

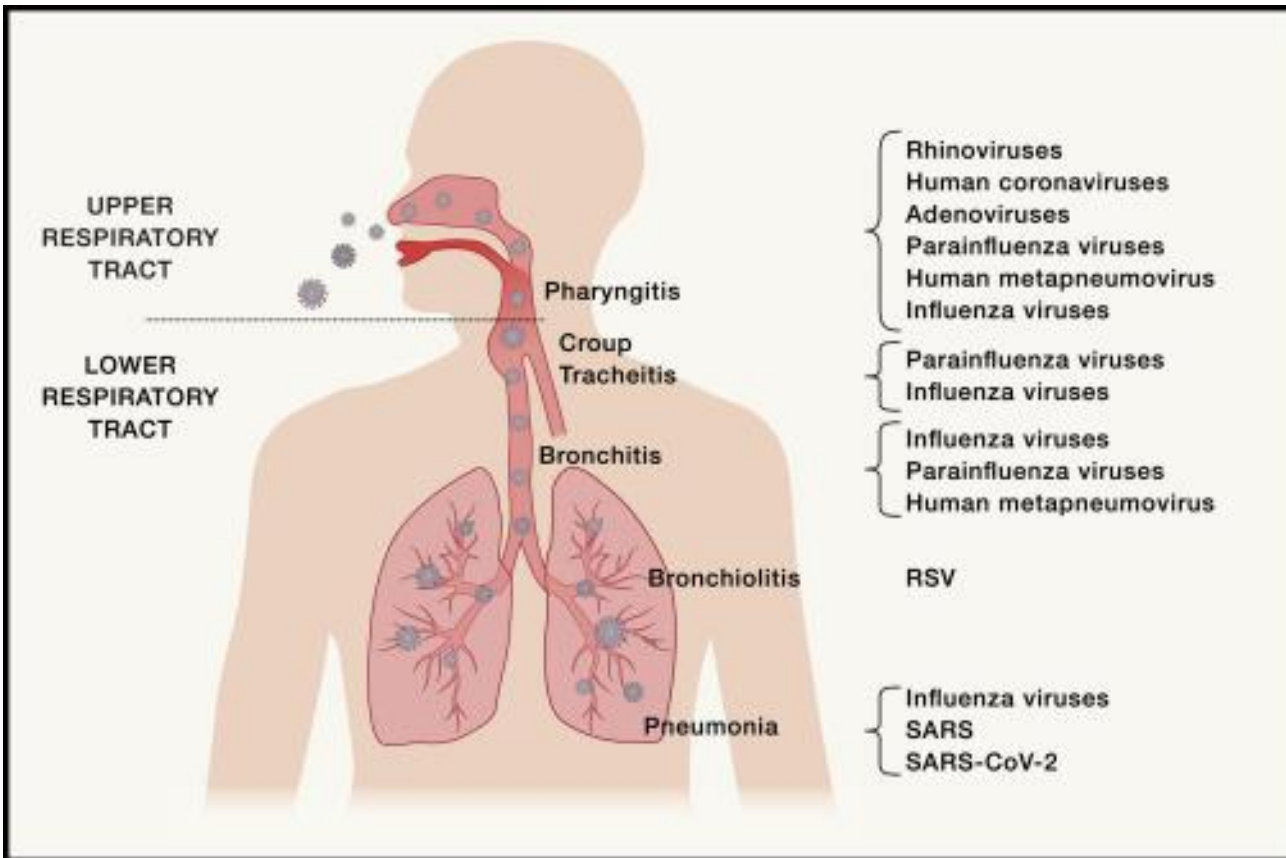
ANTIVIRAL DISCOVERY PIPELINE IN SARS-COV-2

DEVELOPING ANTIVIRALS TO TREAT PERSISTENT INFECTION

SARA CHERRY

JOHN W. ECKMAN PROFESSOR OF MEDICAL SCIENCE
PATHOLOGY AND LABORATORY MEDICINE
SCIENTIFIC DIRECTOR, HIGH-THROUGHPUT SCREENING CORE
DIRECTOR, PROGRAM FOR CHEMOGENOMIC DISCOVERY
LEADER, THERAPEUTICS, INSTITUTE FOR RNA INNOVATION

ACUTE COVID-19



UPPER RESPIRATORY INFECTION

- o HIGH LOADS
- o LOW SYMPTOMS

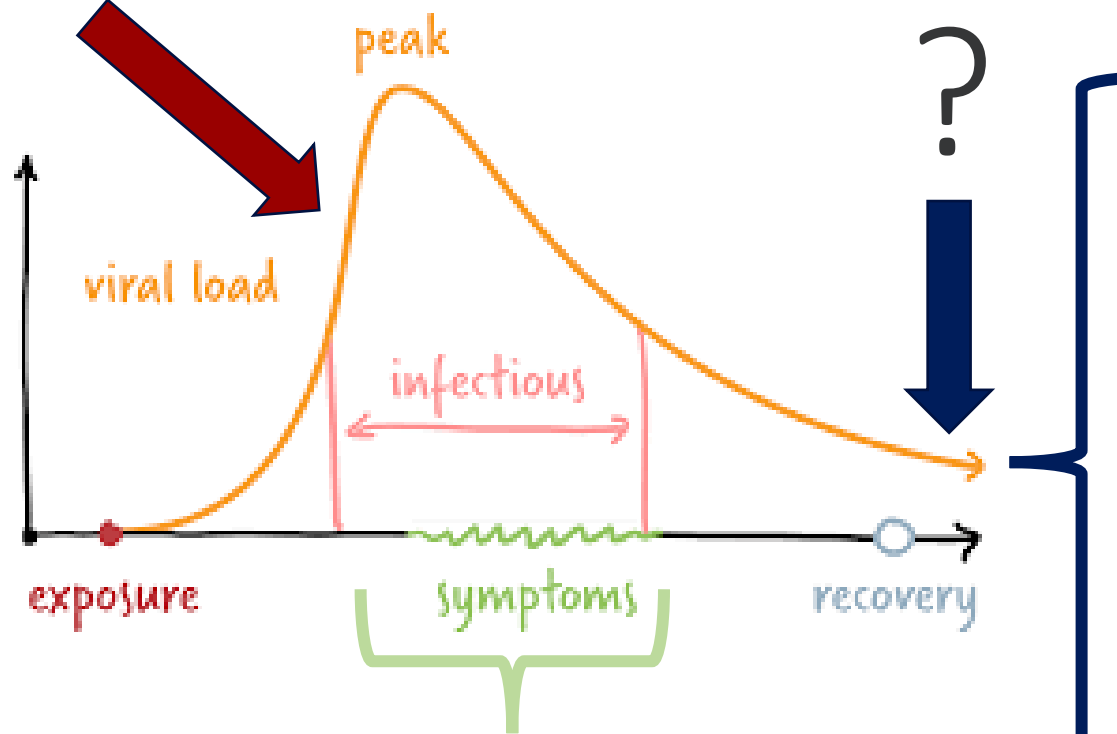
LOWER RESPIRATORY INFECTION

- o MORE SYMPTOMS
- o CAN PROGRESS TO SEVERE

<https://www.sciencedirect.com/science/article/pii/S1074761320302120>

SARS-COV-2 INFECTIONS....

Antivirals



Asymptomatic

Symptomatic Mild

Symptomatic Severe

Health Problems post-COVID

PASC symptoms

Neurologic

- Headache
- Tinnitus
- Loss of smell
- Loss of taste
- Cognitive impairment
- Brain fog
- Memory impairment
- Blurred vision
- Dizziness

Pulmonary

- Shortness of breath
- Cough
- Pulmonary fibrosis
- Dyspnea
- Pulmonary hypertension

Other symptoms

- Kidney disease
- Skin rash
- Hair loss
- Muscle pain
- Joint pain

Psychiatric

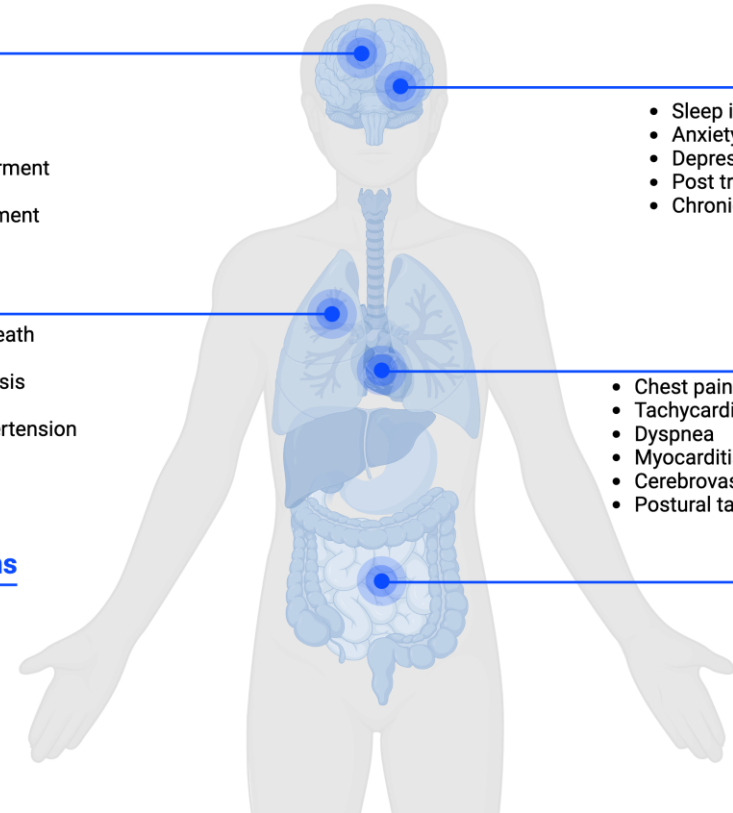
- Sleep issues
- Anxiety
- Depression
- Post traumatic stress disorder
- Chronic fatigue

