EMPOWERING PATIENTS THROUGH
KINOME INNOVATION

ATI-450: A Potential Treatment for Patients with COVID-19

ATI-450, an investigational oral MK2 inhibitor

June 17, 2020

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ATI-450: Potential Treatment for COVID-19-Induced Cytokine Storm

Inhibition of Multiple Pro-inflammatory Cytokines

- Mortality in COVID-19 disease is driven, in large part, by cytokine release syndrome (CRS), resulting in acute respiratory distress syndrome (ARDS)[1,2]
- CRS is characterized by elevated levels of cytokines and chemokines such as: IFNγ, IL-1Ra, IL-1β, IL-2, IL-6, IL-10, IL-18, MCP-1, MCP-3, M-CSF, G-CSF, GM-CSF, IL-8, TNFα, MIP1α, and IP-10[1]
- Biologics targeting IL-6 have demonstrated signs of efficacy in treating COVID-19.[3] Biologics that target **individual** cytokines such as GM-CSF, IL-1, IL-6 and IL-8 are currently in clinical studies[4,5,6,7]
- ATI-450 blocks multiple relevant cytokines such as TNFα, IL-1β, IL-2, IL-6, IFNγ, GM-CSF, IL-8 and MIP1α*

* Data on file

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MK2 Pathway Regulates Key Cytokines Involved in COVID-19-Induced Cytokine Release Syndrome

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The MK2 Pathway is Activated by Coronaviruses

TLR activation, unfolded protein stress response, ER stress response

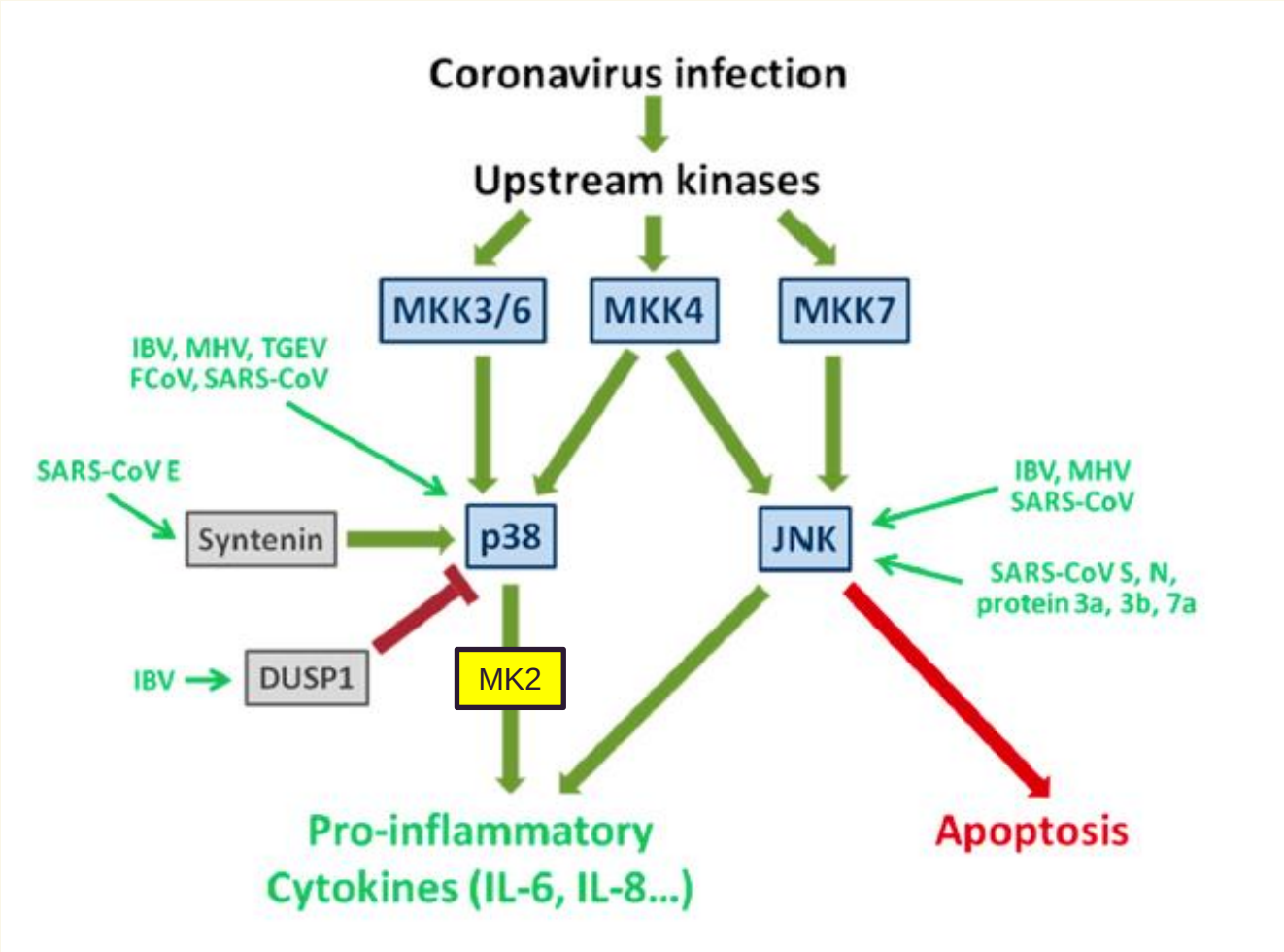

Image Adapted[8]

