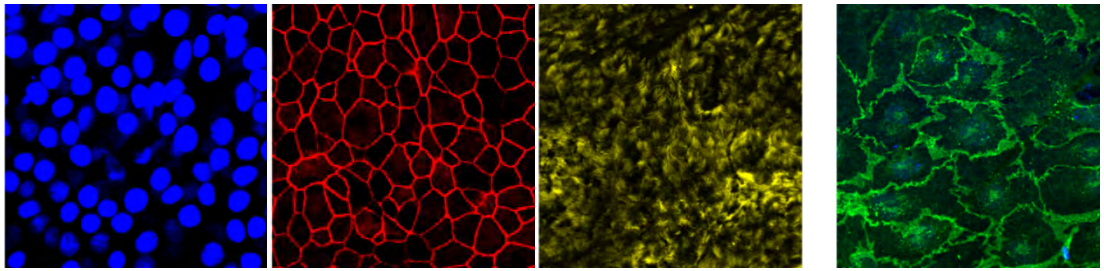
Human Airway Influenza Infection Chip

(Si et al., *bioRxiv* 2020)

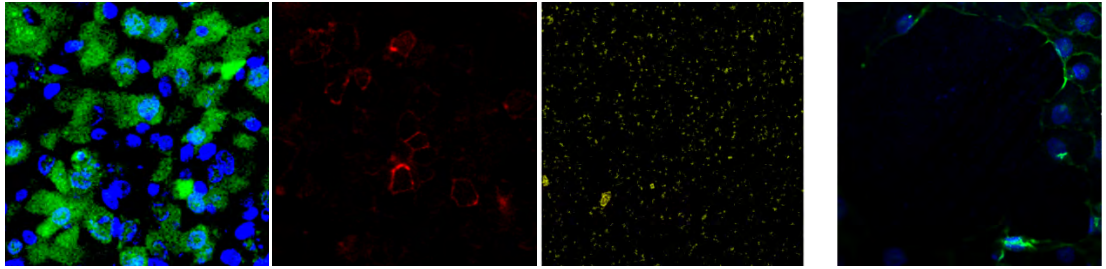
Epithelium **Endothelium**

GFP ZO-1 Cilia VE-cadherin

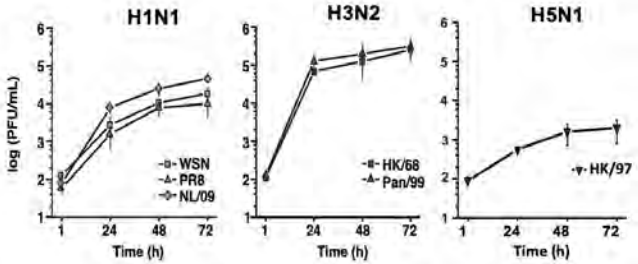
- Virus



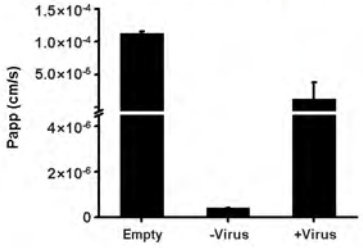
+ Virus



Viral Strain-Dependent Virulence



Compromised Barrier Function



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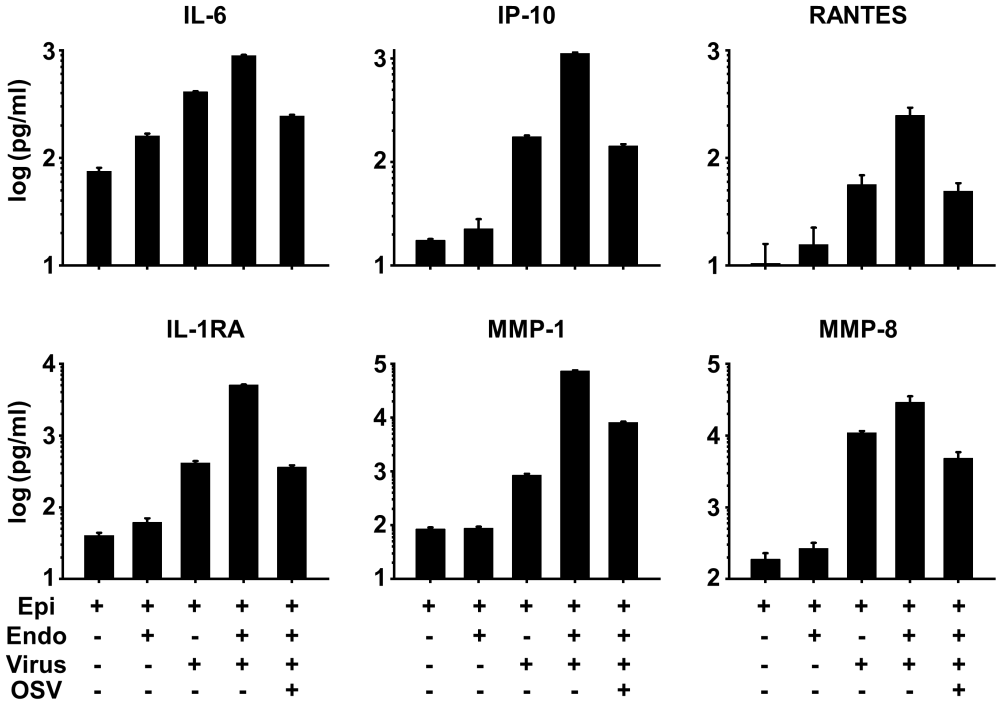
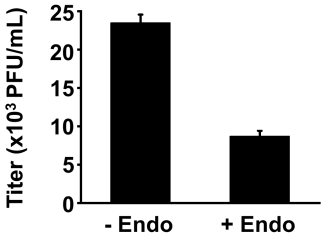
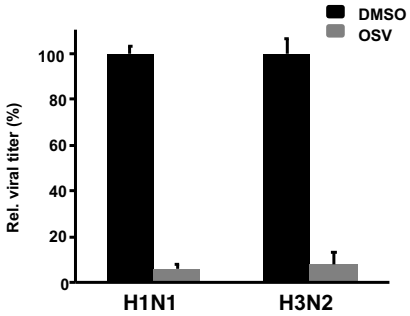
Can Analyze Host Responses to Infection & Drugs