Cardiac

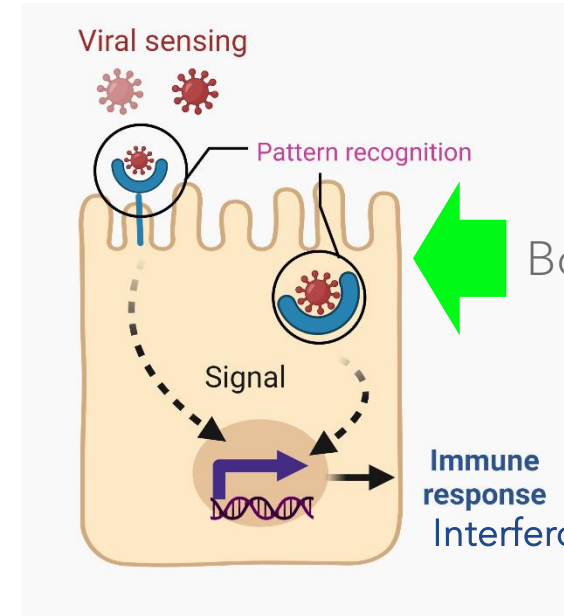
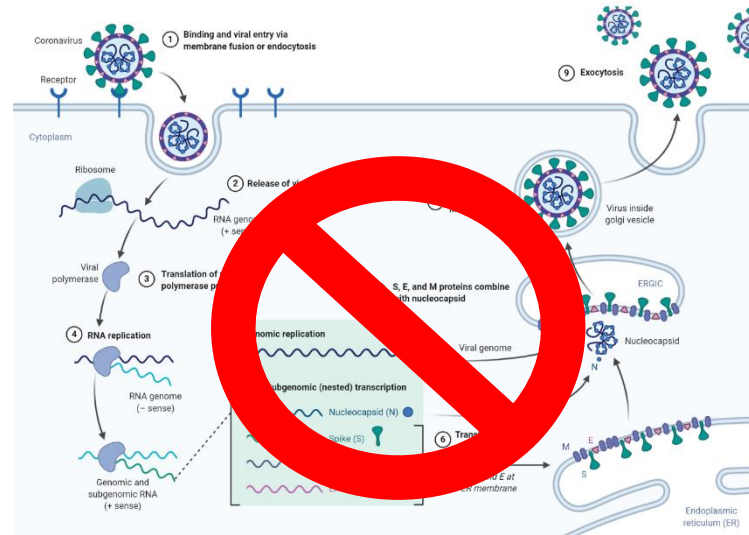
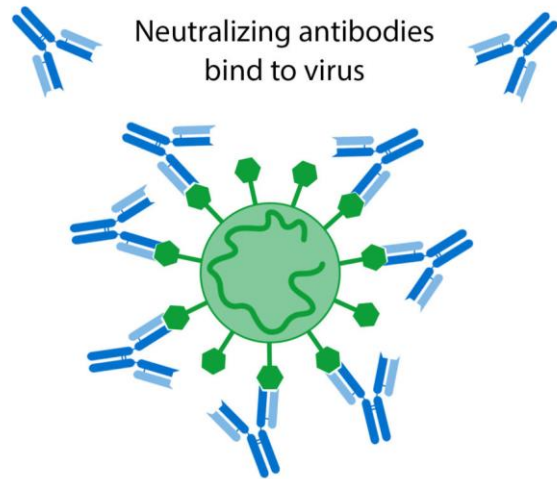
- Chest pain
- Tachycardia & palpitations
- Dyspnea
- Myocarditis
- Cerebrovascular disease
- Postural tachycardia syndrome

Gastrointestinal

- Stomach pain
- Diarrhea & vomiting
- Abdominal pain
- Acid reflux
- Loss of appetite



ANTIVIRALS: COMBATING ACUTE INFECTION



DIRECT ACTING ANTIVIRALS

- o BLOCK VIRUS ITSELF

HOST DIRECTED ANTIVIRALS

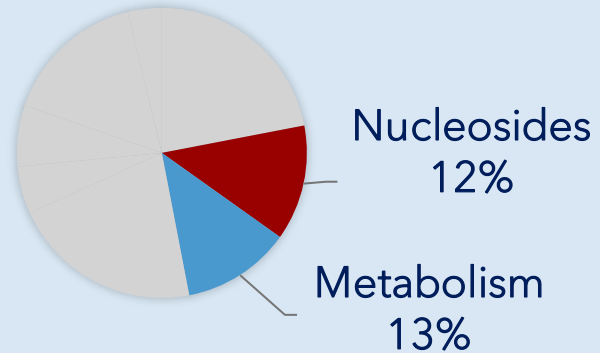
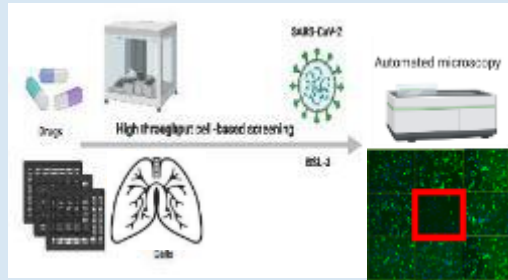
- o TARGET HUMAN PROTEINS