IBV: infectious bronchitis virus

MHV: murine hepatitis virus

TGEV: transmissible gastroenteritis coronavirus

FCoV: feline coronavirus

SARS-CoV: severe acute respiratory syndrome coronavirus

TLR = Toll-like receptor
ER = Endoplasmic reticulum

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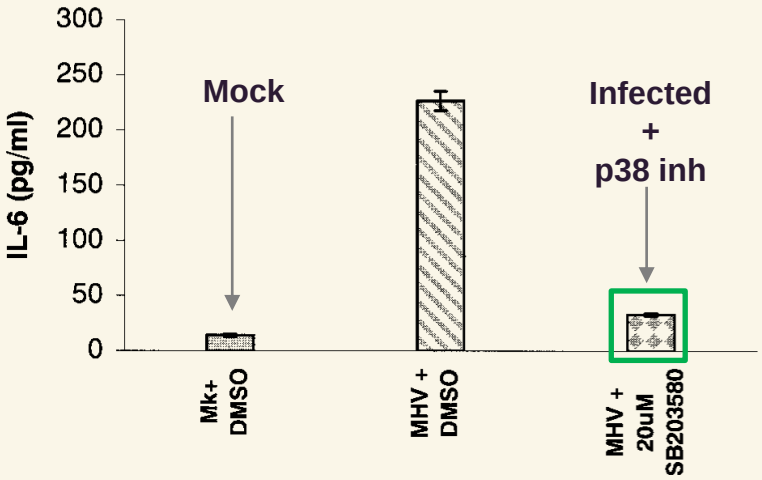
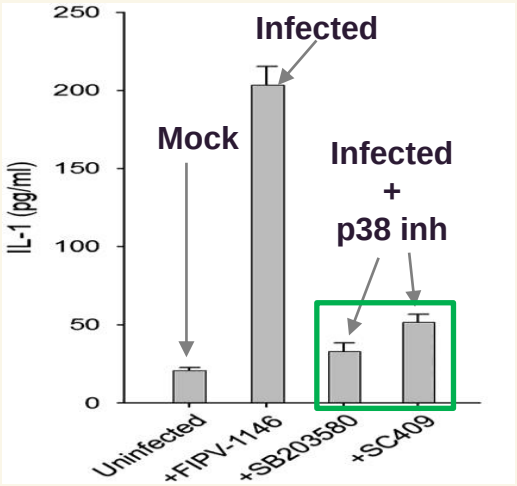
In Vitro: The MK2 Pathway Drives Coronavirus-Induced Cytokines
MK2 is a required p38MAPK substrate that drives cytokine production

p38MAPK/MK2 inhibition reduces IL-6 production in MHV infected cells[9]



p38MAPK/MK2 inhibition reduces TNFα and IL-1β production in FIPV infected cells[10]



- IL-6 and IL-8 induction are dependent on the p38MAPK/MK2 pathway in IBV infected cells[11]

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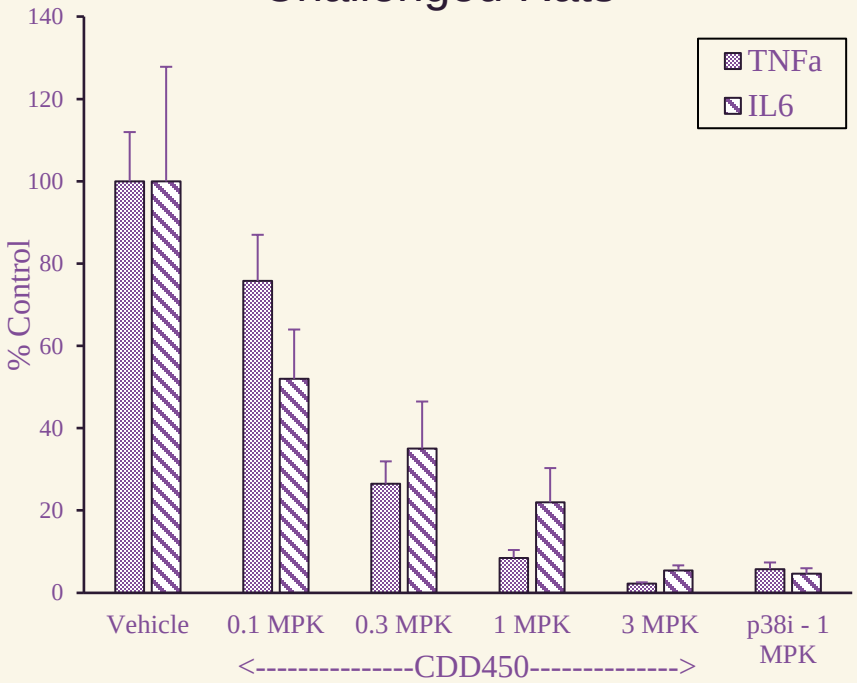
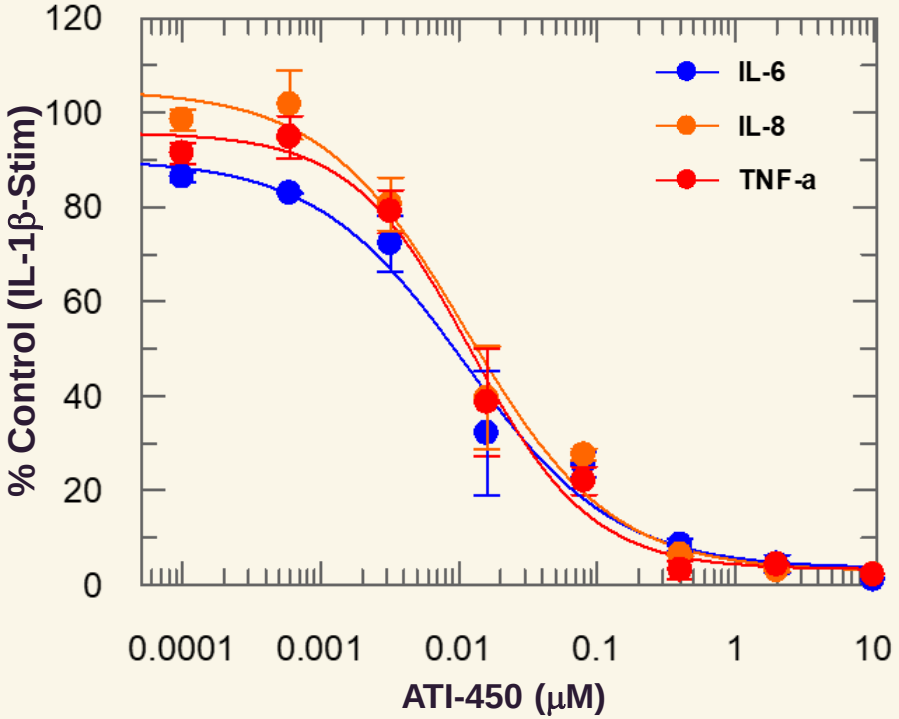
ATI-450 Inhibited TNFα and IL-6 Production *In Vivo* and *In Vitro*

Comparable potency against both cytokines

Lipopolysaccharide (LPS) Challenged Rats



IL-1β-Stimulated Human Whole Blood (HWB)



