Effect of JAK inhibitor treatment on clinical outcome, lung pathology, and viral load in a mouse model of pathogenic SARS-CoV-2 infection

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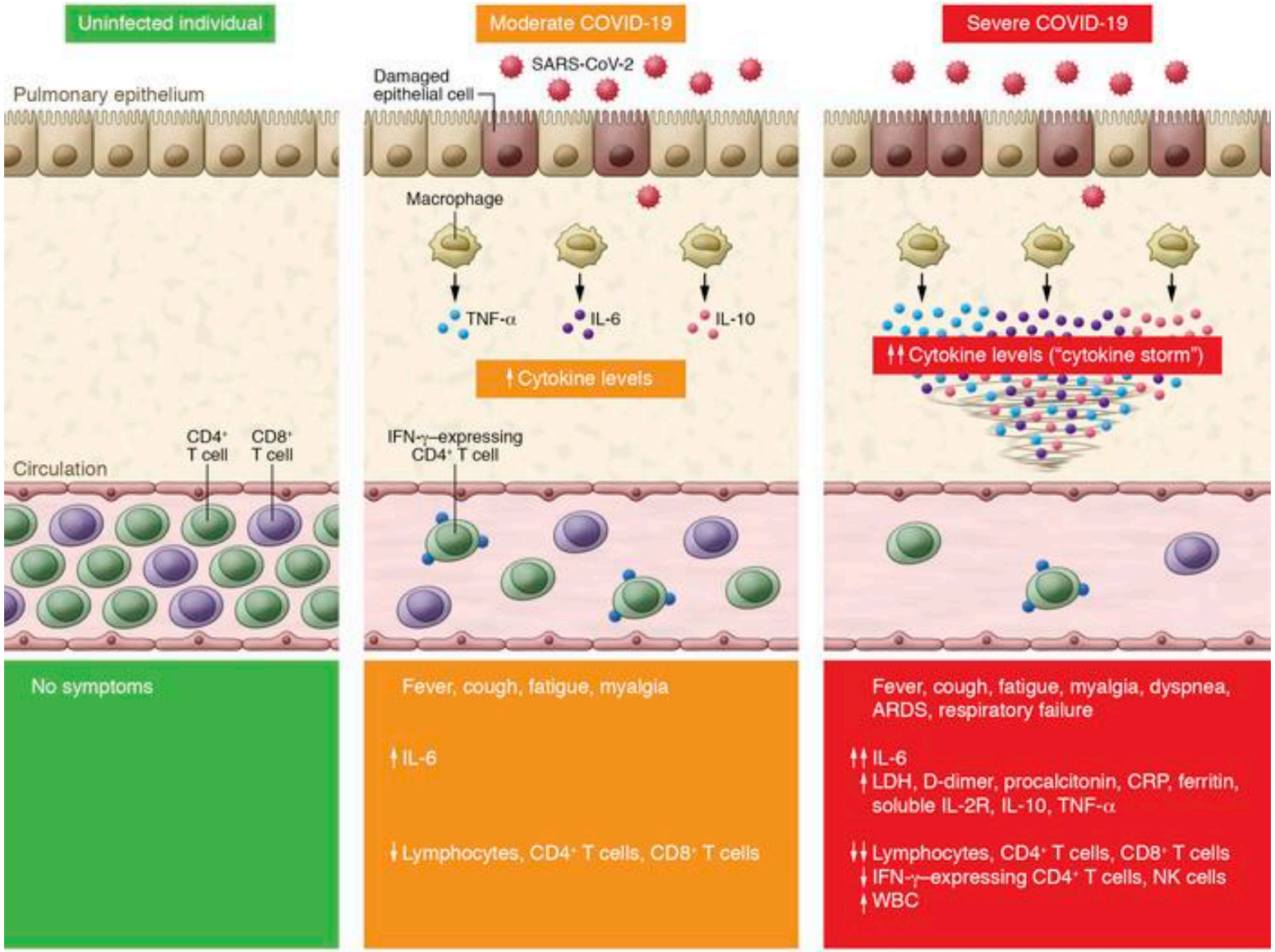
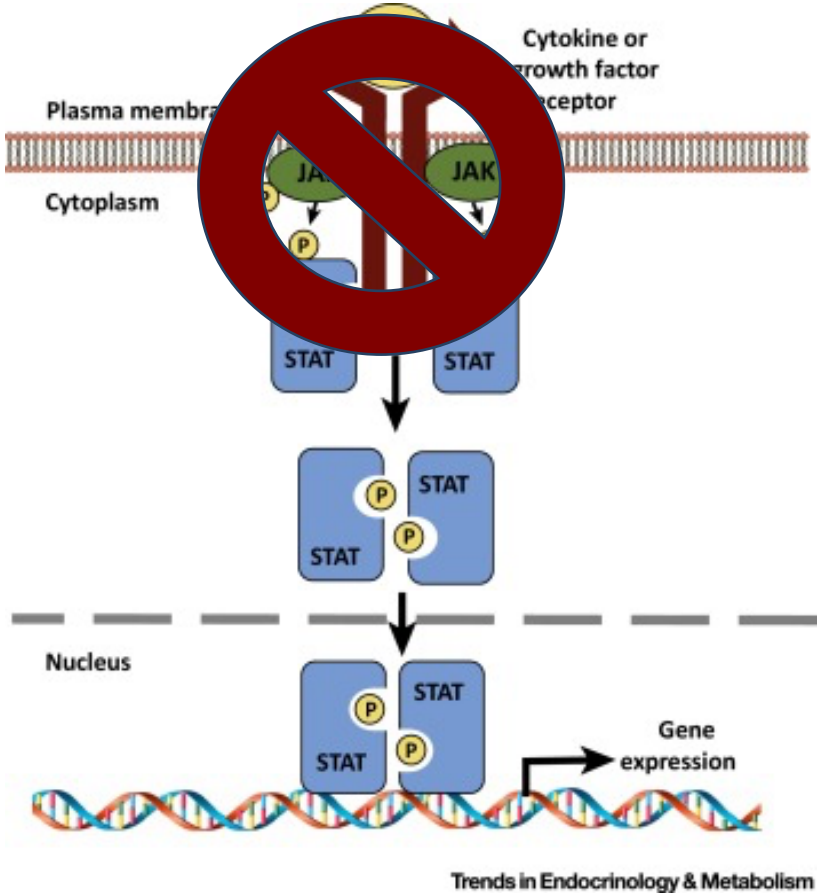