IMMUNOMODULATORS

- o BOOST EARLY IMMUNITY

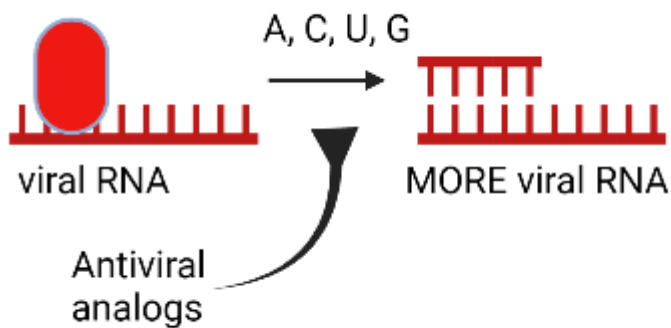
Antivirals

>20,000 DRUGS SCREENED, VALIDATED ~150 DRUGS



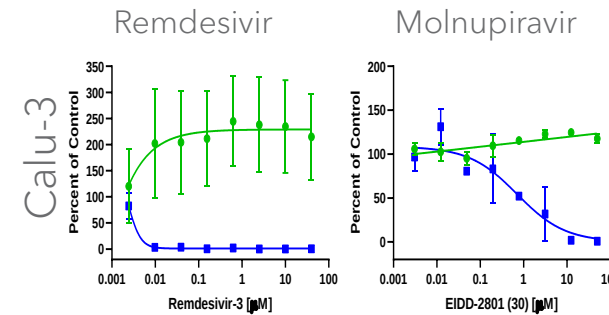
Pyrimidine bio

Purine biosyn

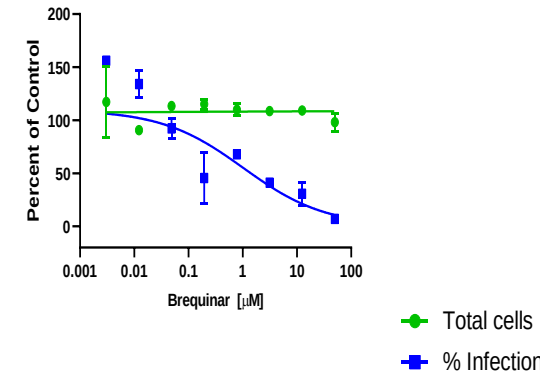


Schultz et al 2022

NUCLEOSIDE ANALOGS



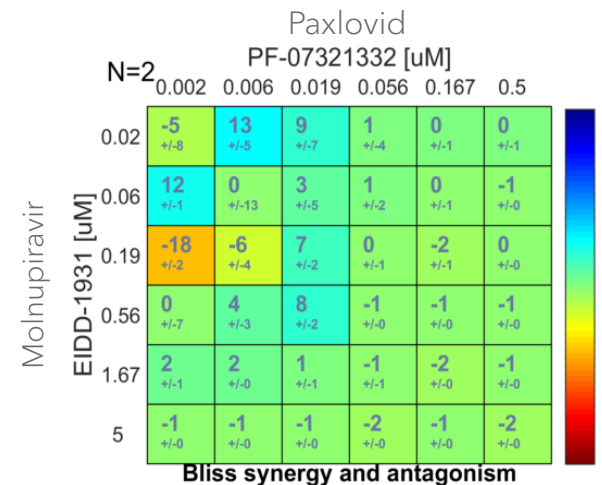
NUCLEOSIDE BIOSYNTHESIS



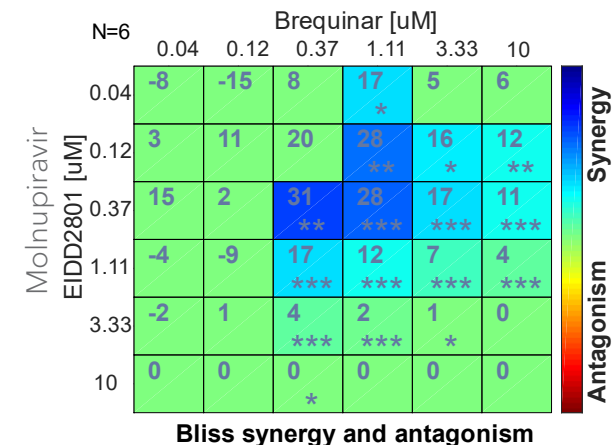
COMBINATION THERAPIES

SYNERGIES: ORAL COMBINATIONS
LOWER DOSES, HIGH BARRIER TO RESISTANCE

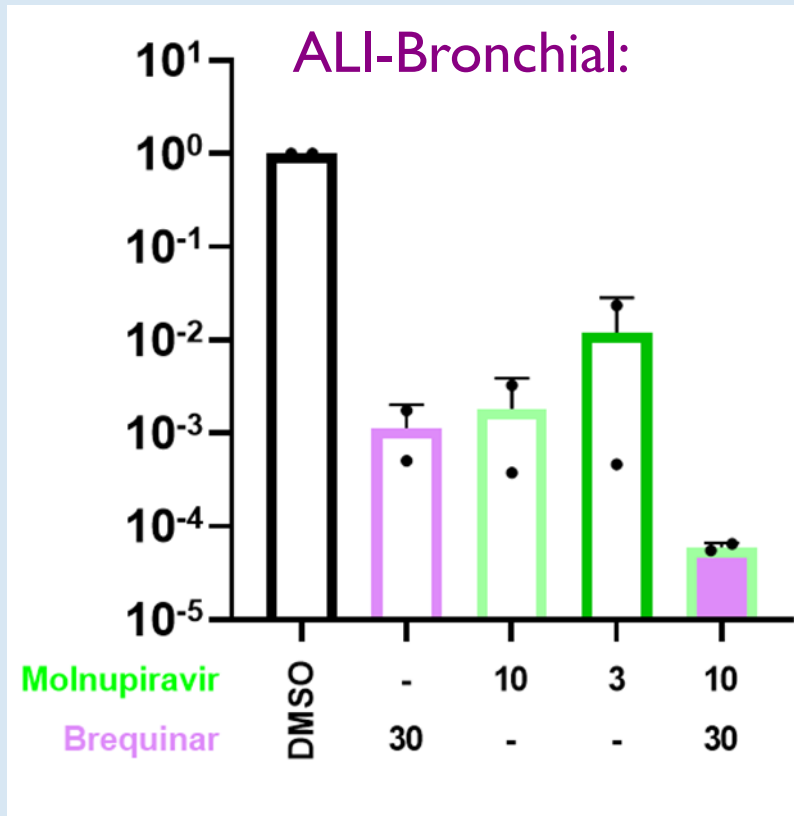
ADDITIVITY



SYNERGY



AIR-LIQUID INTERFACE CULTURES

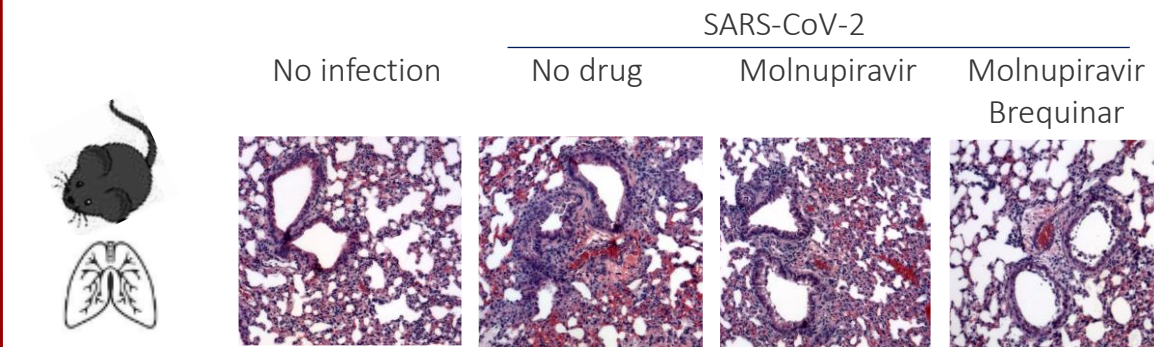
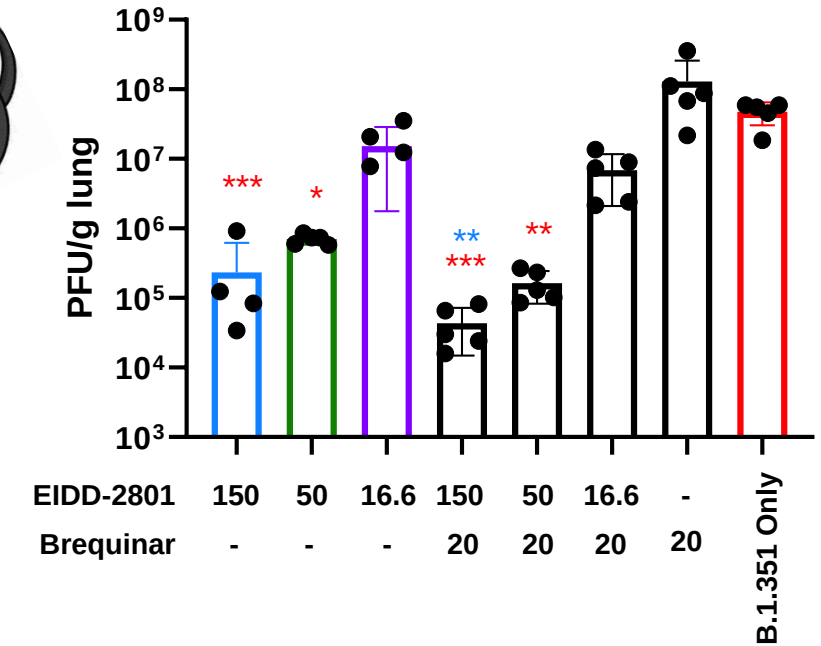
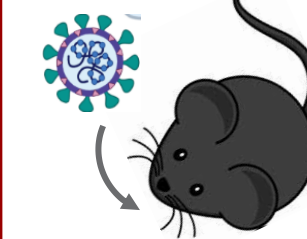


COMBINATION REDUCED TITERS AND INFLAMMATION

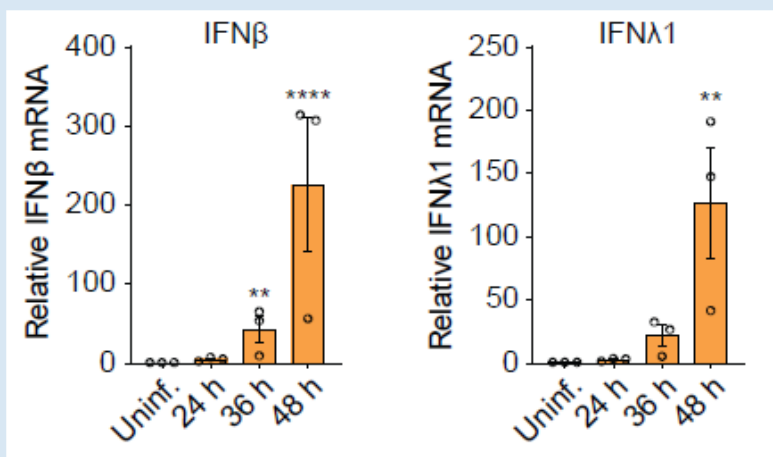
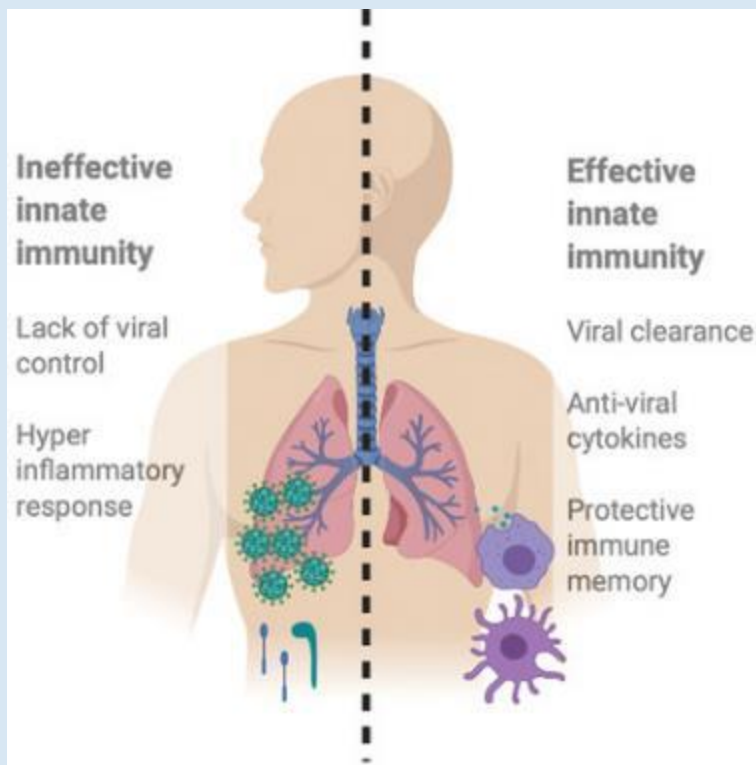
Freiman lab