* Data on file

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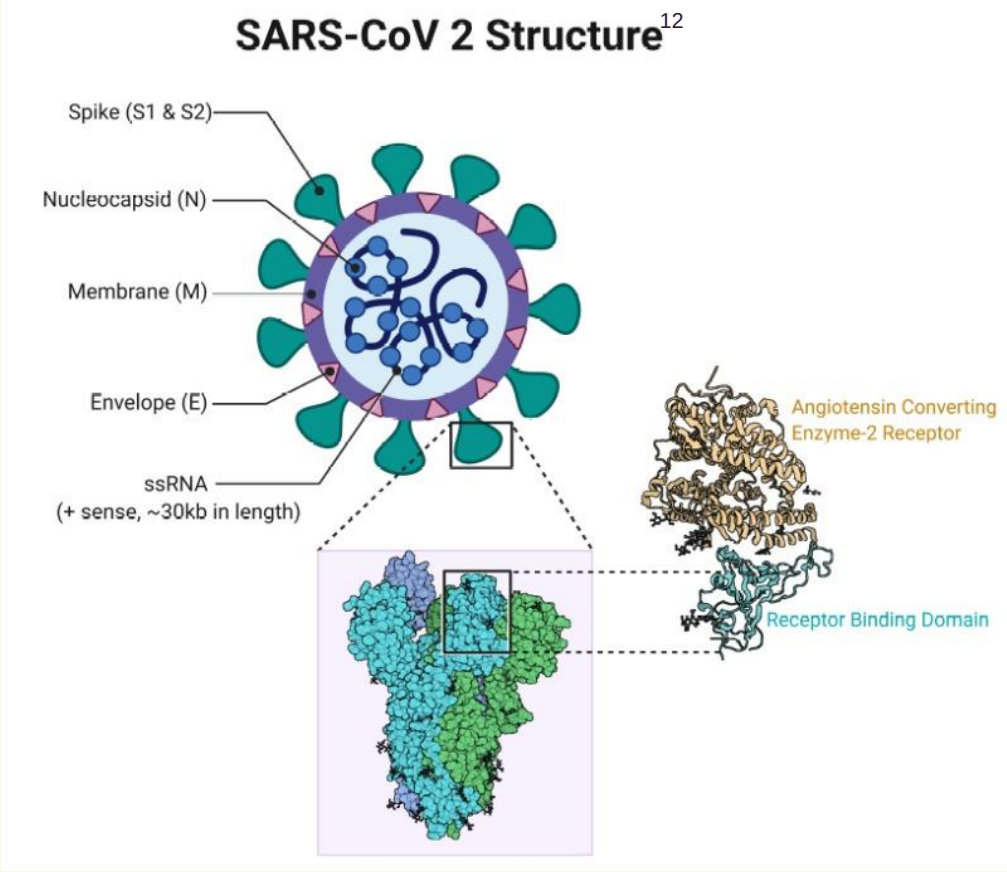
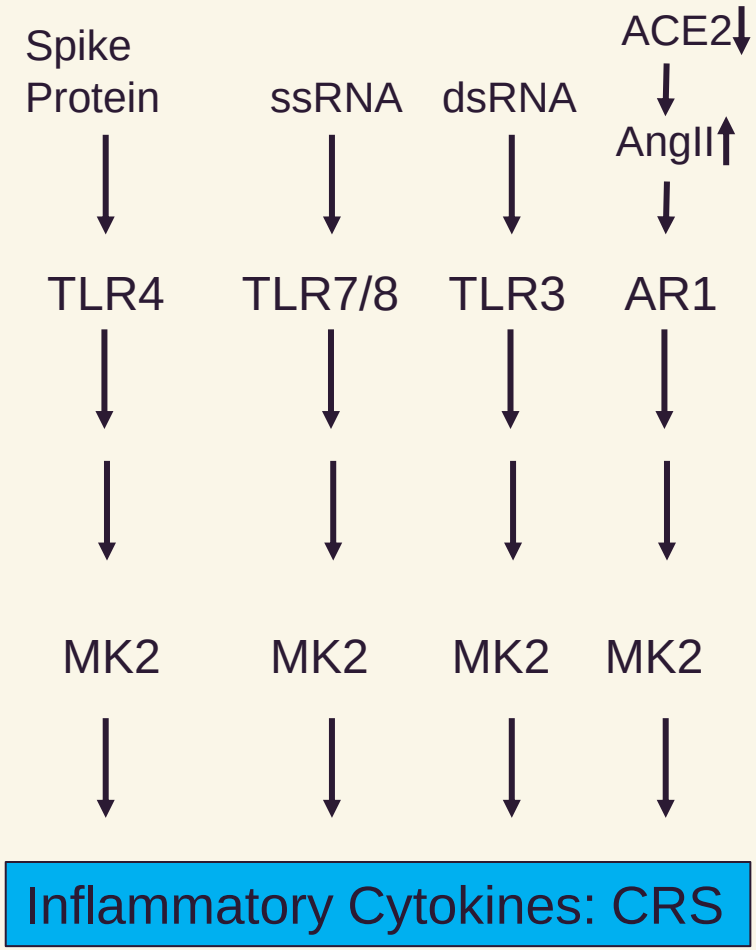
SARS-CoV-2-Induced CRS Signals Through MK2





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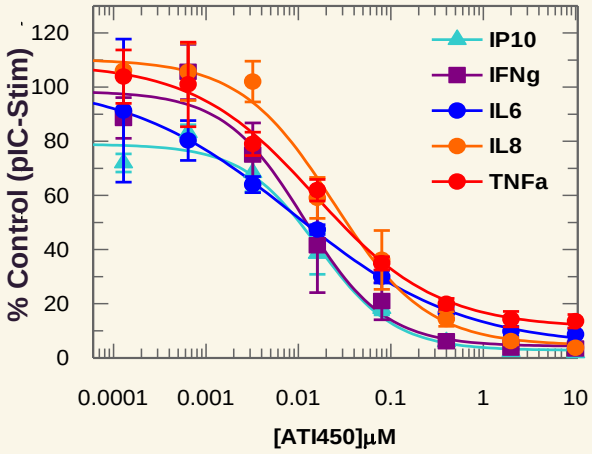
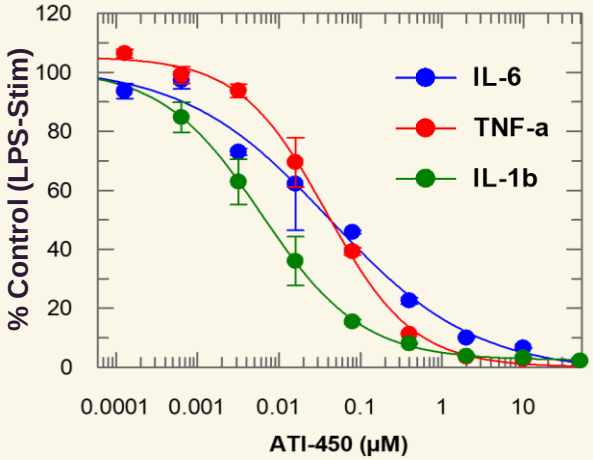
In Vitro: ATI-450 Blocked TLR3/4/7/8 Stimulated Cytokines in HWB