Pederson and Ho, *JCI*, 2020

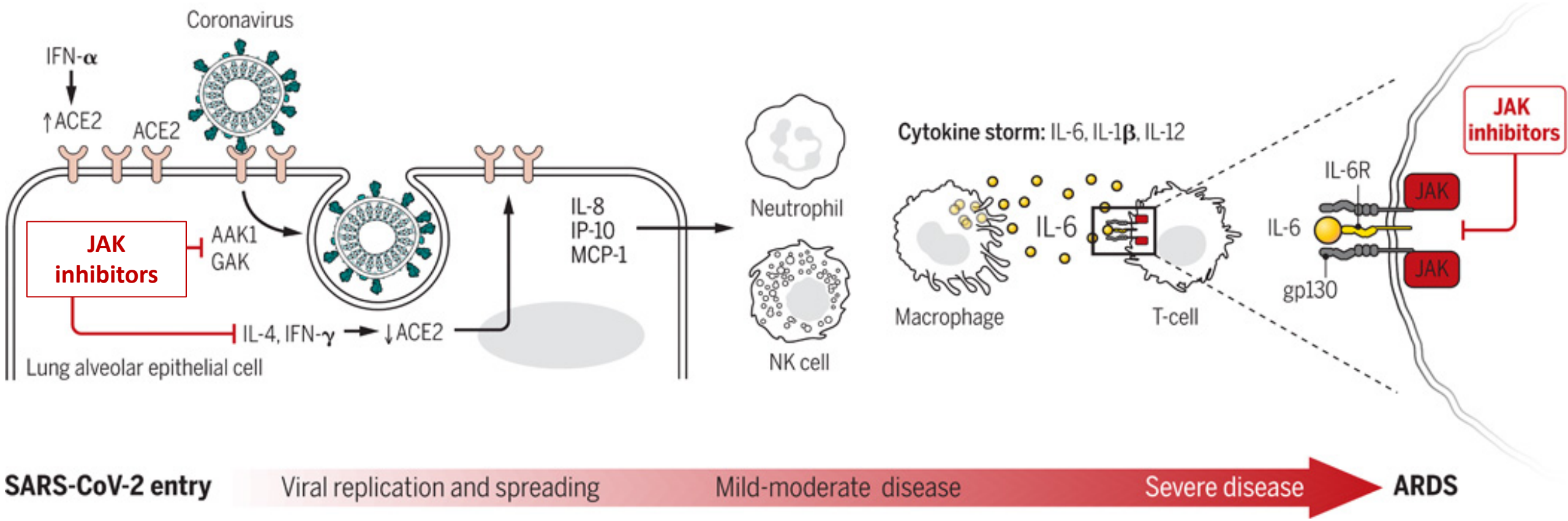


Example of cytokines that signal through JAK/STAT combinations

γ-chain cytokines*	IFNγ	IL-10 IL-22 IFNα/IFNβ	IL-12 IL-23	IL-6ʸ IL-11	EPO TPO GM-CSF
JAK1 JAK3	JAK1 JAK2	JAK1 TYK2	JAK2 TYK2	JAK1 JAK2 TYK2	JAK2 JAK2
STAT 1, 3, 5, 6	STAT 1, 3, 5	STAT 1, 3, 5	STAT 3, 4	STAT 1, 3, 5	STAT 5

Hodge et al, *Clin Exp Rheumatol*, 2016

JAK Inhibitors: Proposed Mechanisms of Action



Spinelli *et al, Science Immunol*, 2020

JAK Inhibitors

- Reversible, competitive inhibitors that binds to the ATP binding site in the catalytic cleft of the kinase domain of JAK

Tofacitinib

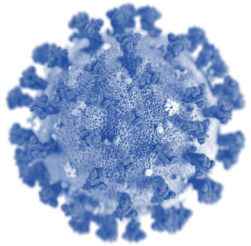
- Preferentially inhibits JAK1 and JAK3, with some effect on JAK2
- Orally available, FDA approved for treatment of rheumatoid arthritis and IBS in humans

Baricitinib

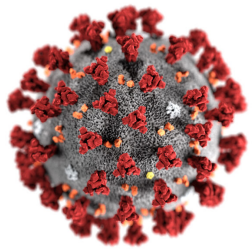
- Potent JAK1 and JAK2 inhibitor, with some activity against JAK3 and TYK2
- Orally available, FDA approved for treatment of rheumatoid arthritis in humans

Tofacitinib	Baricitinib	
5 mg/kg PO BID	3 mg/kg PO BID	Low Dose (Therapeutic Equivalent)
15 mg/kg PO BID	10 mg/kg PO BID	Medium Dose
50 mg/kg PO BID	30 mg/kg PO BID	High Dose