Endothelium Influences Infection



Oseltamivir Inhibits Infection



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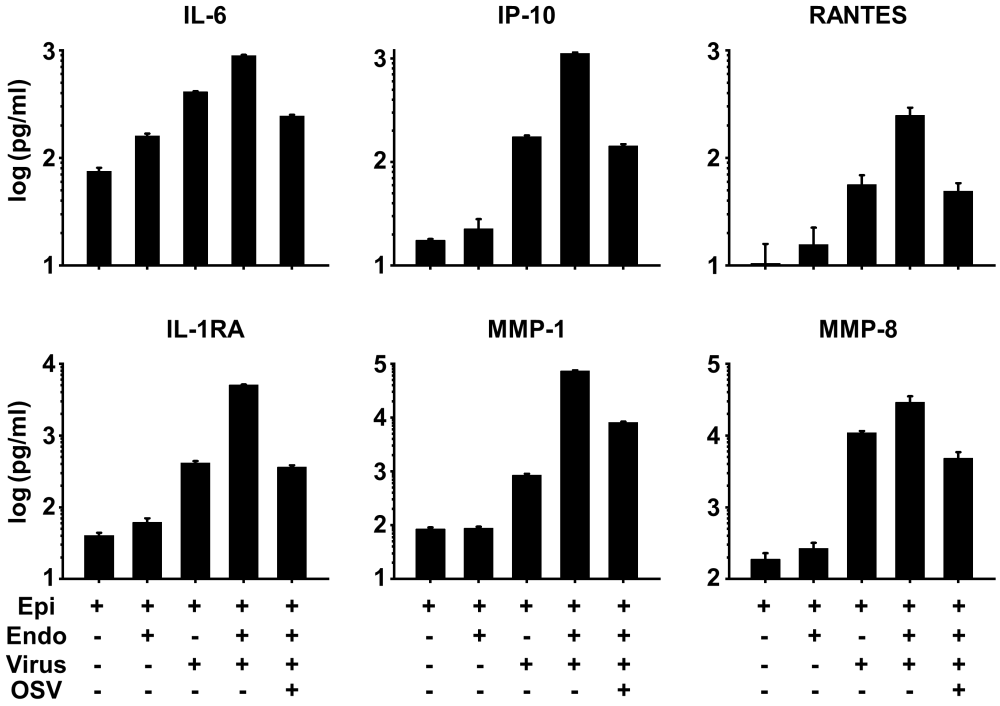
Can Analyze Host Responses to Infection & Drugs



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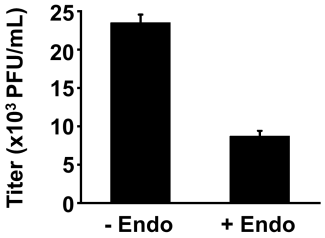
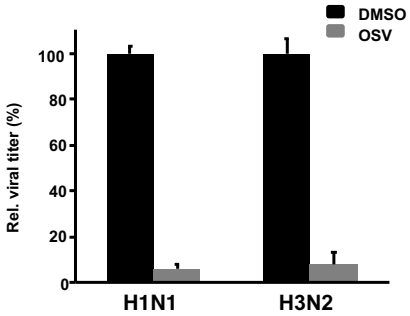


Oseltamivir Inhibits Infection



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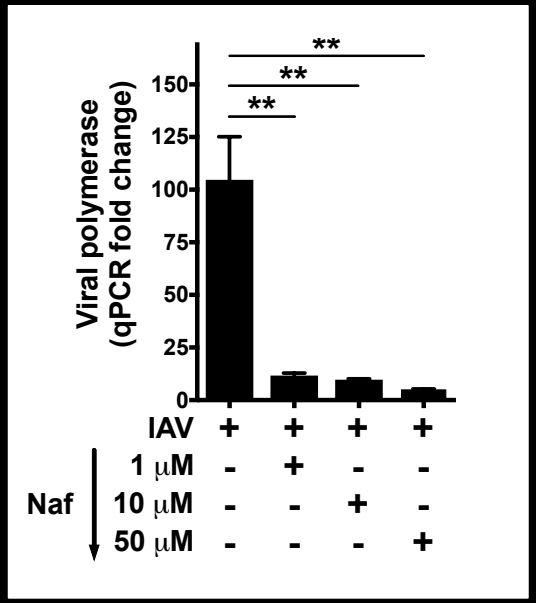
Nafamostat is a Potent Inhibitor of Influenza H1N1 Infection

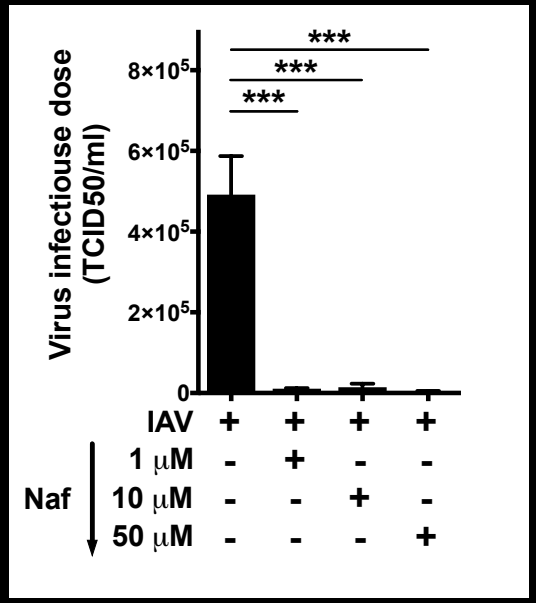
Nafamostat is an anticoagulant drug & protease inhibitor

Lung Airway Transwell

Virus RNA
(PCR / Apical Wash)



Virus Titer
(TCID50 / Apical Wash)



54hr Rx starting 6 hr prior to infection

IAV = Influenza A Virus
Naf. = Nafamostat Mesylate

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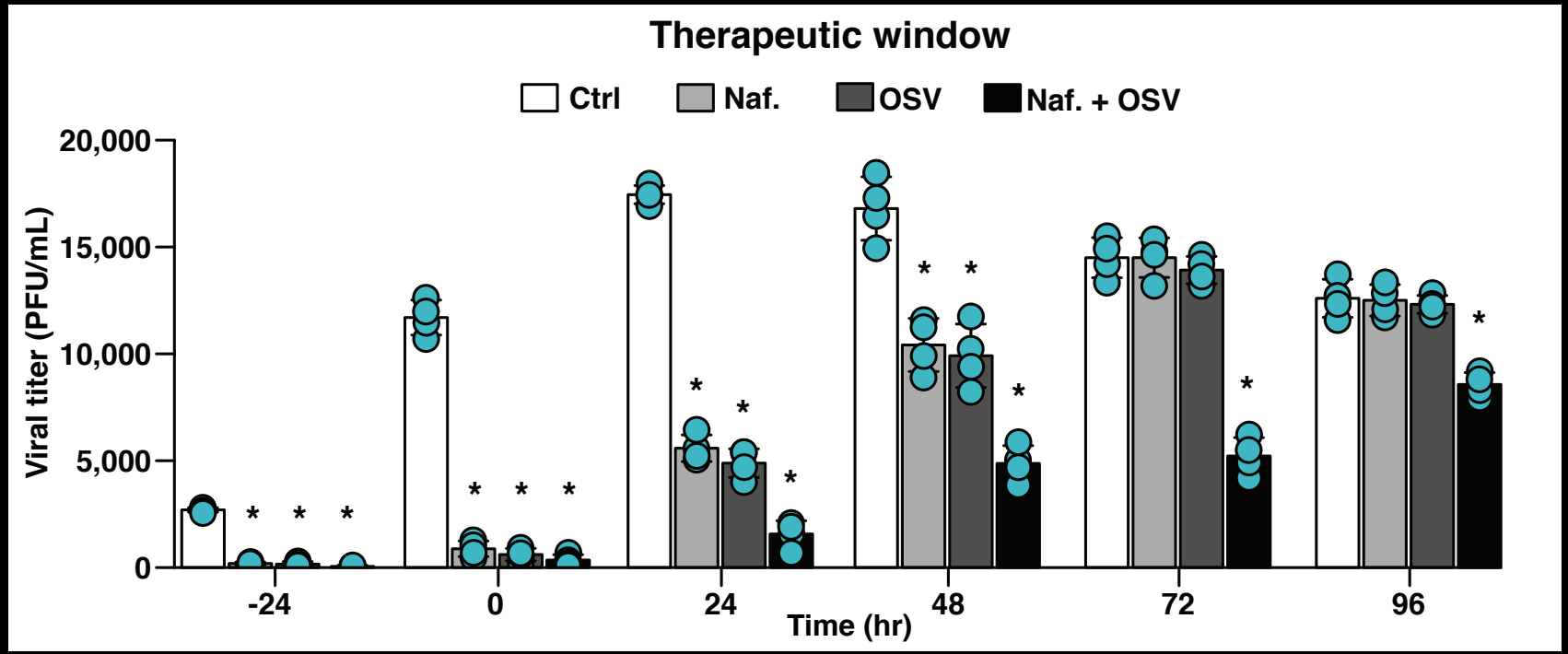
Nafamostat Doubles Oseltamivir's Therapeutic Time Window to 4 days