TLR3: poly(I:C)-Stimulated HWB



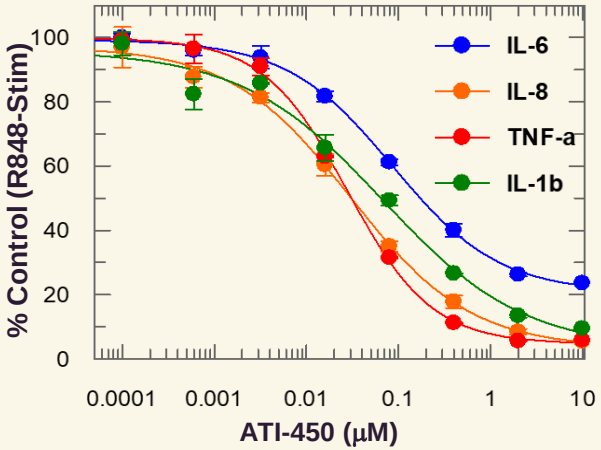
0 ATI-450 — 1hr 100ug/ml Poly(I:C) — 24hr Cytokines quantified by MSD

TLR4: LPS-Stimulated HWB



0 ATI-450 — 1hr 100ng/ml LPS — 4hr Cytokines quantified by MSD

TLR7/8: R848-Stimulated HWB



0 ATI-450 — 1hr 0.5ug/ml R848 — 5hr Cytokines quantified by MSD

ATI-450 potently inhibited multiple COVID-19 associated proinflammatory cytokines induced by multiple disease relevant stimuli in HWB

* Data on file

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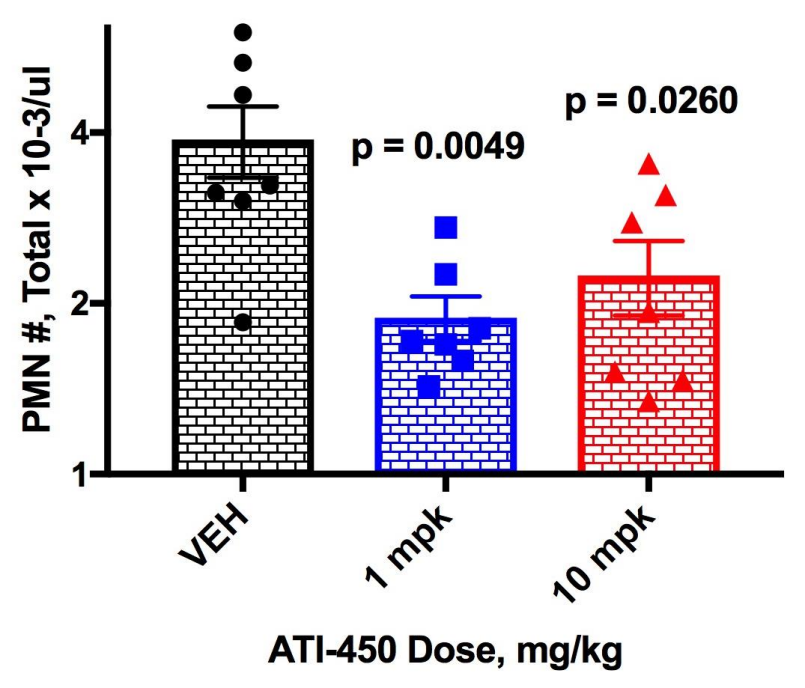
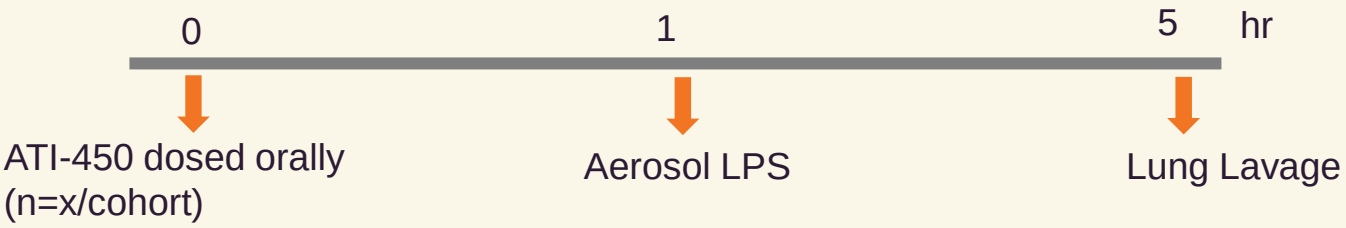
Rat Model: MK2 Inhibition Blocked Pulmonary Inflammation

ATI-450 reduced neutrophil influx into lungs



p value relative to vehicle



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ATI-450 Impact on Human Blood Cytokines & Chemokines:
Ex Vivo LPS-Stimulated HWB Phase 1 SAD/MAD Trial

- LPS (TLR4) stimulated cytokine and chemokine production
  - Blood samples from the ATI-450-PKPD-101 Trial
  - Cytokines and chemokines elevated in patients with COVID-19 were analyzed including: IL1-β, IL-2, IL-6, IL-8, GM-CSF, IFNγ, MIP1α and TNFα
    - TNFα, IL-1β, IL-6 and IL-8 analyzed pre-dose and 4hr/12hr post-dose in the Day 7 MAD cohorts
    - Follow up analysis of IL-2, GM-CSF, IFNγ and MIP1α from SAD 100mg cohort (1hr post-dose) and MAD 4hr post-dose Day 7 cohorts

* Data on file

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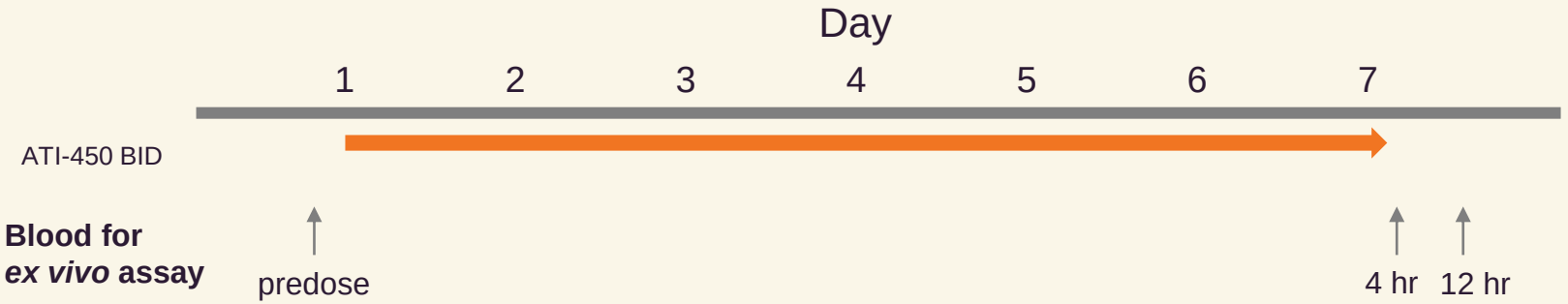
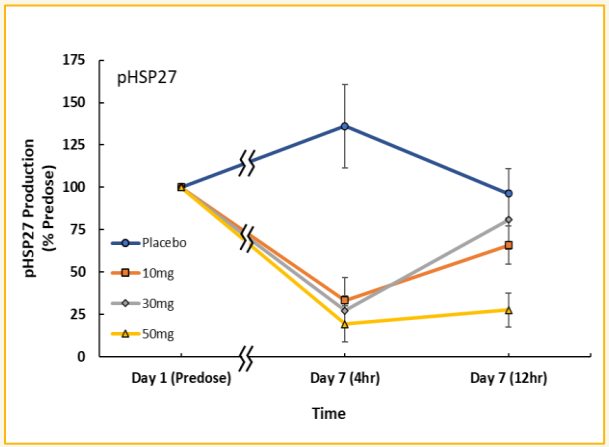
ATI-450-PKPD-101: Day 7 MAD PD Marker Time Dependence