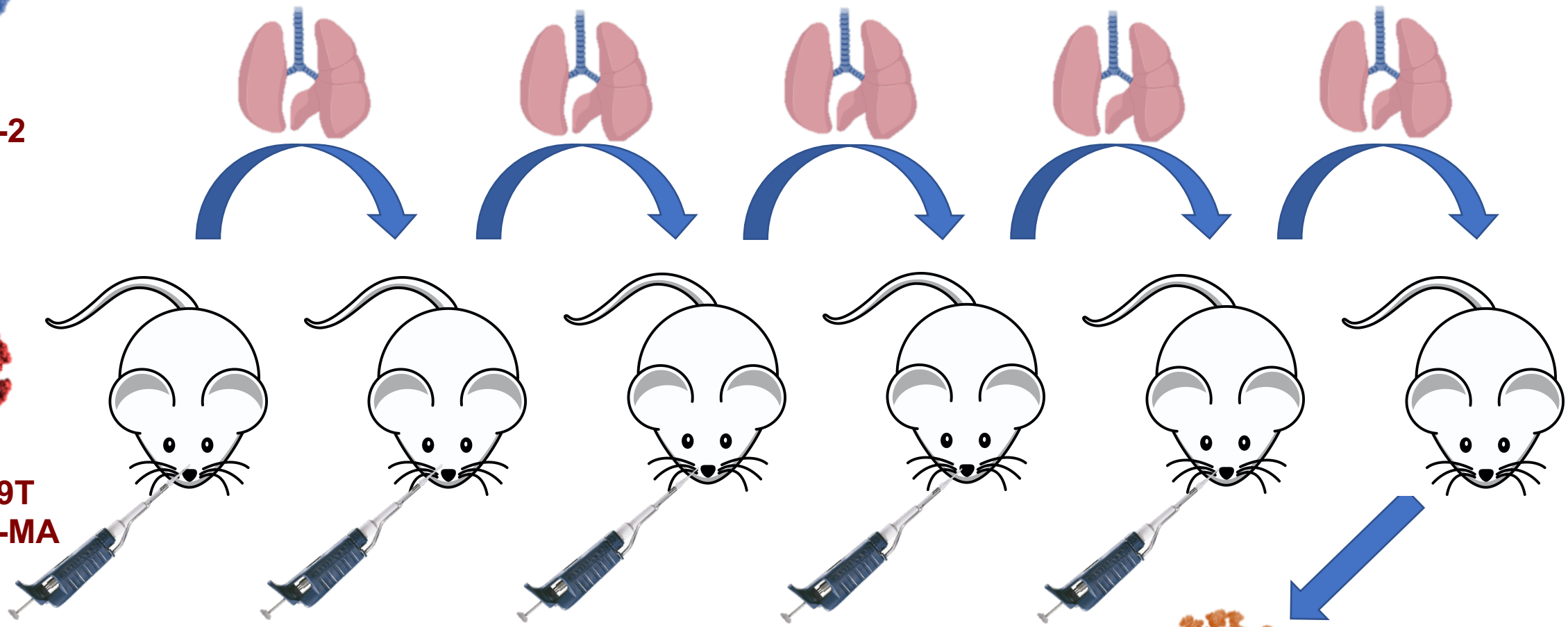
Mouse Adaptation of SARS-CoV-2

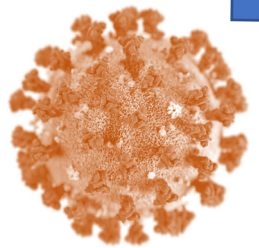


Original
SARS-CoV-2



Q498Y/P499T
SARS-CoV-2-MA





Pathogenic
SARS-CoV-MA10