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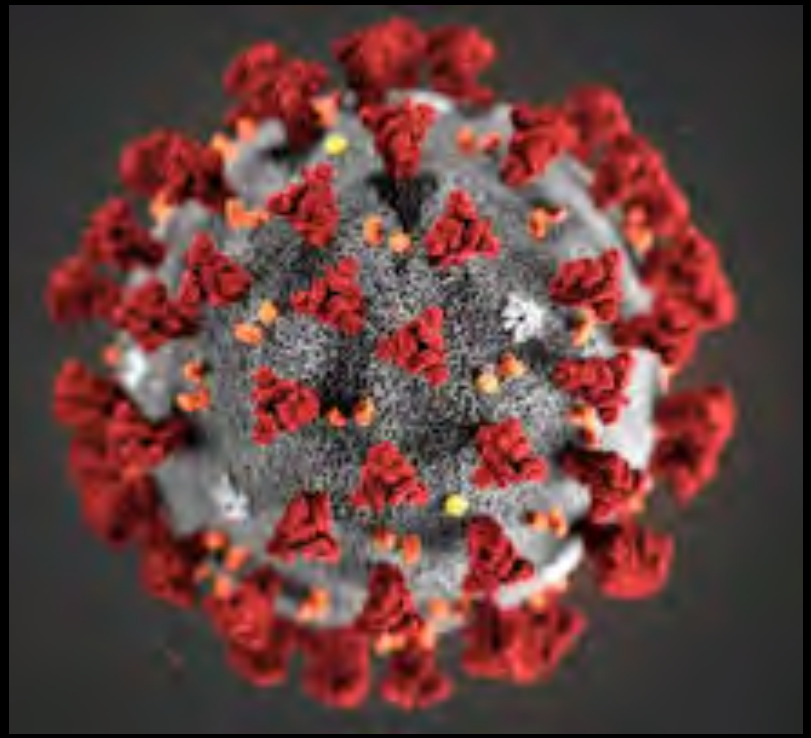
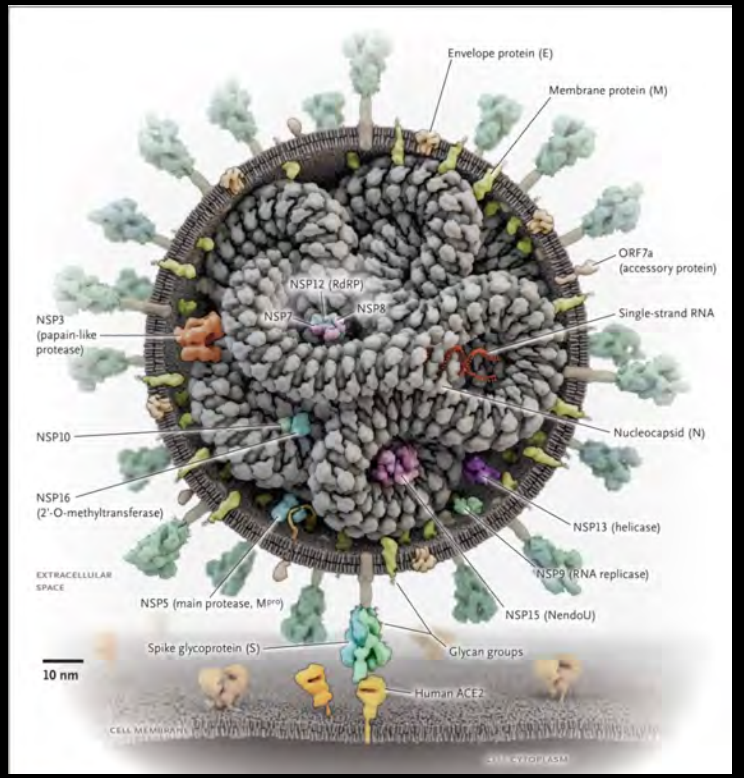
Confronting the COVID19 Challenge





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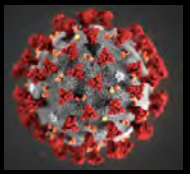
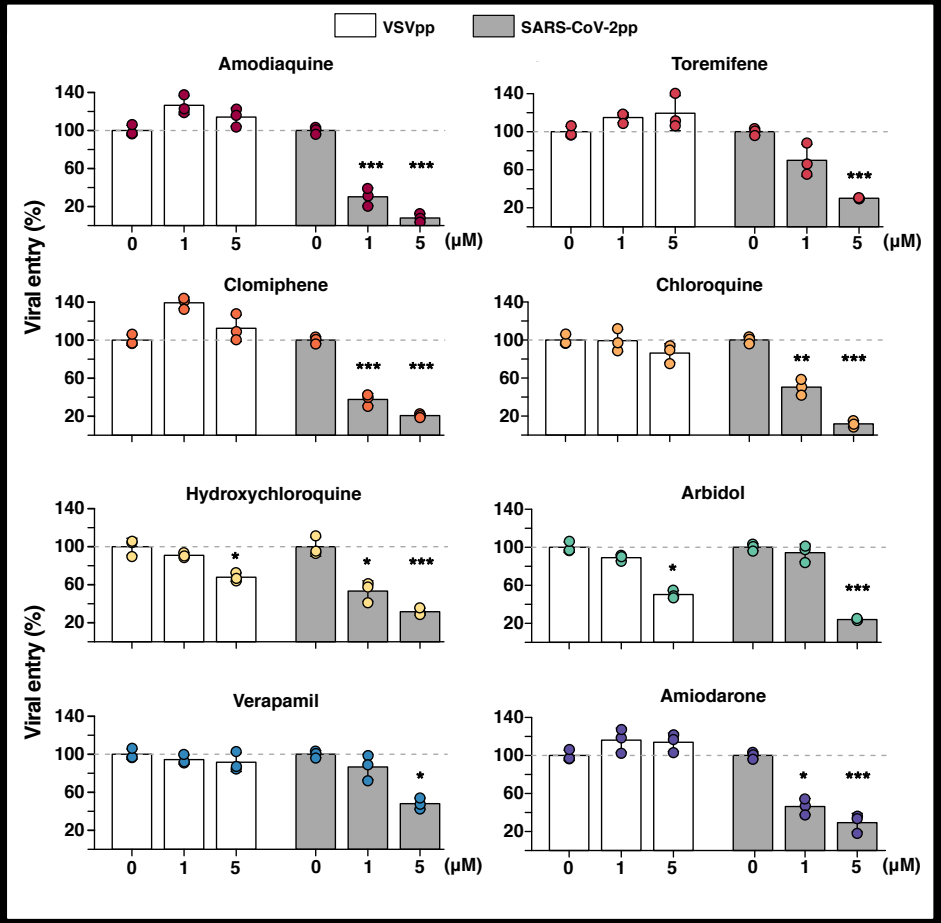
Pivot to COVID19