SARS-CoV-2- South Africa

1e5 PFU/mouse

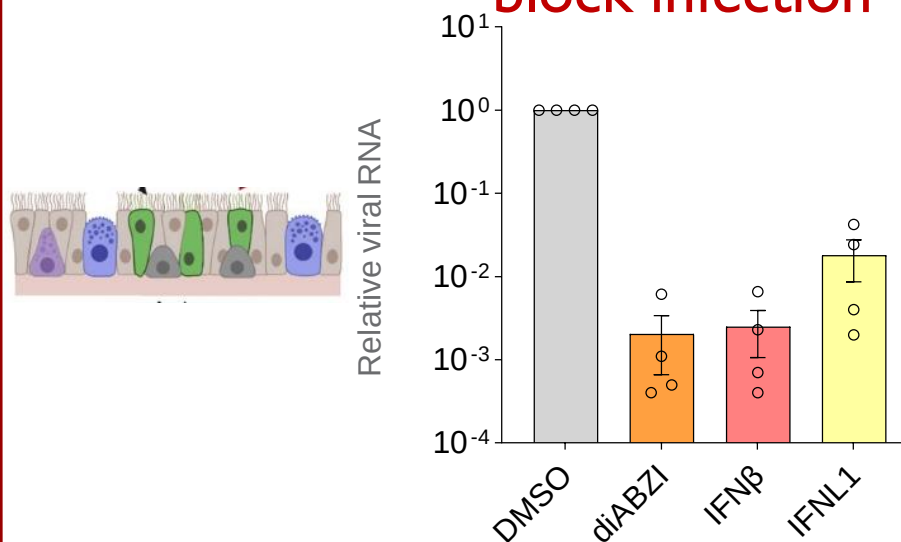


EARLY RESPONSES DELAYED...



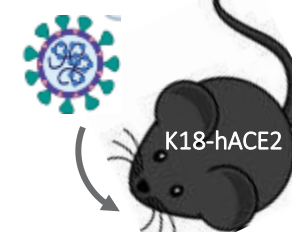
BOOSTING EARLY IMMUNITY BLOCKS INFECTION

Interferons and STING agonists can block infection



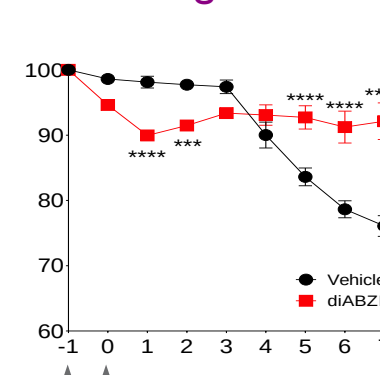
SARS-CoV-2- WA1

1e4 PFU/mouse

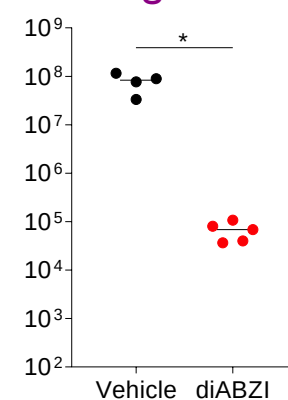


Diamond lab

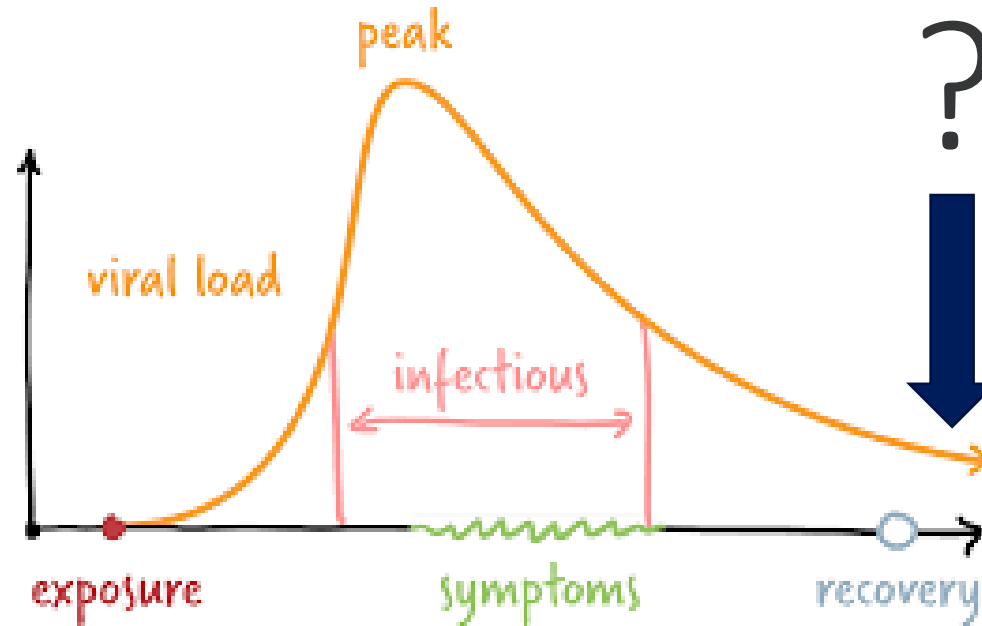
Weight loss



Lung infections



SARS-COV-2 INFECTIONS...LONG COVID



?



PASC symptoms

Neurologic

- Headache
- Tinnitus
- Loss of smell
- Loss of taste
- Cognitive impairment
- Brain fog
- Memory impairment
- Blurred vision
- Dizziness

Pulmonary

- Shortness of breath
- Cough
- Pulmonary fibrosis
- Dyspnea
- Pulmonary hypertension

Other symptoms

- Kidney disease
- Skin rash
- Hair loss
- Muscle pain
- Joint pain

Psychiatric

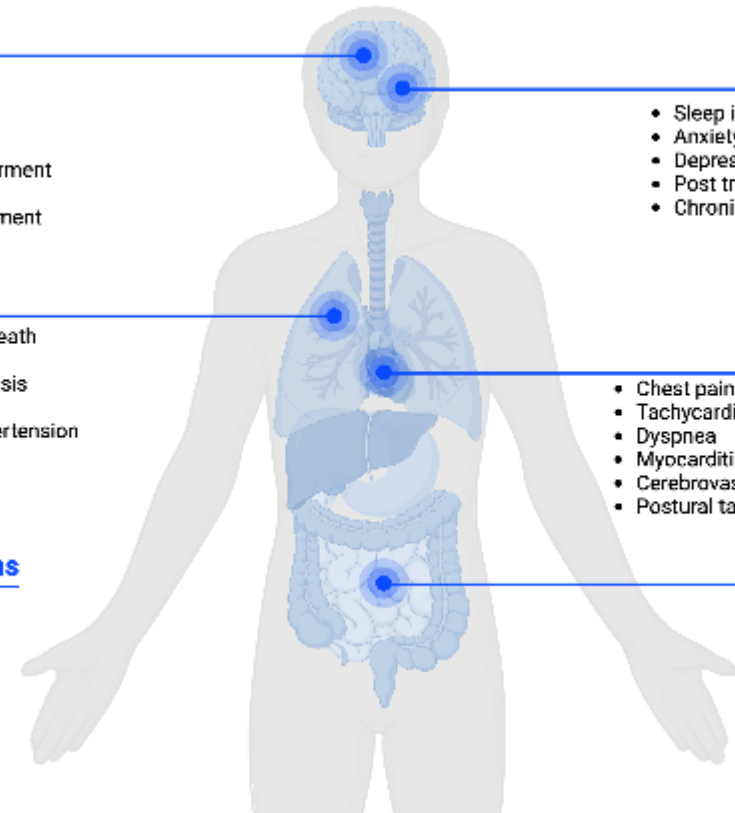
- Sleep issues
- Anxiety
- Depression
- Post traumatic stress disorder
- Chronic fatigue