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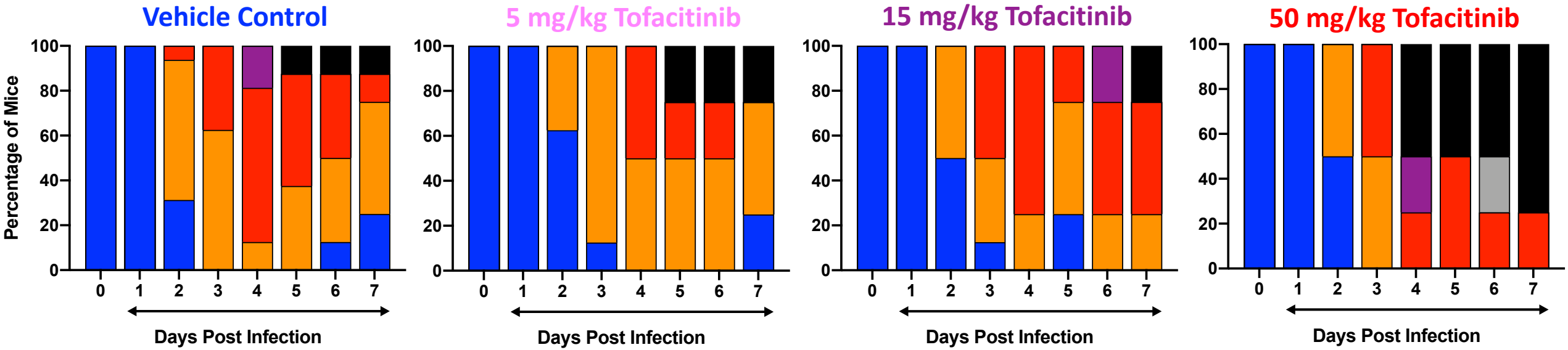
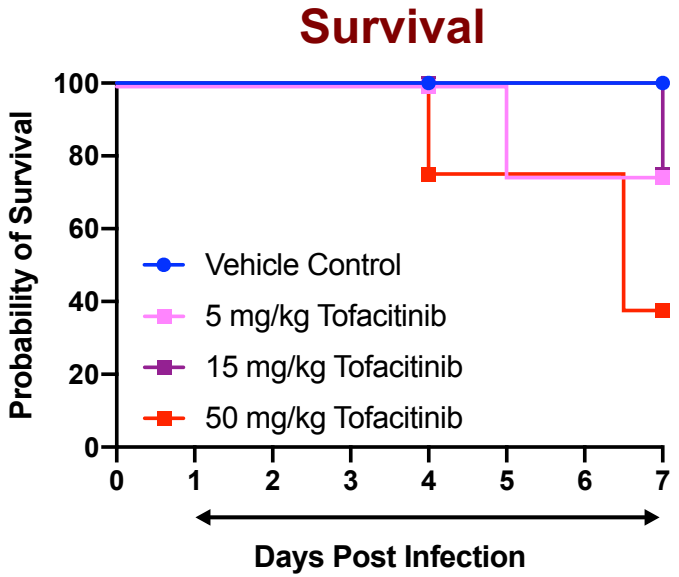
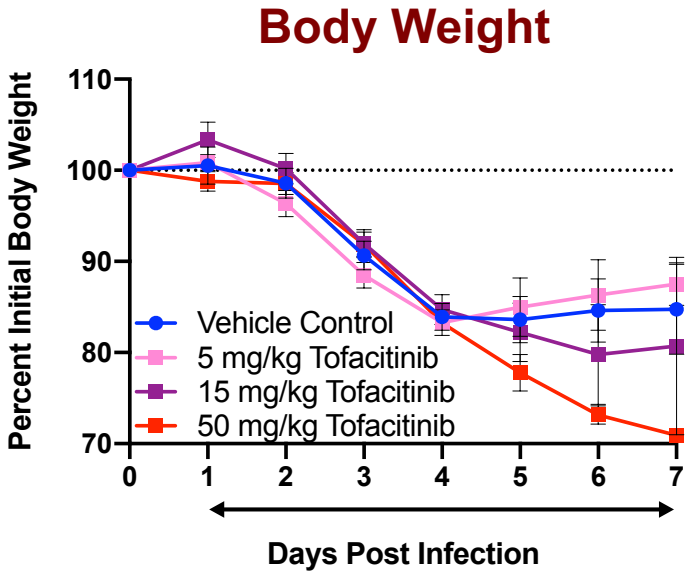
Dinnon *et al, Nature* 2020
Leist et *al, in press*