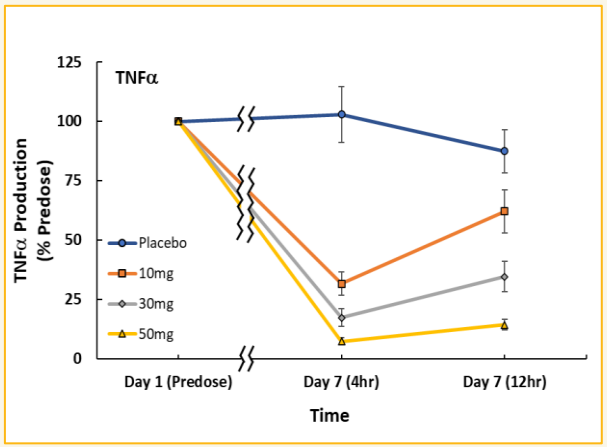
Target Biomarker pHSP27 and Cytokines TNFα and IL-1β



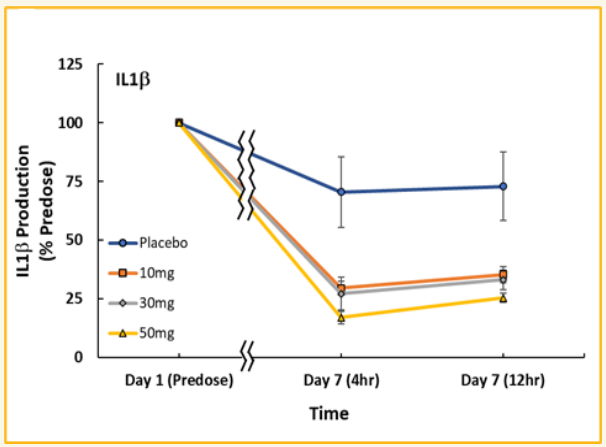
pHSP27



TNFα



IL-1β



- ATI-450 dosed orally BID for 7 days in healthy subjects at doses of 10mg, 30mg and 50mg
- Day 1 (predose) is from blood taken on day 1 just prior to the first dose of ATI-450
- Samples *ex vivo* stimulated with LPS
- Data expressed as mean +/- SEM

* Data on file

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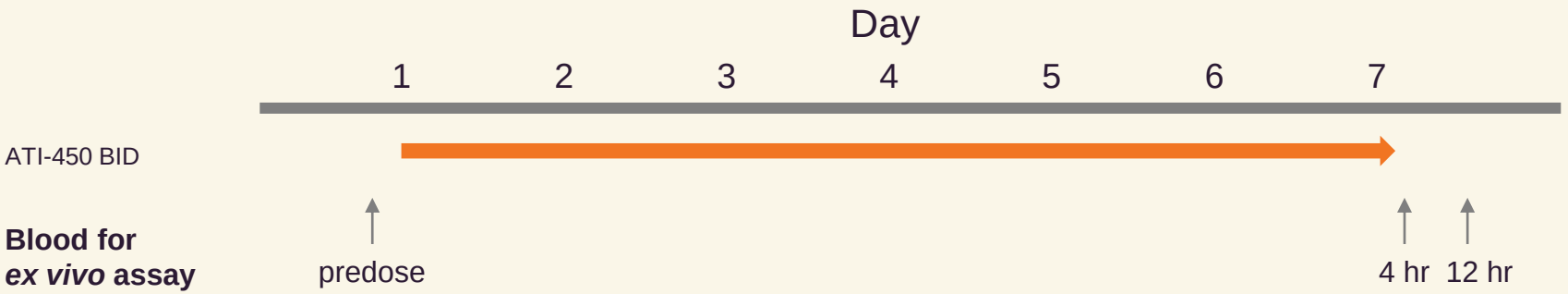
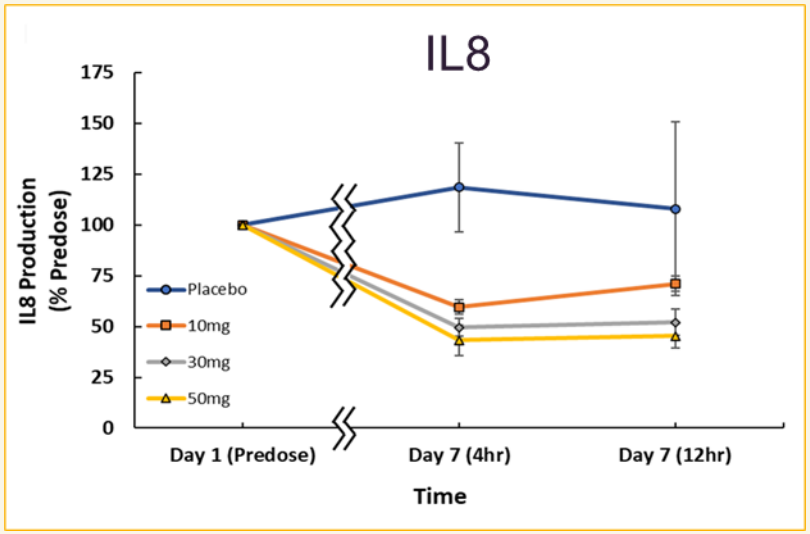
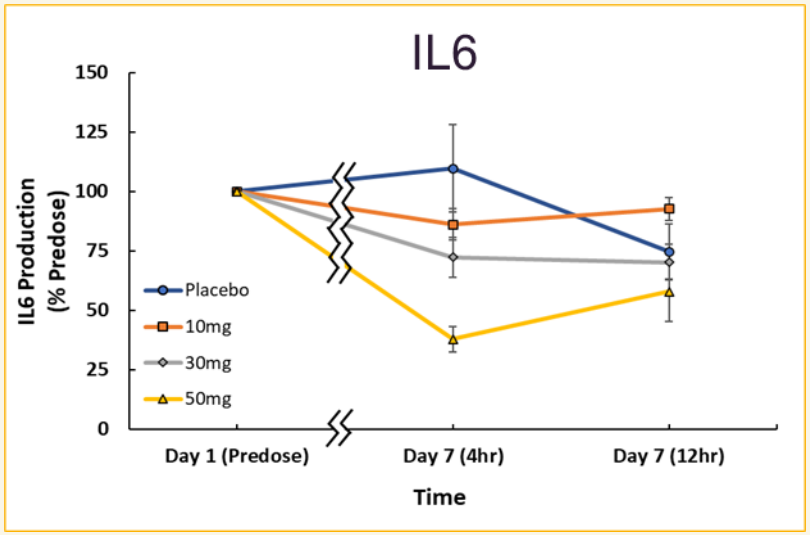
ATI-450-PKPD-101: Day 7 MAD PD Biomarker Time Dependence