SARS-CoV2 Spike Pseudovirus for BSL2 work

Huh7 Cell Line

Drugs selected based on reported activities vs. Ebola, MERS, SARS



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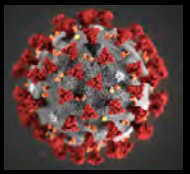
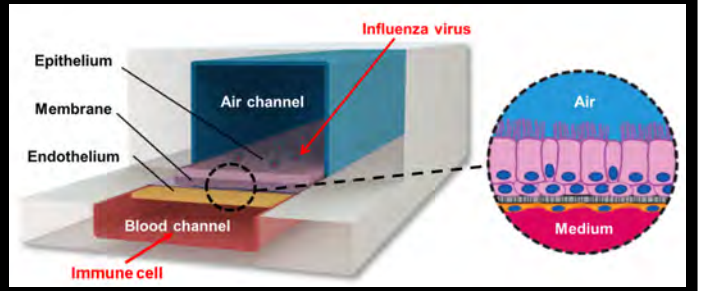
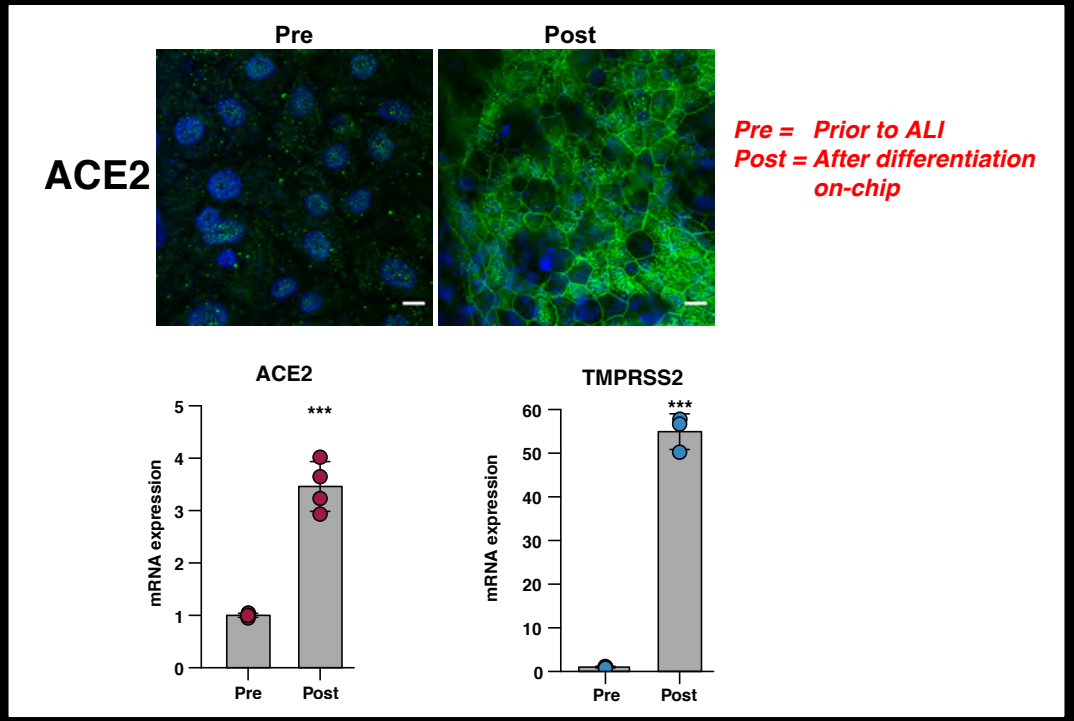


ACE2 & TMPRSS2 are Highly Expressed in Human Lung Airway Chips





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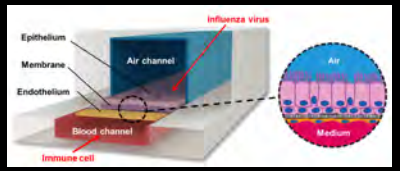
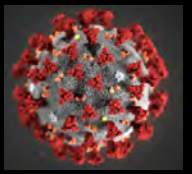
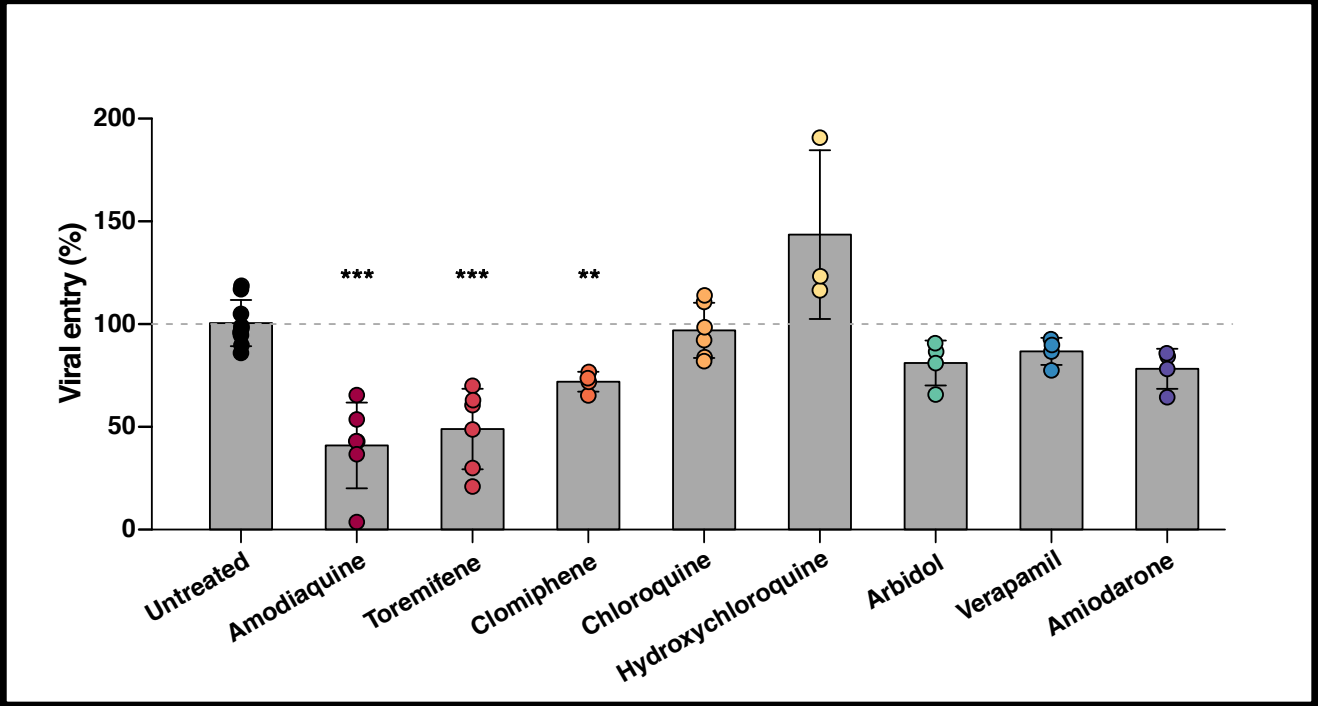




Drug Effects in Human Lung Airway Chips

(February 2020)

Flowed at Human Blood C_{max}



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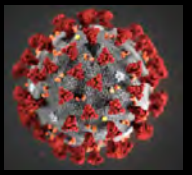