Effect of Tofacitinib Treatment on Clinical Disease



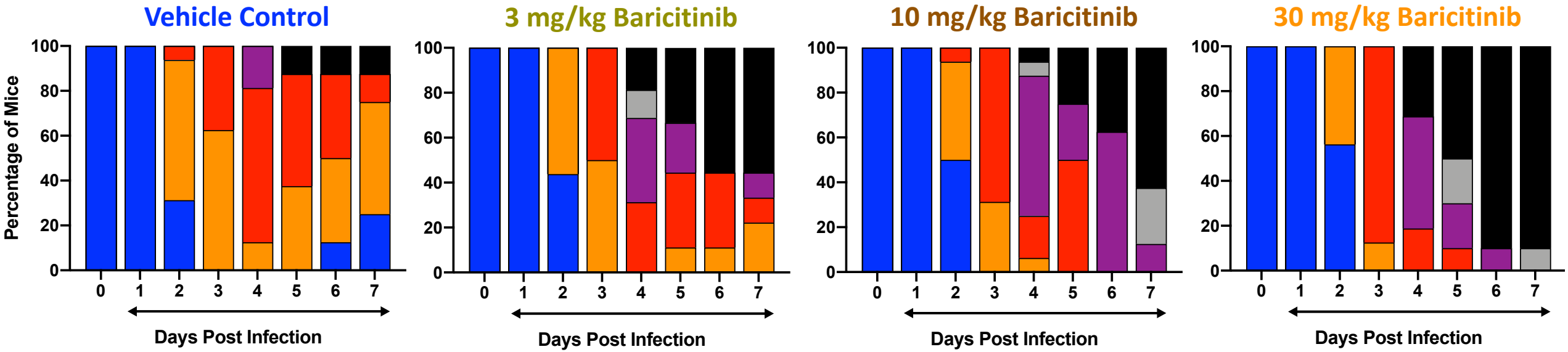




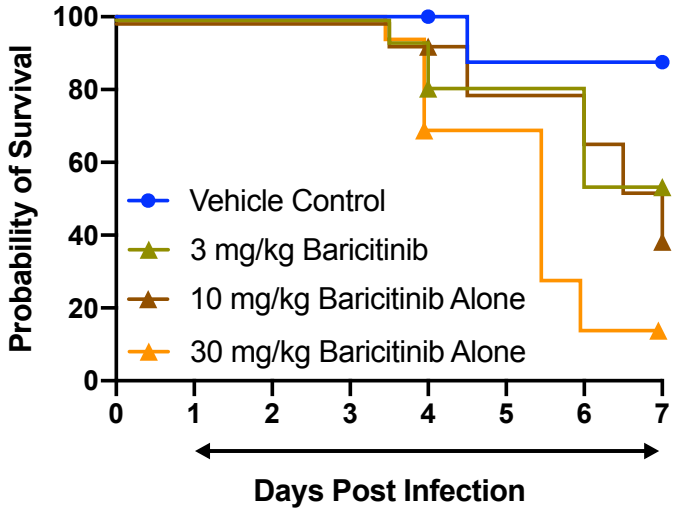
- 5 = dead/moribund
- 4 = severe hunched posture, minimal spontaneous activity, labored breathing
- 3 = hunched posture, reduced activity
- 2 = scruffy haircoat, mild hunched posture
- 1 = mild scruffy haircoat
- 0 = clinically normal

n = 8 mice/group

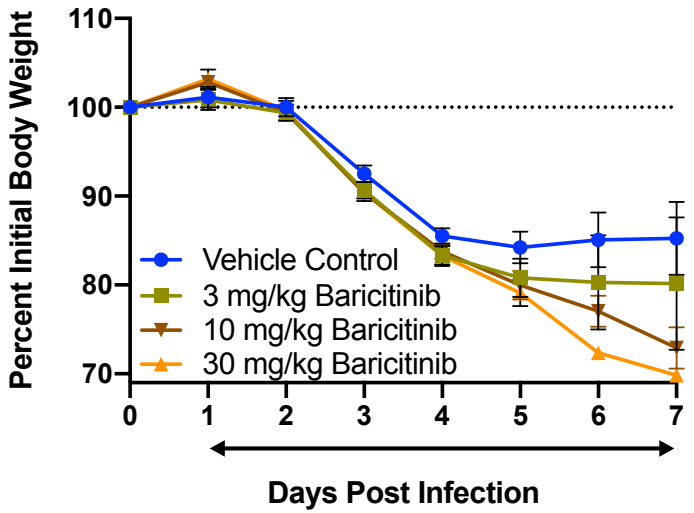
Effect of Baricitinib Treatment on Clinical Disease