Cardiac

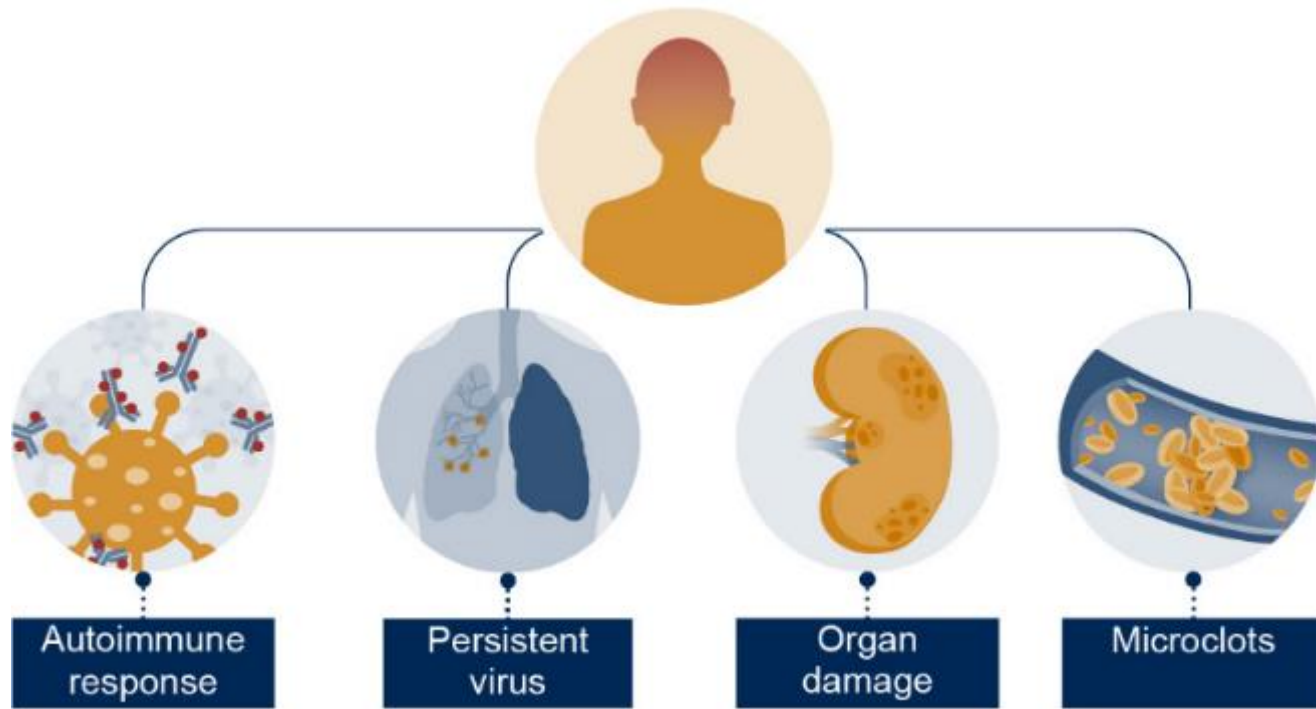
- Chest pain
- Tachycardia & palpitations
- Dyspnea
- Myocarditis
- Cerebrovascular disease
- Postural tachycardia syndrome

Gastrointestinal

- Stomach pain
- Diarrhea & vomiting
- Abdominal pain
- Acid reflux
- Loss of appetite



WHAT DRIVES CHRONIC SYMPTOMS?



Source: GAO analysis of medical literature. | GAO-22-105666

IS THERE VIRAL ANTIGEN?

◦WHERE?

HOW IS INFECTION SIMILAR OR DIFFERENT FROM RESPIRATORY TRACT?

◦SENSITIVITIES TO THERAPEUTICS

◦IMMUNE RESPONSES

GASTROINTESTINAL TRACT?

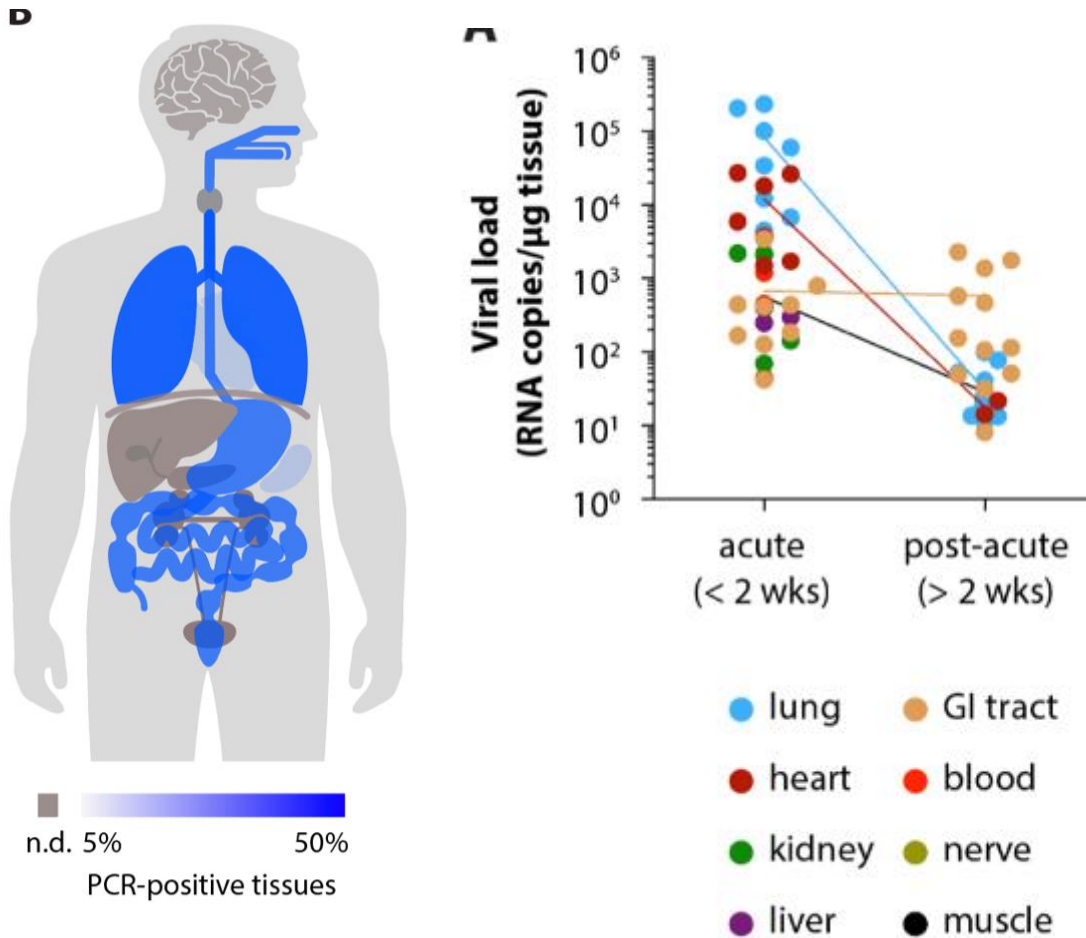
◦HIGH SHEDDING (SEWAGE)

◦BIOPSIES

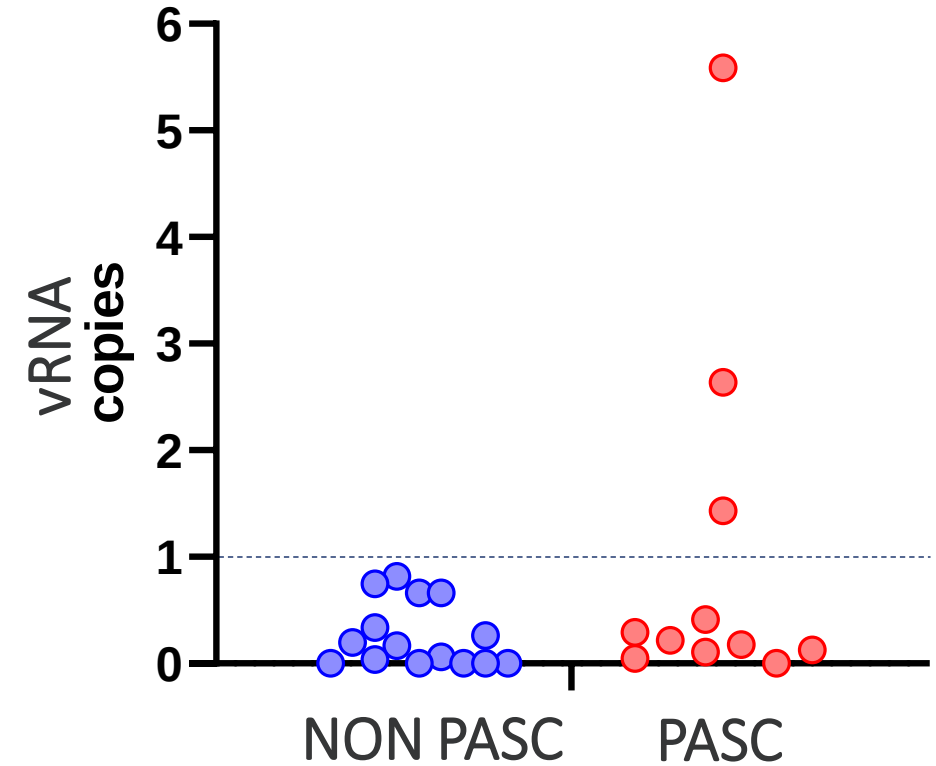
◦AUTOPSIES

PASC: IS THE GUT A VIRAL RESERVOIR?