DARPA COVID19 Program

Structural Similarity and SAR

MDS + Medicinal Chemistry Pipeline

Transcriptomic Data from COVID patients

Computational Machine Learning Pipeline

Transcriptomic Data from COVID patients

Computational Network Analysis Pipeline

FDA Approved Drugs

Native CoV2 Multiplexed Cell Assays *[Matt Frieman, U. Maryland Sch. Med.]*

Human Organ Chips (Airway, Alveolus, Intestine)

Hamster/PK

Hamster Native CoV2 Models *[Ben tenOever, Mt Sinai Sch. Med.i]*

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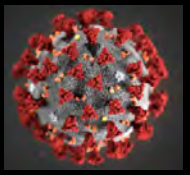
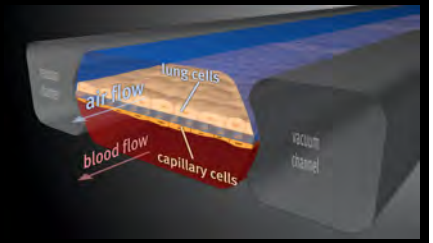
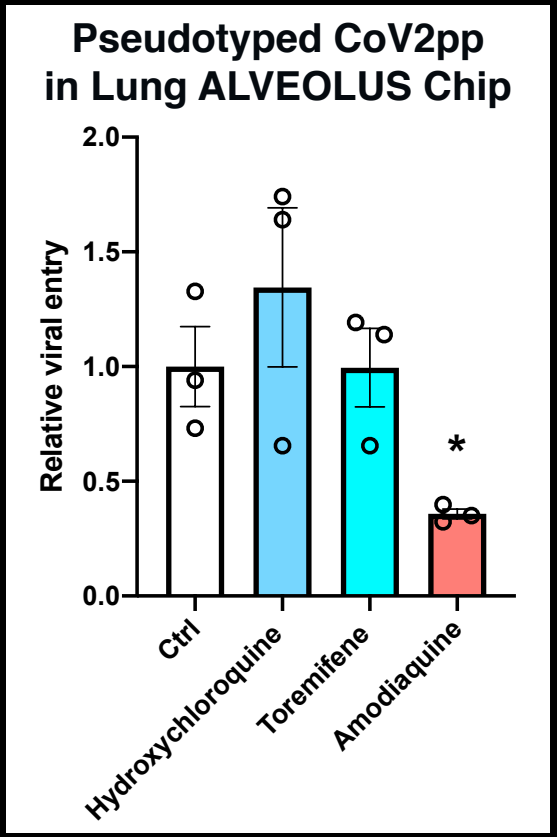
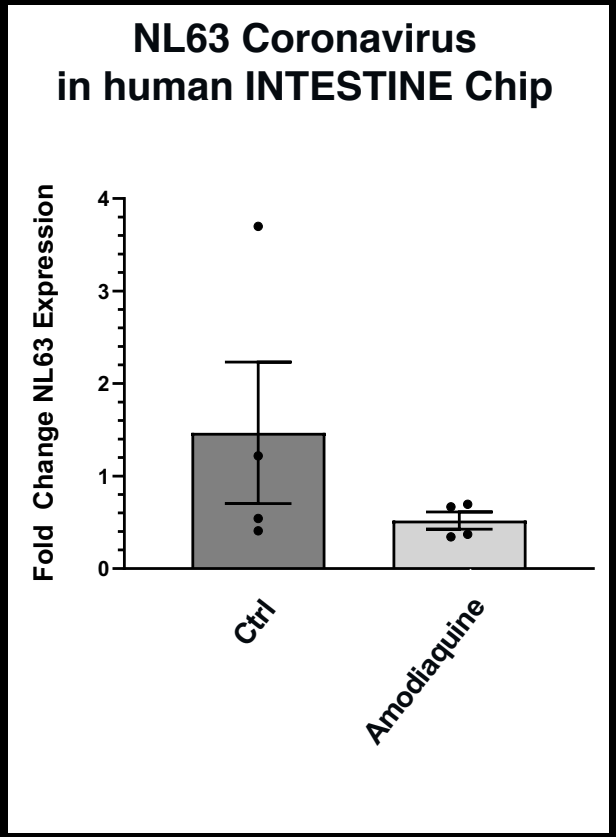
Amodiaquine



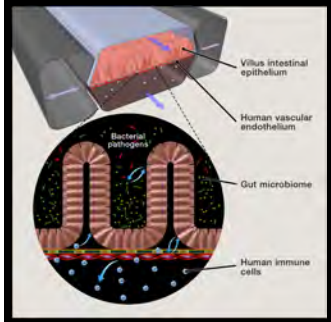
Lung ALVEOLUS Chip







INTESTINE Chip



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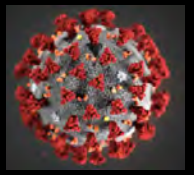
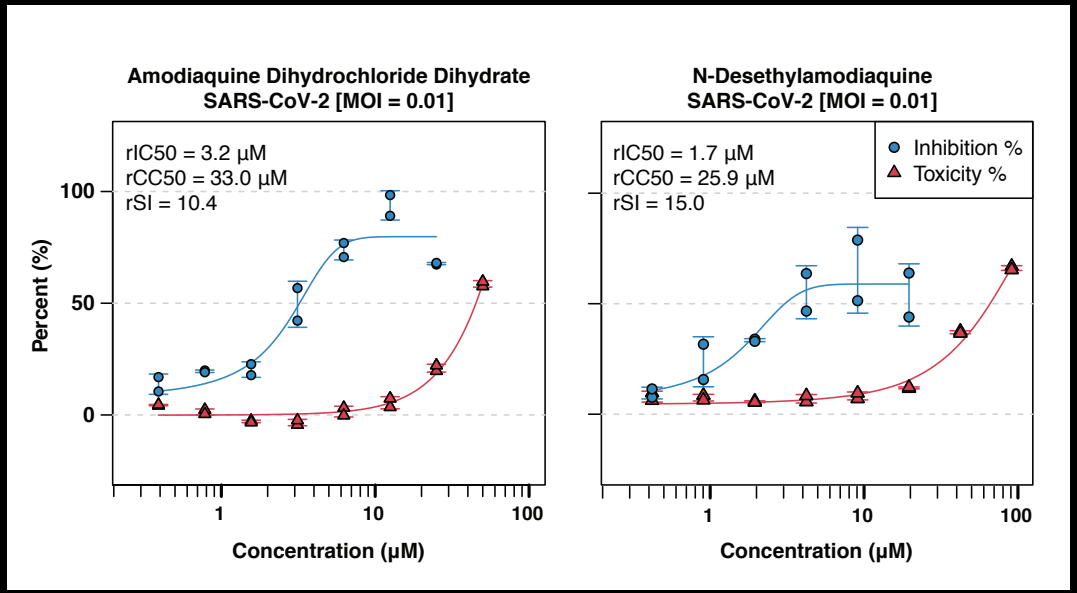
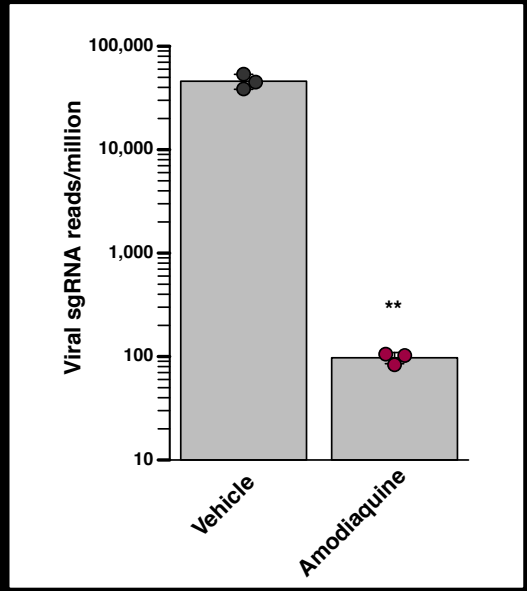