Survival



Body Weight



- 5 = dead/moribund
- 4 = severe hunched posture, minimal spontaneous activity, labored breathing
- 3 = hunched posture, reduced activity
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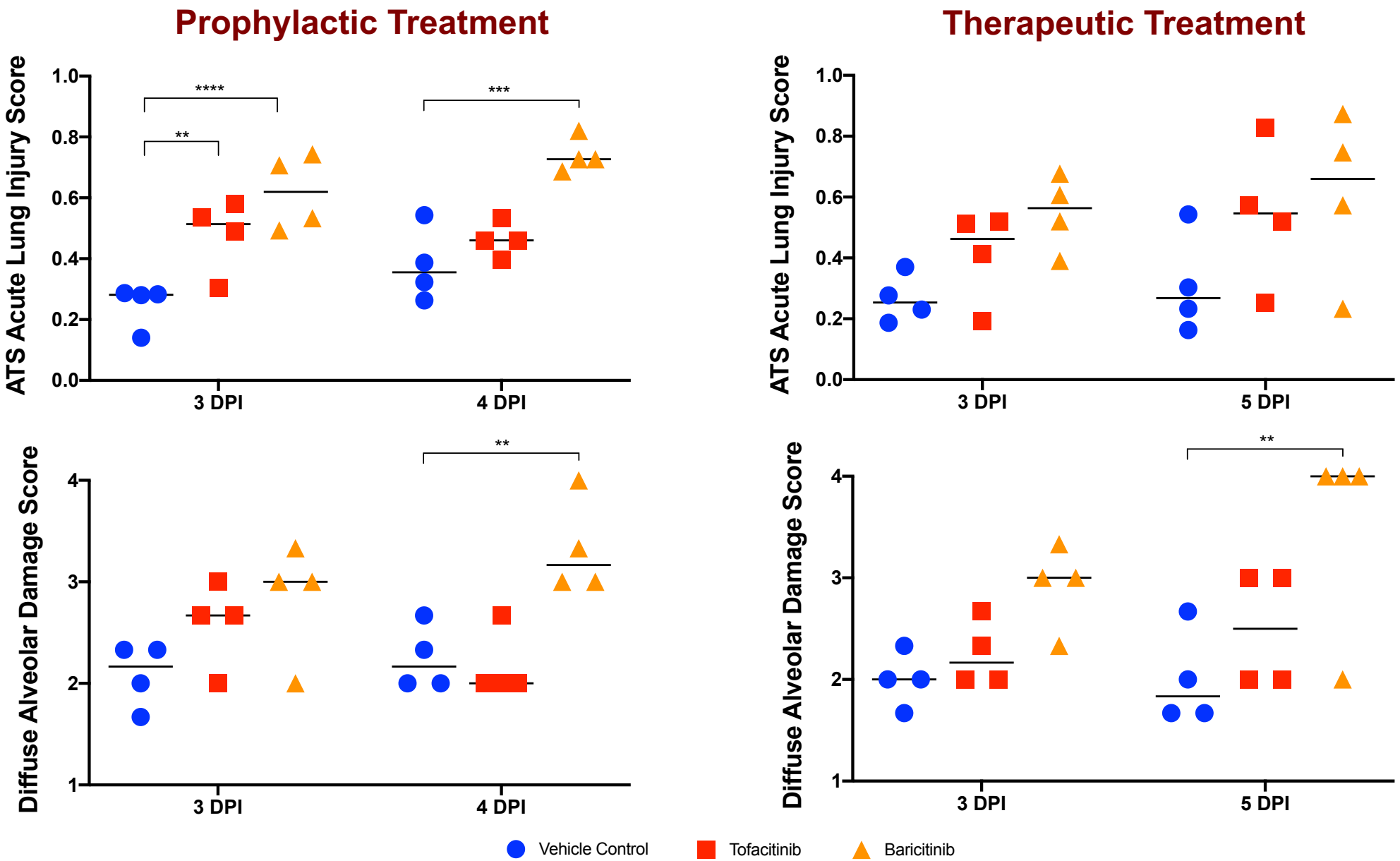
- 1 = mild scruffy haircoat
- 0 = clinically normal