AUTOPSIES AT PENN



STOOL SAMPLES OUR LONG COVID COHORT



SARS-COV-2 AND GASTROINTESTINAL TRACT

MODELING INFECTION

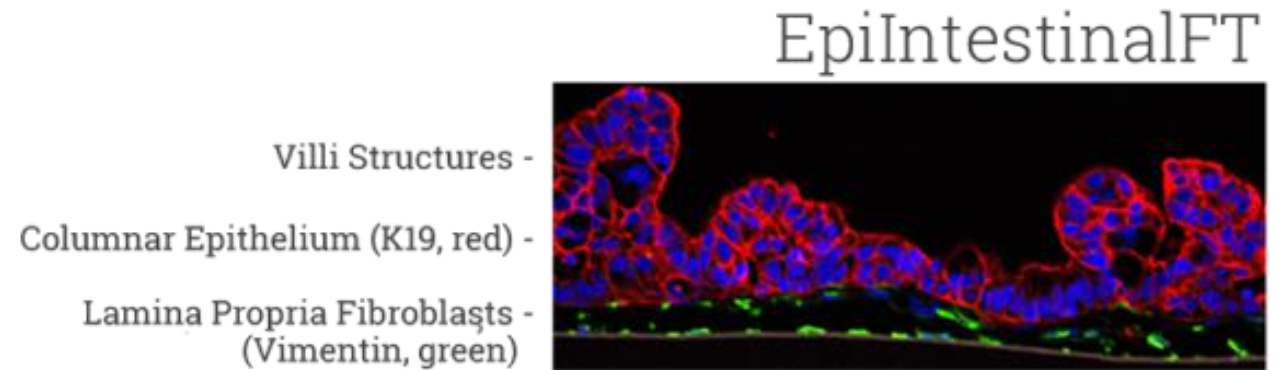
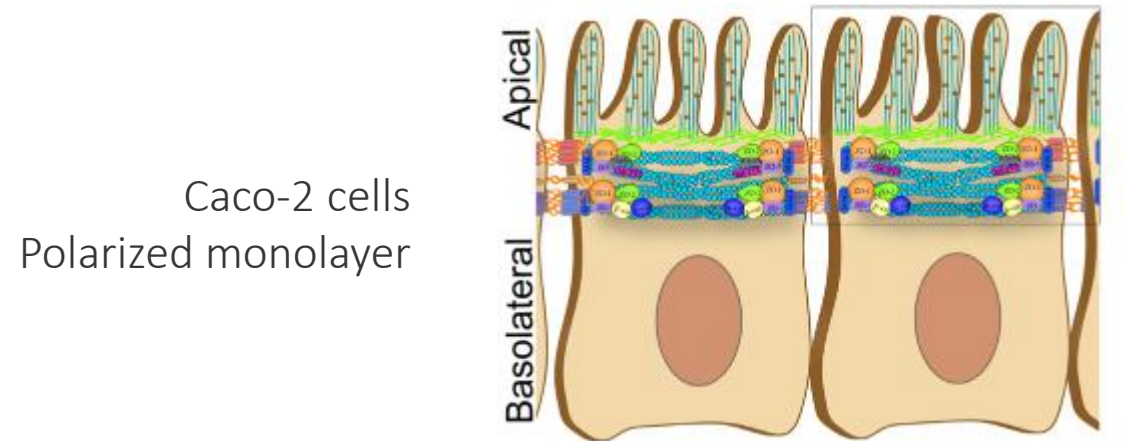
- CULTURED CELLS
- ORGANOID MODELS

ANTIVIRALS ACTIVE?

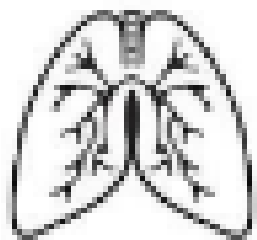
- KNOWN AND IN TRIALS
- AGAINST VARIANTS?

RESPONSES TO INFECTION?

- PERSISTENT?
- INNATE IMMUNE ROLE

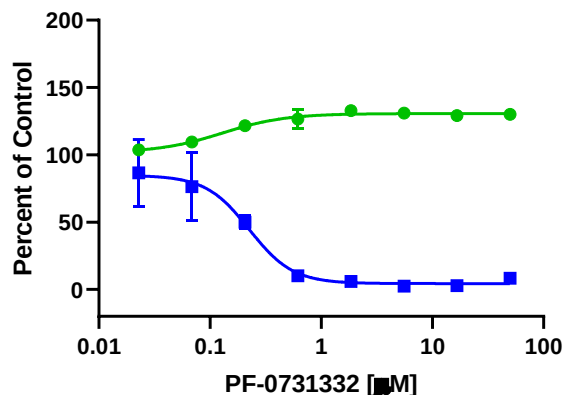


ARE THERE DIFFERENCES IN ANTIVIRAL ACTIVITY?

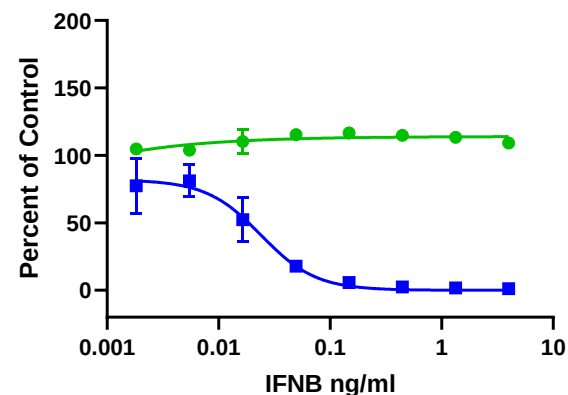


CALU-3

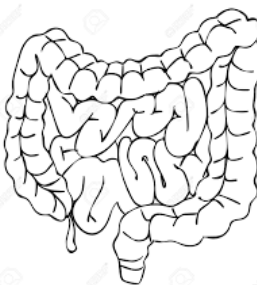
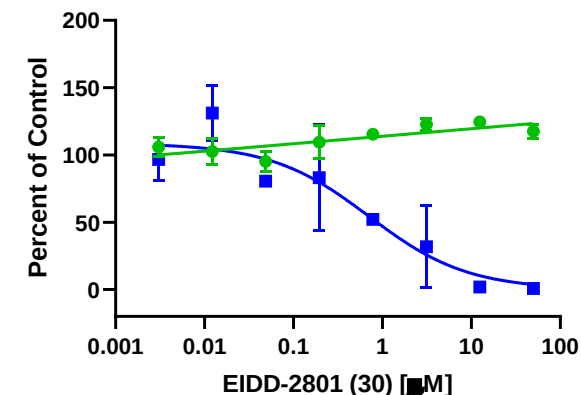
Paxlovid



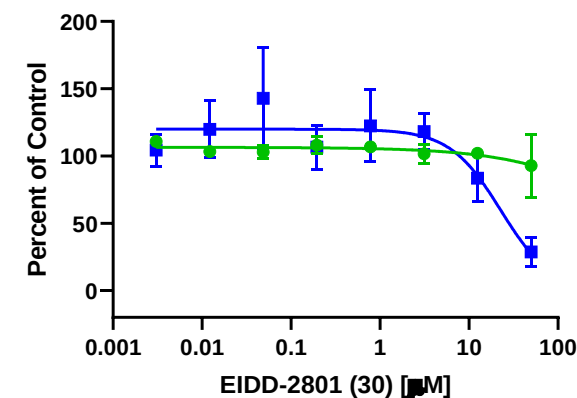
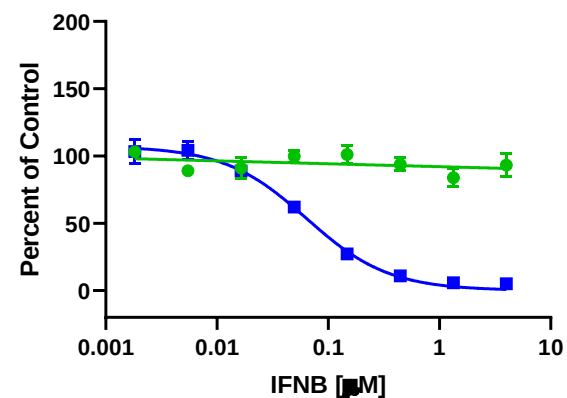
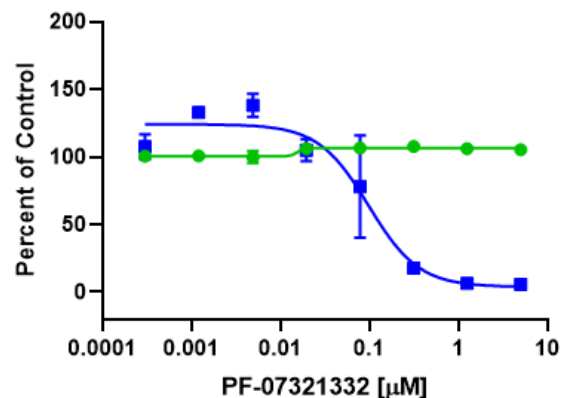
Interferon β