Cytokines IL-6 and IL-8







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- Day 1 (pre-dose) is from blood taken on day 1 just prior to the first dose of ATI-450
- Samples *ex vivo* stimulated with LPS
- Data expressed as mean +/- SEM

* Data on file

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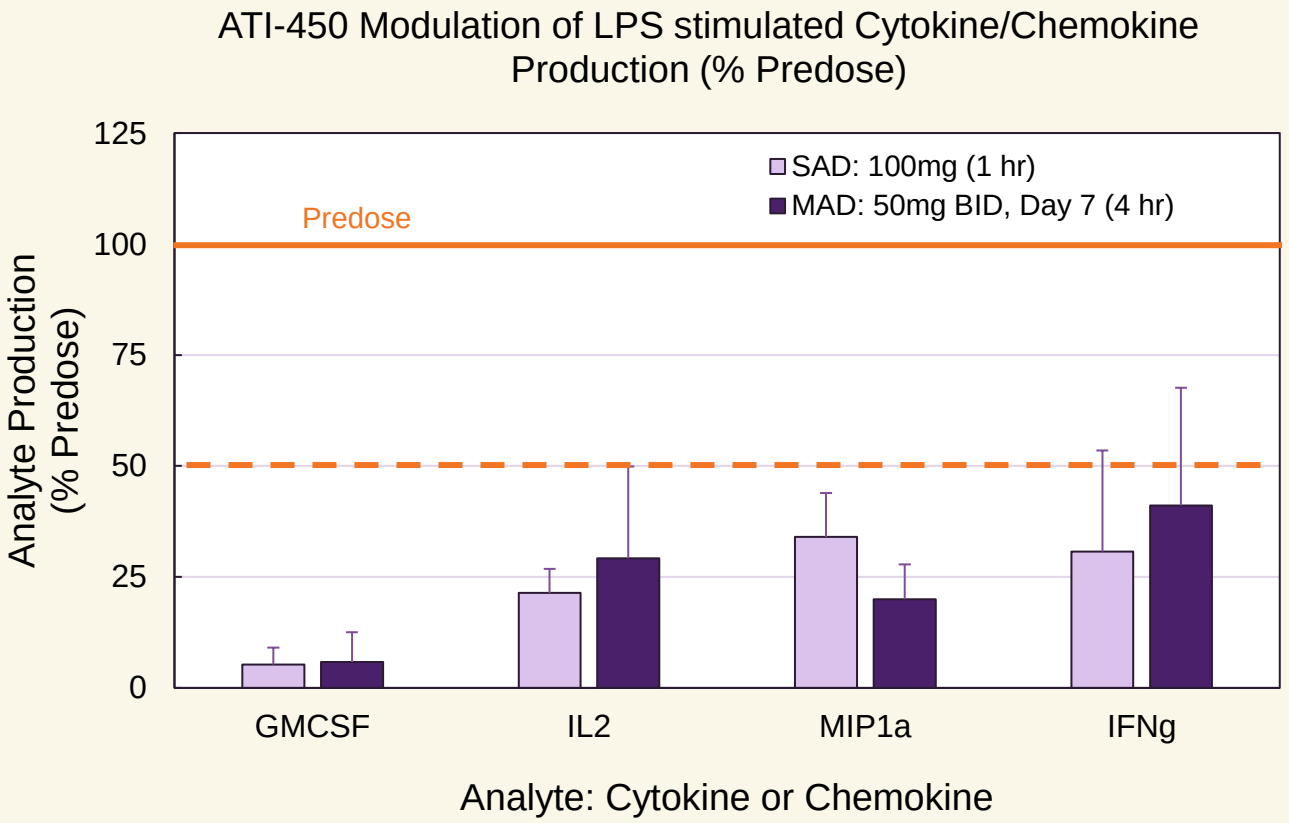
ATI-450 Inhibited Additional CRS-Related Proteins in HWB

Ex Vivo LPS-Stimulated HWB from Phase 1 SAD/MAD Trial



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The MK2 Pathway Regulates Coronavirus Replication/Pathology

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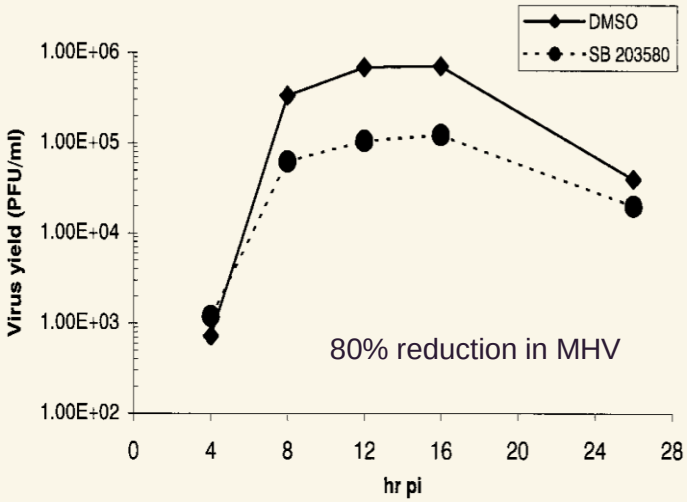
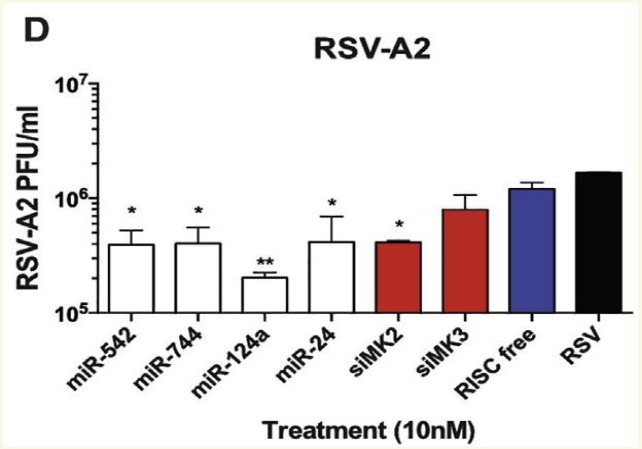
In Vitro: The p38/MK2 Pathway is Involved in Viral Replication