Amodiaquine Inhibits SARS-CoV-2 Infection *In Vitro*

Vero E6 cells



Human Lung A549/ACE2 cells



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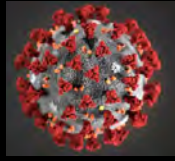
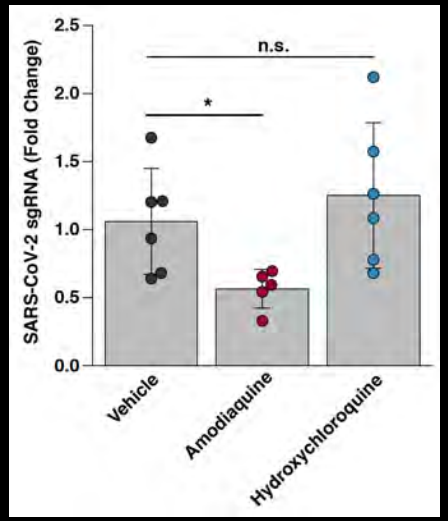


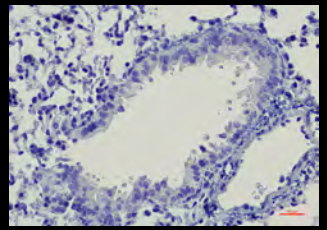
Amodiaquine Inhibits SARS-CoV-2 Infection *In Vivo*

(Hamster COVID-19 model with Ben tenOever, Mt. Sinai)

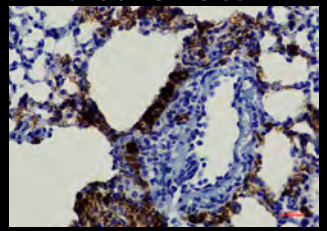
PROPHYLAXIS



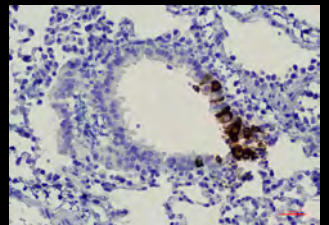
Mock Infected



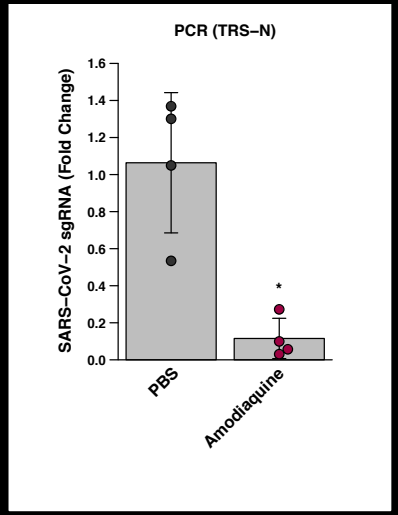
Vehicle + SARS-CoV-2



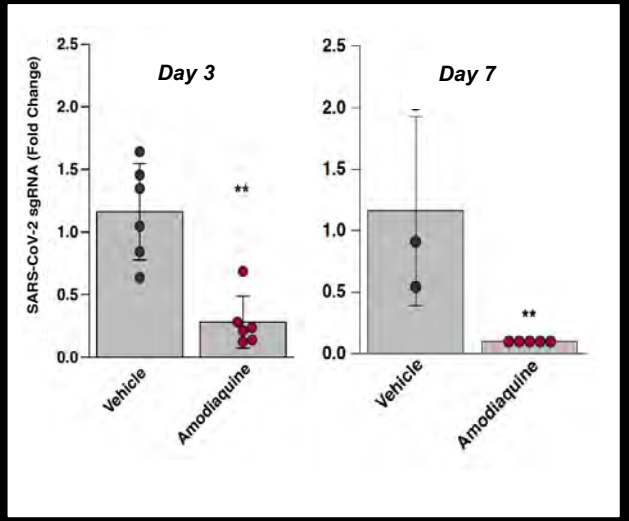
Amodiaquine + SARS-CoV-2



Animal-to-Animal TRANSMISSION



TREATMENT



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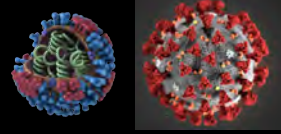
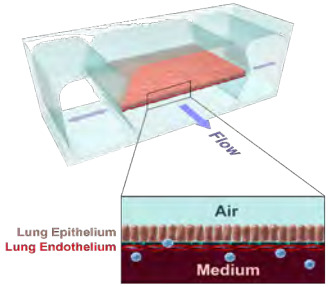
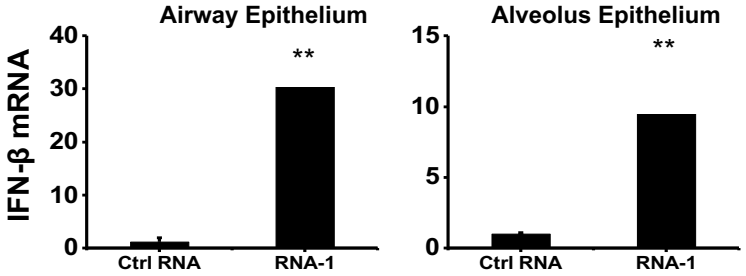
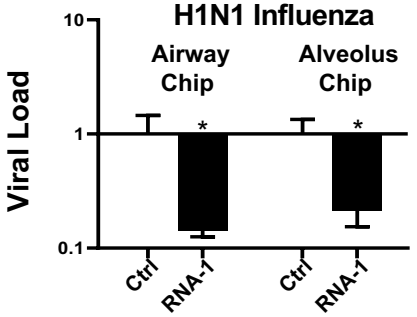


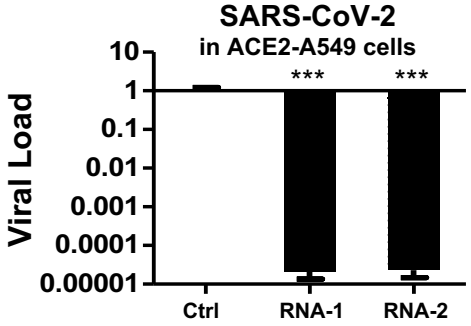
Type I Interferon-Inducing Short Duplex RNAs that Potently Inhibit SARS-CoV-2 Infection

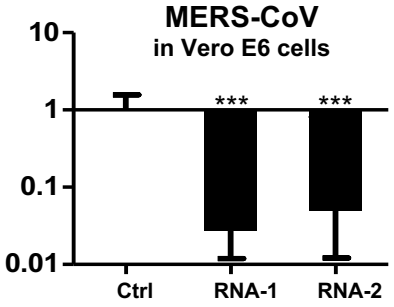
- *Novel immunostimulatory duplex RNAs with unique sequence motif and 5'-monophosphate or 5'-hydroxyl group*
- *BROAD SPECTRUM anti-viral activity*