Molnupiravir

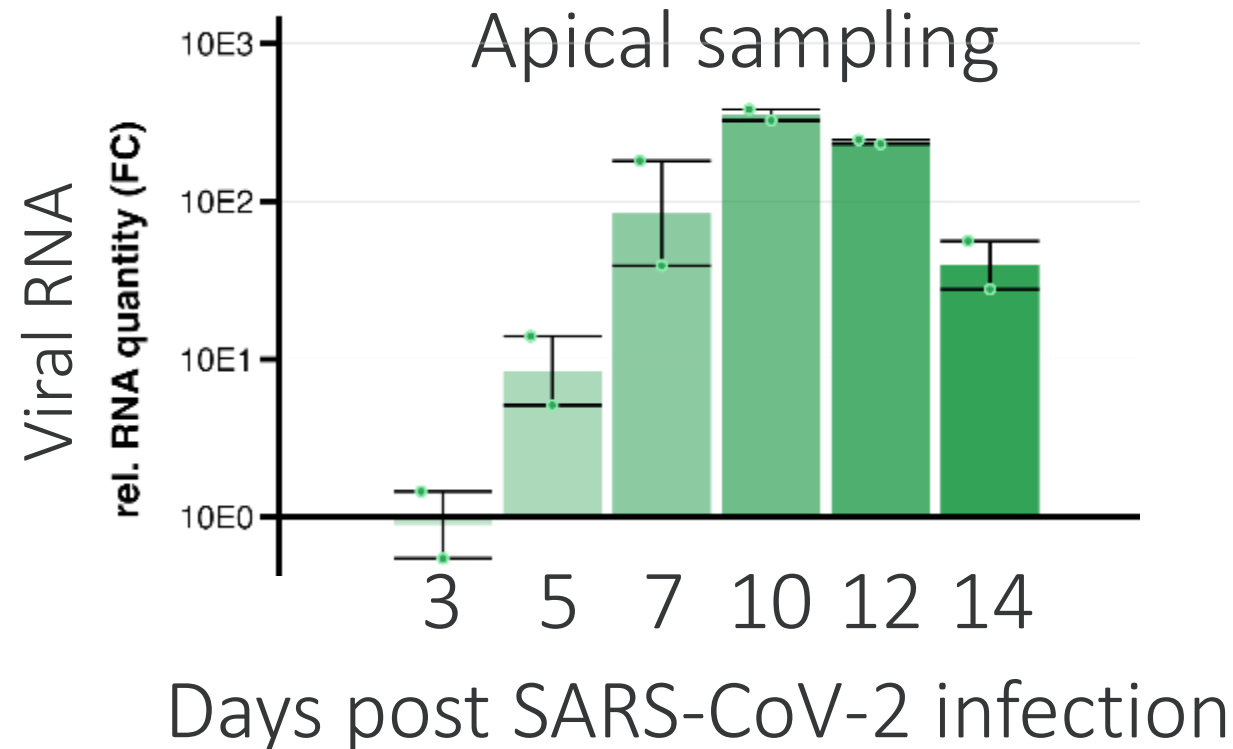
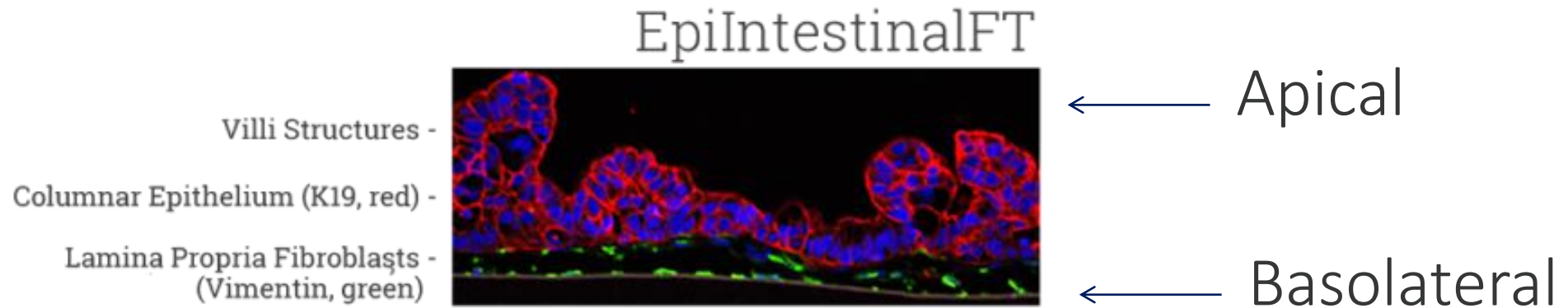


CACO-2



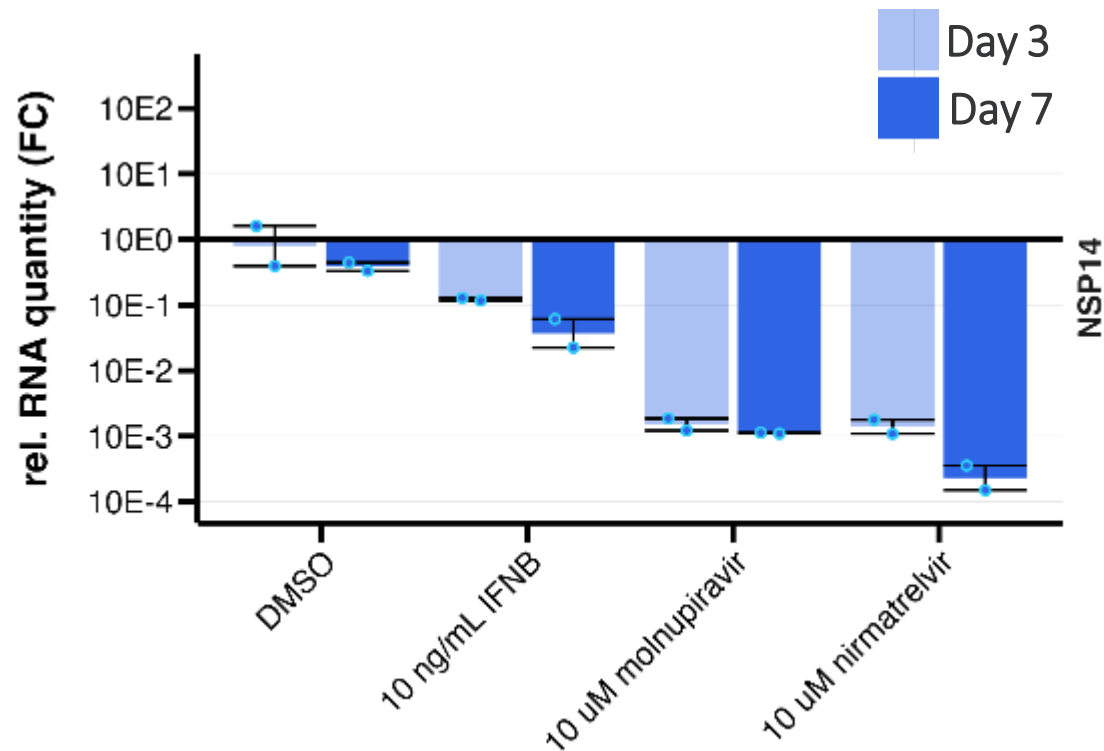
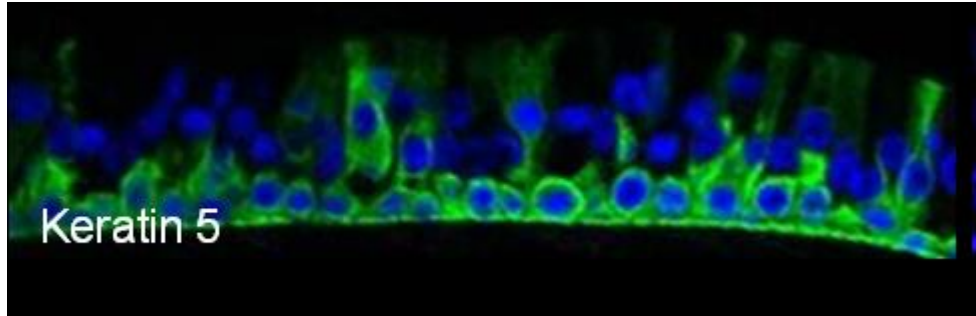
- Total cells
- % Infection