MHV Replication is p38 Dependent[9]



MHV infected J774.1 Cells

RSV Infectivity is MK2 Dependent[13]



RSV infected A549 Cells

- p38 inhibition blocked murine hepatitis virus (coronavirus) replication in murine macrophage cell line (J774.1)[9]
- SARS-CoV activation of p38MAPK promoted replication and enhanced its cytopathic function upon infection of Vero E6 cells[14]
- MK2 knockdown inhibited RSV infection in human lung epithelial cells[13]
- MK2 knockdown reduced avian influenza virus A titers in human lung and breast cancer cell lines[15]

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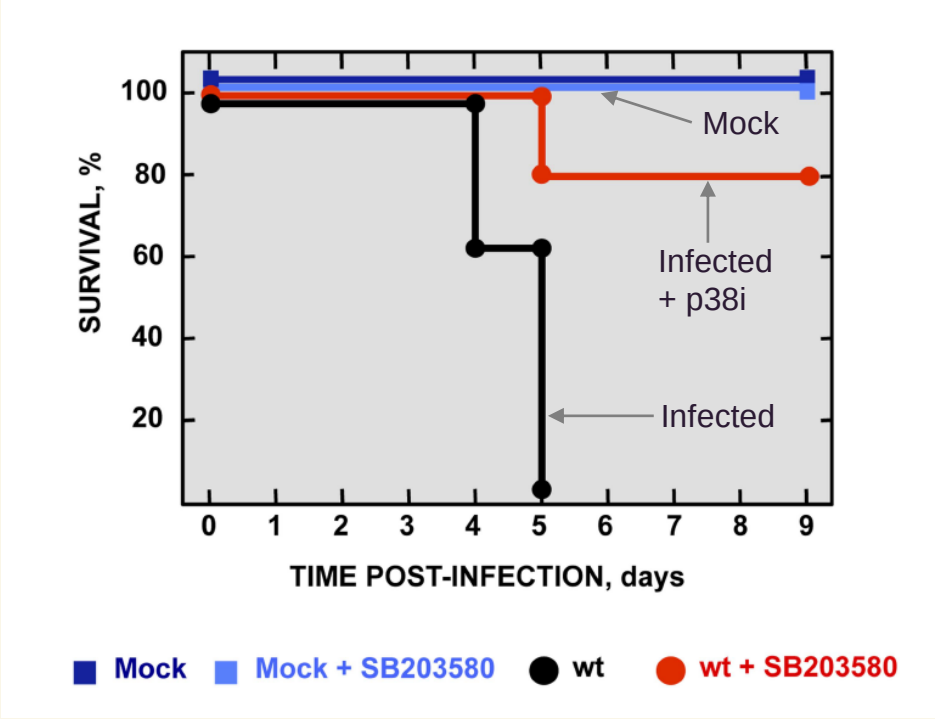
Mouse Model: p38MAPK/MK2 Inhibition Increased Survival of SARS-CoV Infected Mice

p38MAPK/MK2 Inhibition Improves Survival[16]



- Mice infected with SARS-CoV intranasal
- p38MAPKi dosed 8mpk ip BID for 8 days
- Mortality measured daily

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MK2 Inhibition Prevents Pulmonary Fibrosis

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COVID-19 Induced ARDS and Pulmonary Fibrosis

- Severe cases of respiratory SARS-CoV-2, SARS-CoV and MERS-CoV coronavirus infections often result in ARDS and the development of pulmonary fibrosis[17]
- A substantial number of ARDS survivors die as a result of progressive pulmonary fibrosis[18]
- Pulmonary fibrosis is thought to be driven by TGFβ and the cytokines IL-1β, IL-6 and TNFα may be involved[19,20]
- The evaluation of anti-fibrotic therapy in the treatment of patients with COVID-19 has been proposed[21]