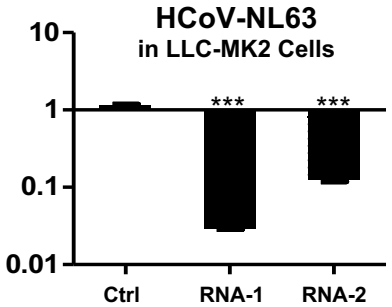


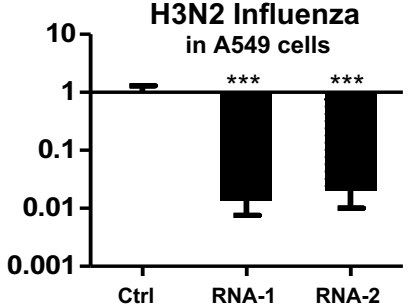












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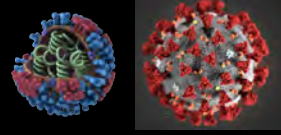
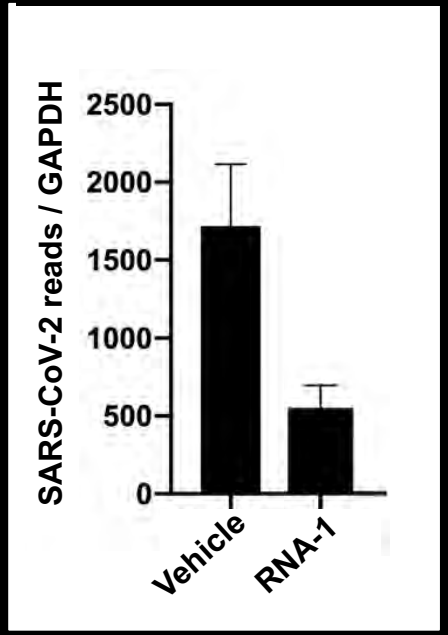
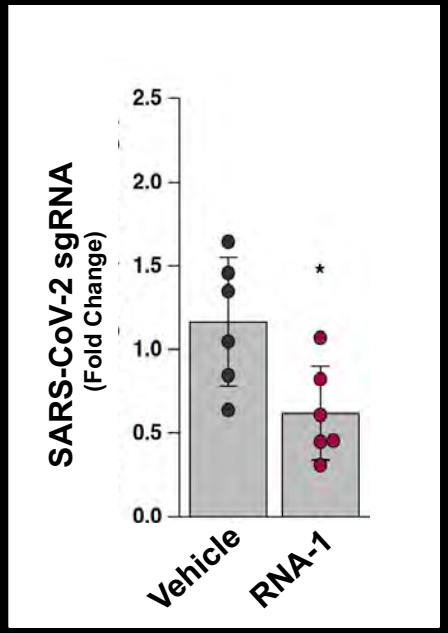


Type I Interferon-Inducing Short Duplex RNAs Inhibit SARS-CoV-2 Infection *In Vivo*

PROPHYLAXIS



TREATMENT



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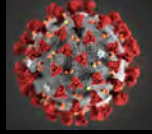
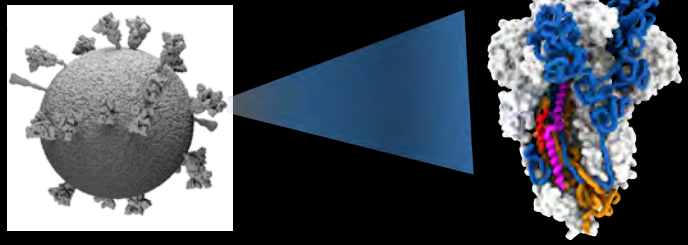
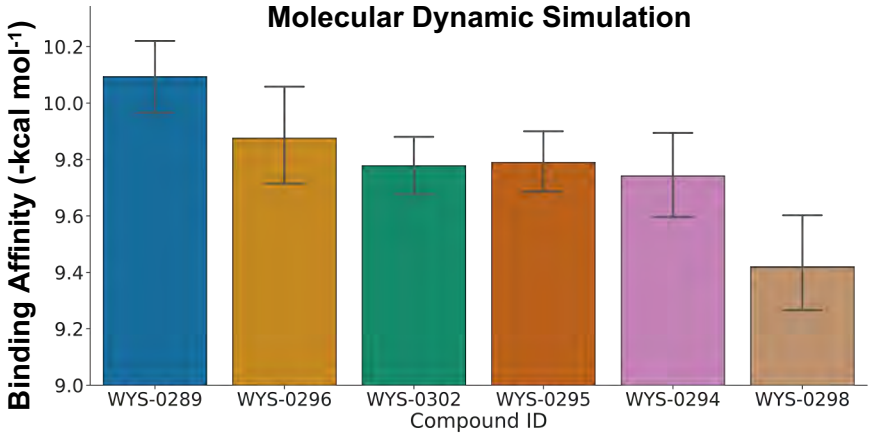
Funded by DARPA & NIH

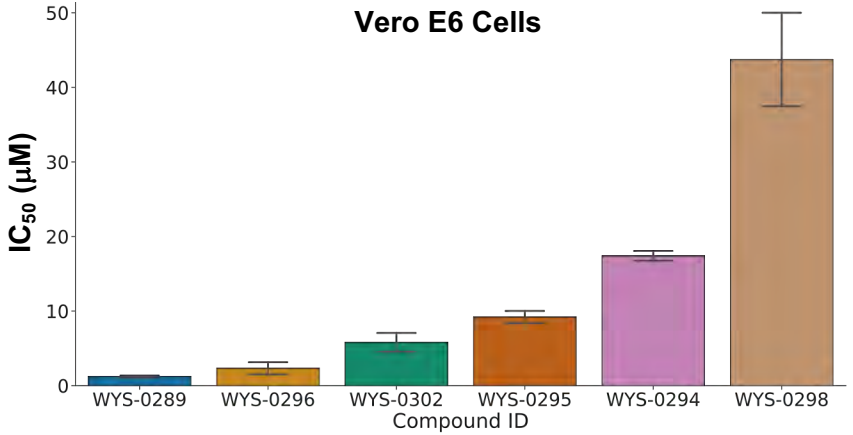


SARS-CoV-2 Drug Discovery and Repurposing by Modeling Viral Fusion Dynamics



Simulated Conformations Using MDS





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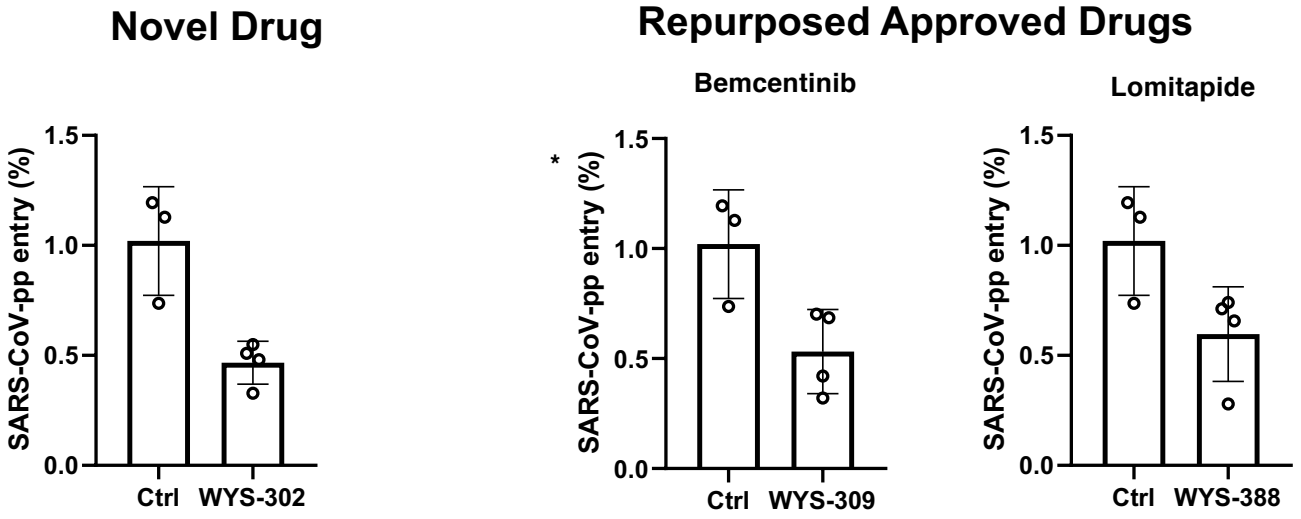
MDS-identified Compounds Inhibit CoV-2pp Infection in Human Lung Airway Chips