WE CAN MODEL INFECTION IN 3D CULTURES

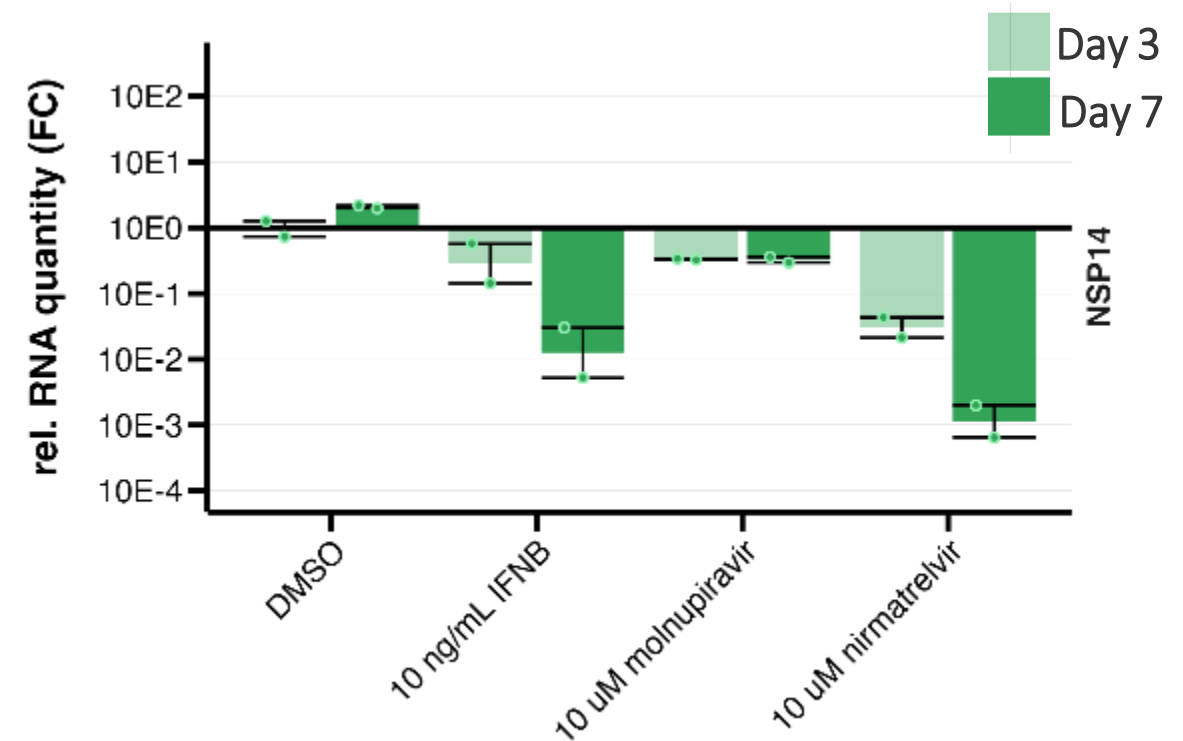
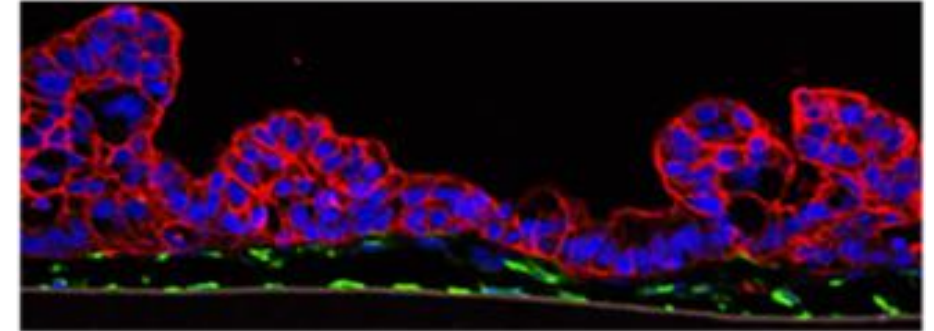


WE SEE DIFFERENT SENSITIVITIES

BRONCHIAL CULTURES

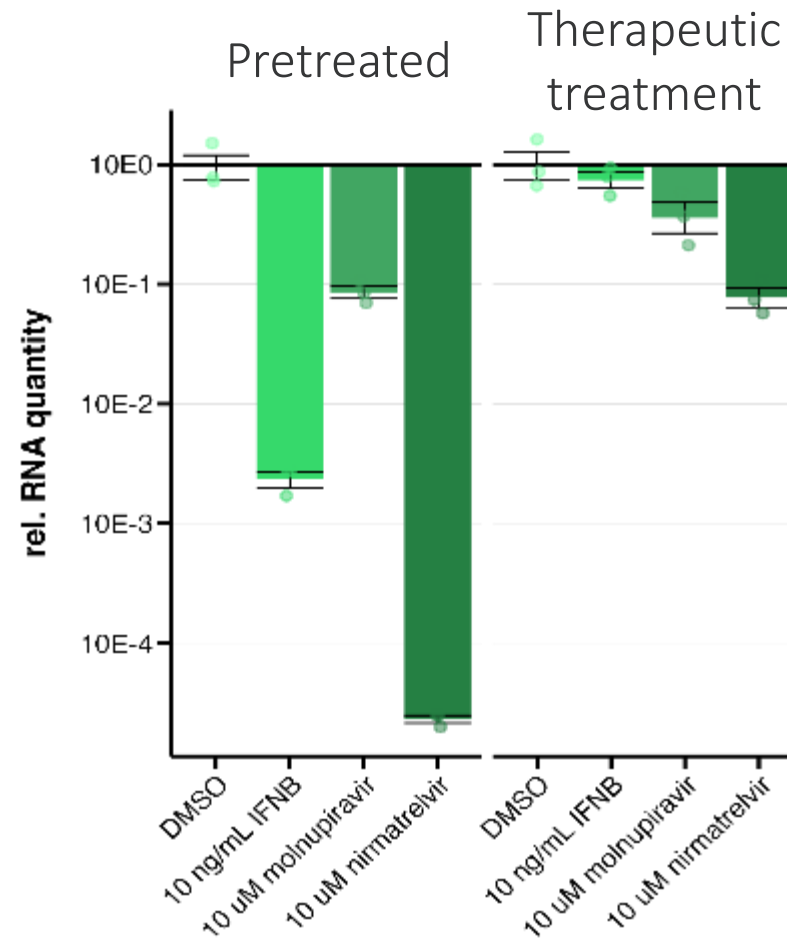


INTESTINAL CULTURES



CAN WE DETERMINE EFFECTIVE TREATMENT SCHEDULE

ADMINISTERED SINGLE DOSE....



PASC AND THE GASTROINTESTINAL TRACT

IS THE GI TRACT A RESERVIROR?

- FOR WHICH PATIENTS?
- WHERE IS THE VIRUS?
- IS IT REPLICATING?

ANTIVIRALS ACTIVE IN GI?

- WHICH ANTIVIRALS MOST ACTIVE
- HOW LONG TO TREAT?
- WHAT COMBINATIONS

RESPONSES TO INFECTION?

- WHAT ARE THE CELLULAR RESPONSES?
- CAN WE REDIRECT?

ACKNOWLEDGEMENTS

Cherry Lab:

Benjamin Gabriel
Jesse Hulahan
Alex Huber
Max Ferretti
Kasirajan Ayyanathan
Mark Dittmar
Trevor Greisman
Iulia Tapescu
Rachel Braun
Jorge Acuna
Kaeri Martinez
Tamanna Srivastava
Jae Seung Lee
Zienab Etwebi
Steven Miller
Priyanka Bhakt
Jesse Miller
Beth Gold
Swechha Pokherel
Megha Basavappa*
Minghua Li*

HTS Core:

David Schultz
Kanuypriya Whig
David Nguyen
Emilia Roberts
Christina Freeman
Hongzhuang Peng
Yongqing Zhu

NCATS/NIH  National Center
for Advancing
Translational Sciences

Marc Ferrer, Emily Lee
J. Shrimp, M. Hall

Medicines for Malaria Venture
Kirandeep Samby, Timothy Wells

Gates Foundation

Monalisa Chatterji, Rob Jordan, Ken Duncan

Calibr  Calibr

Biorender

Animal Studies:

Michael Diamond (Wash U)
Matthew Frieman (UMD)
Kellie Jurado

PATH Lab:

Micheal Feldman
Kathleen Montone

NIAID/NIH  National Institute of
Allergy and
Infectious Diseases

Ann Eakin, Mindy Davis

MMV 
Medicines for Malaria Venture

BILL & MELINDA
GATES foundation

Collaborations:

Christoph Thaiss
Maayan Levy
Benjamin Abramoff
Kristen Lynch

Cell Models:

MatTek, Epithelix,, iPSC Core

Metabolomics:

Chris Petucci, WISTAR

 POLYBIOLAB

Funding:

NIH, Gates Foundation, BWF. Mercatus
Fast Grant, Linda and Laddie
Montague, Deans Innovation Fund,
Penn Center for Precision Medicine,
PolyBio Research