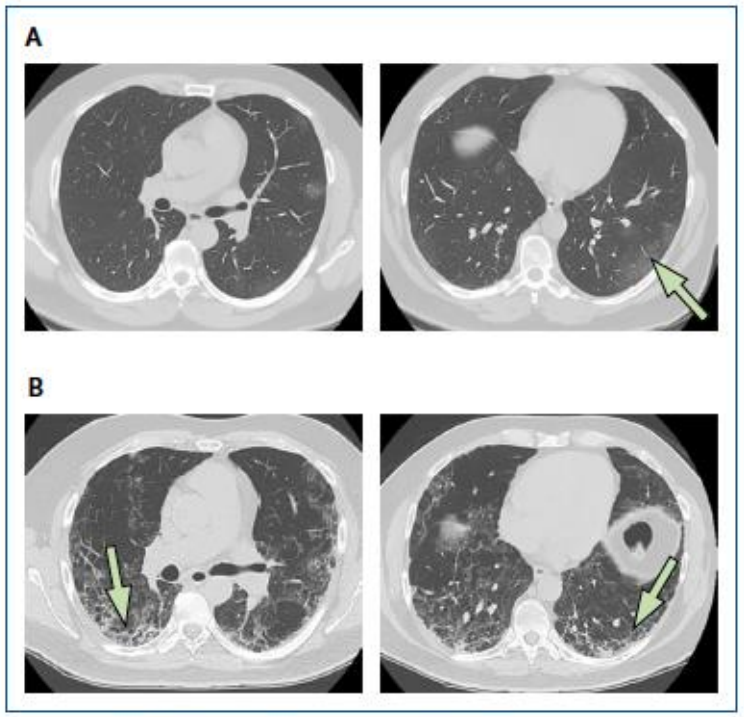
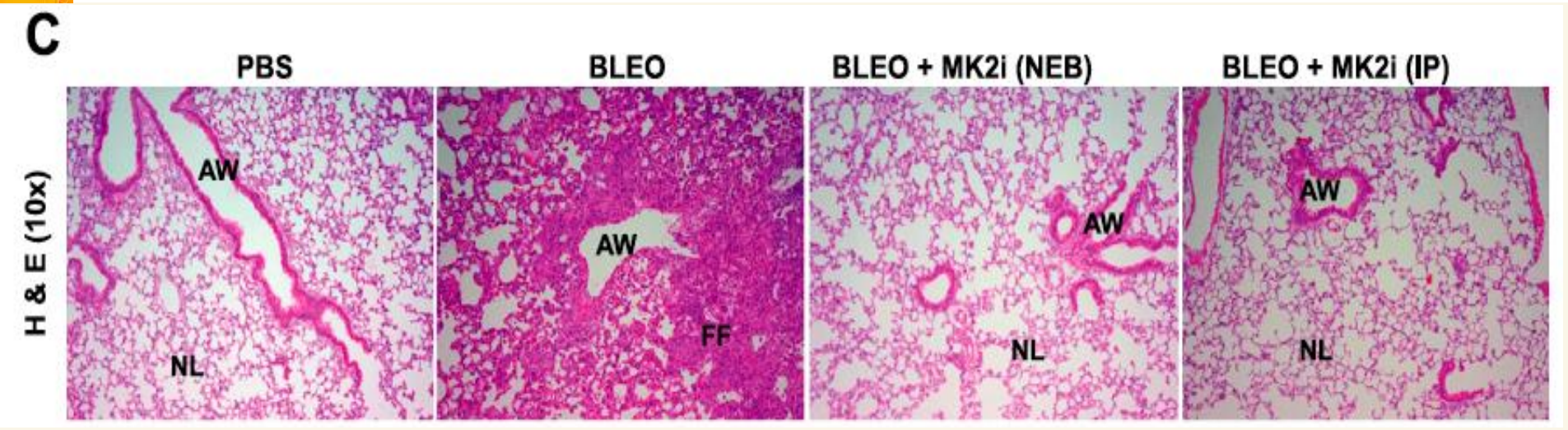
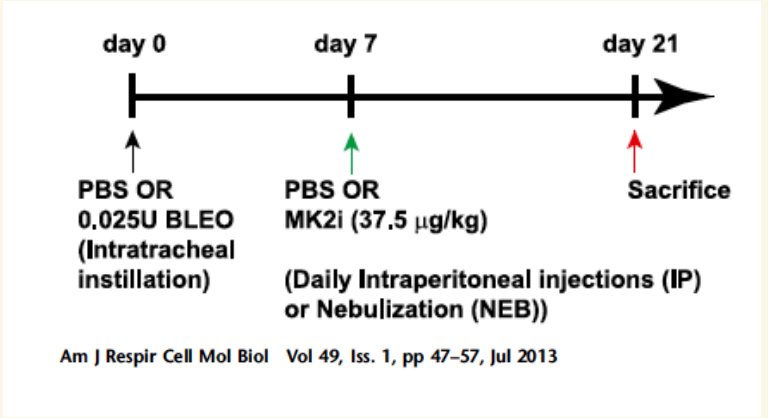


Figure: **Lung CT of a patient with coronavirus disease 2019**
(A) Images of peripheral mild ground glass opacities in the left lower lobe (arrow). (B) Three weeks later, at the same lung zones, the disease has rapidly progressed and fibrotic changes are now evident (arrows). 17

Mouse Model: MK2 Inhibition Protected Mice from Bleomycin-Induced Pulmonary Fibrosis



- The MK2 inhibitor MMI-0100 inhibited murine bleomycin-induced pulmonary fibrosis (above)[22]
- Murine tissue specific MK2 KO in collagen producing fibroblasts attenuated bleomycin-induced pulmonary fibrosis[23]



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ATI-450 as a Potential Treatment for COVID-19
Summary

- ATI-450 has the potential to:
  - Inhibit **multiple** key inflammatory cytokines associated with CRS in patients with COVID-19;
  - Inhibit coronavirus replication and infectivity; and
  - Block COVID-19-induced pulmonary fibrosis.
- Next step: Investigator-Initiated Trial (IIT)-2020-ATI-450-COVID-19 will evaluate if ATI-450's inhibition of multiple key inflammatory cytokines provides benefits for CRS in patients with COVID-19

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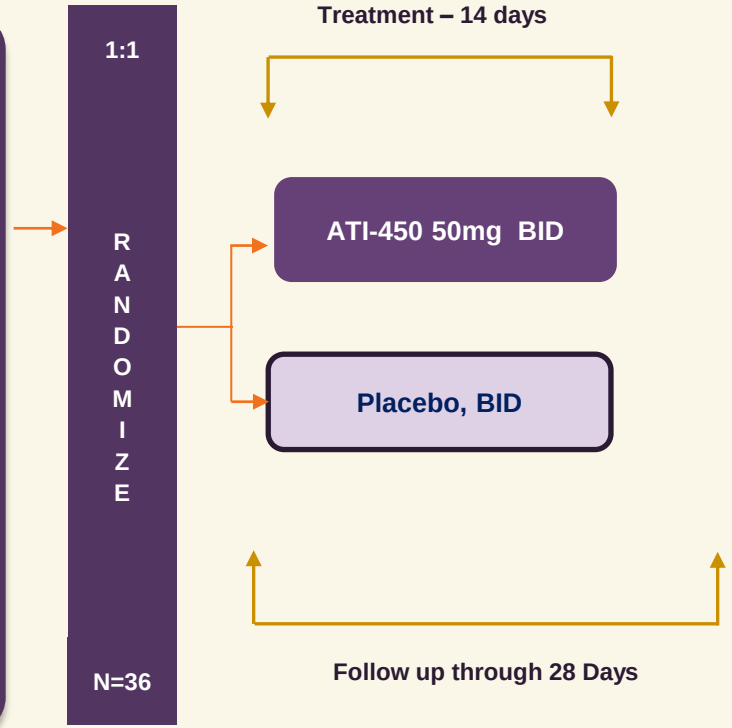
IIT-2020-ATI-450-COVID-19: University of Kansas Medical Center

A double-blind, randomized, controlled trial of ATI-450 in pts with moderate-severe COVID-19

Eligibility

- COVID-19 positive confirmed
- Hospitalized as a result of COVID-19 infection
- Evidence of pulmonary involvement by chest imaging or exam, or respiratory failure:
  - SpO2 ≤ 93% on room air; or
  - SpO2 > 93% requiring ≥ 2L O2; or
  - Pa02/Fi02 ratio <300mmHg; or
  - Tachypnea



Endpoints

Primary Endpoint

- Responders on Day 14
  - alive, free of resp failure (no supplemental oxygen)

Secondary Endpoints include:

- Change in oxygenation
- Time of Hospitalization
- Time to intubation
- ARDS
- Mortality
- Safety (incl infections)
- Cytokines

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