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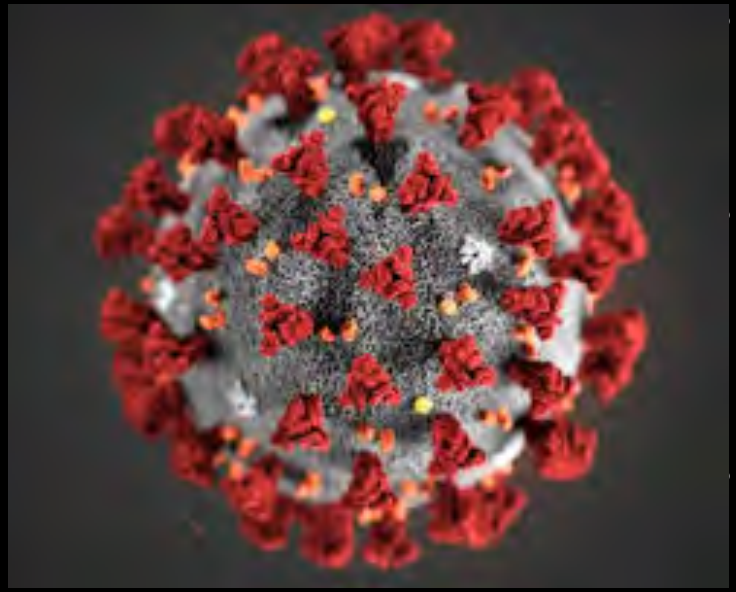
Overall Progress So Far



Screened over 550 compounds in Vero E6 assay

Identified 65 compounds with IC50 < 4 uM and 7 compounds < 100 nM in Vero assay

- Many not yet in clinical trials

88 of the 550 compounds predicted to be active by our Computational Repurposing Algorithms are currently in COVID-19 clinical trials

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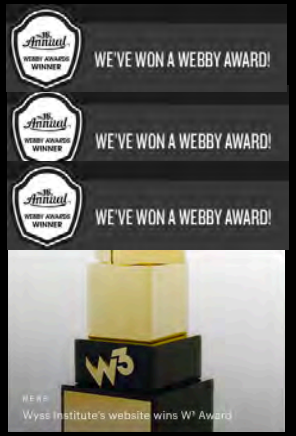
Organ Chips–
- Longlong Si, PhD
- Haiqing Bai, PhD
- Girija Goyal, PhD
- Rachelle Prantil-Baun PhD

Vero E6 Assays –
Lab of Matt Frieman, PhD
(U. Maryland Sch. Medicine)

Hamster Model –

Lab of Ben tenOever, PhD
(Icahn Mt. Sinai Sch. Medicine)



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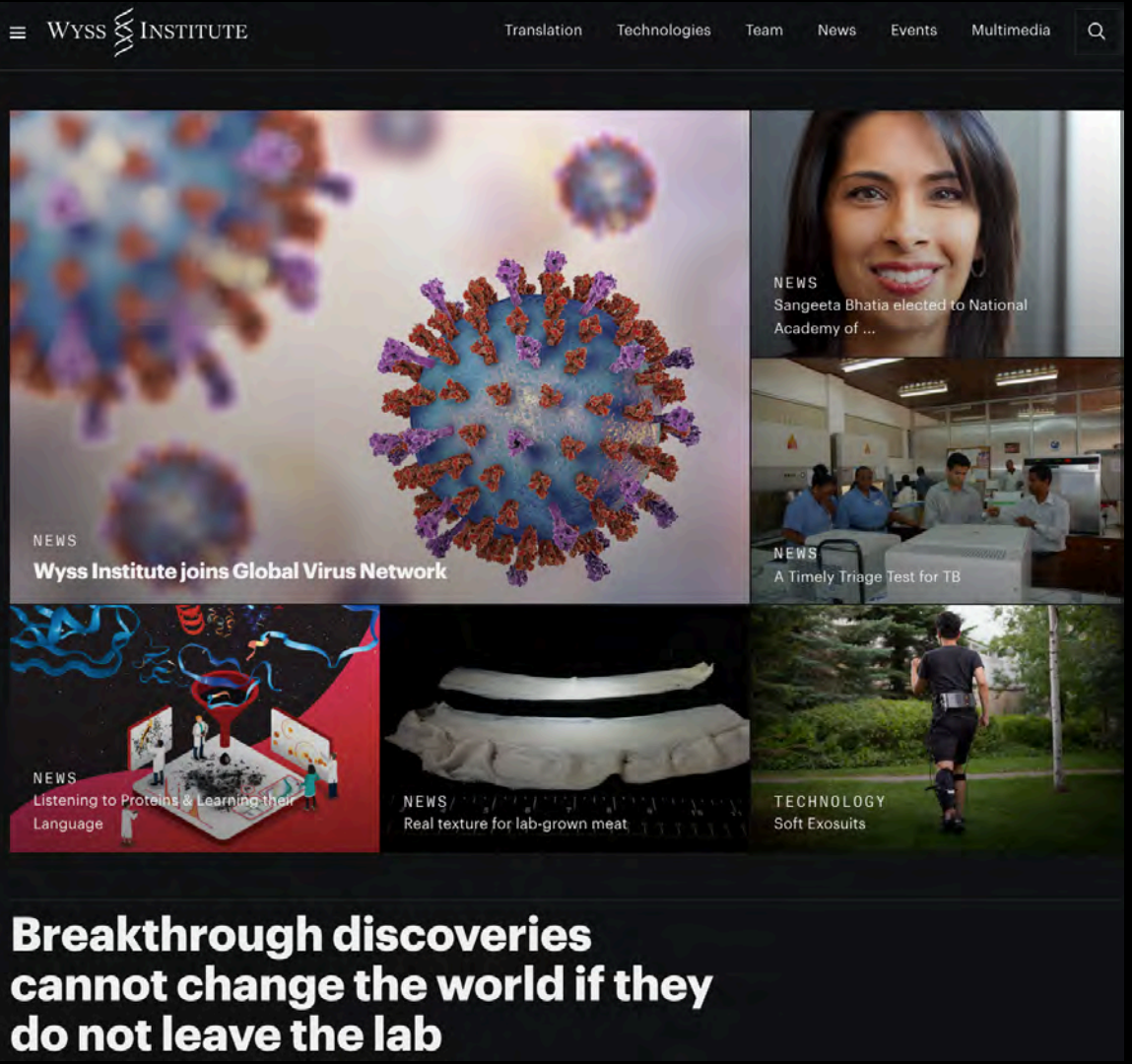


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