n = 16 mice/group

Effect of JAK Inhibitor Treatment on Lung Pathology

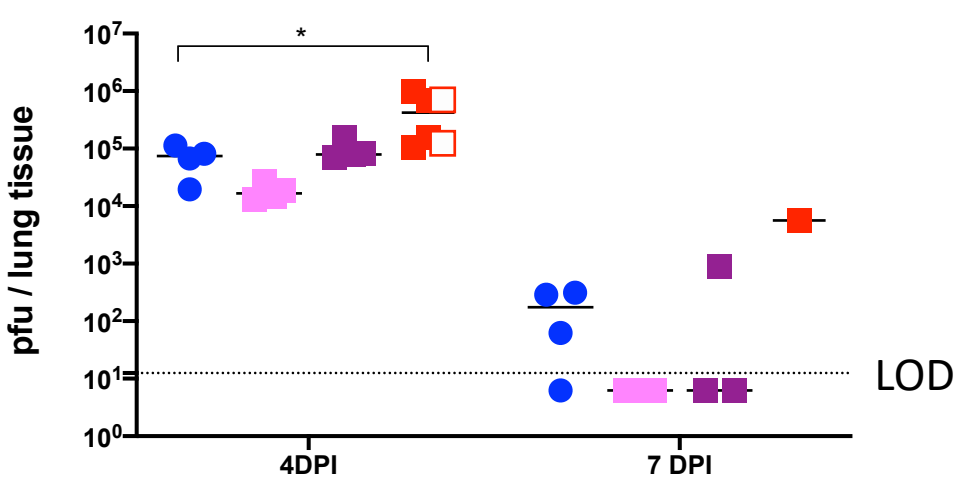


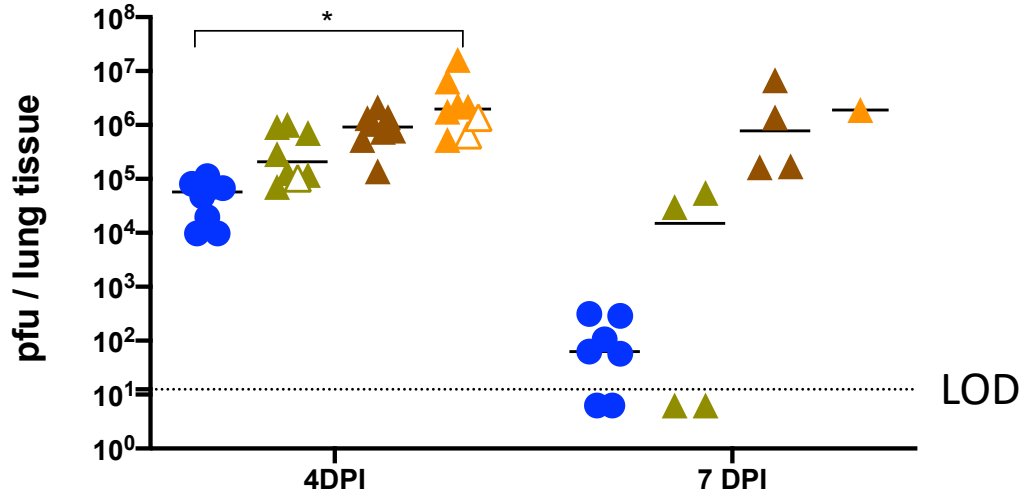
Effect of JAK Inhibitor Treatment on Lung Viral Load

Tofacitinib

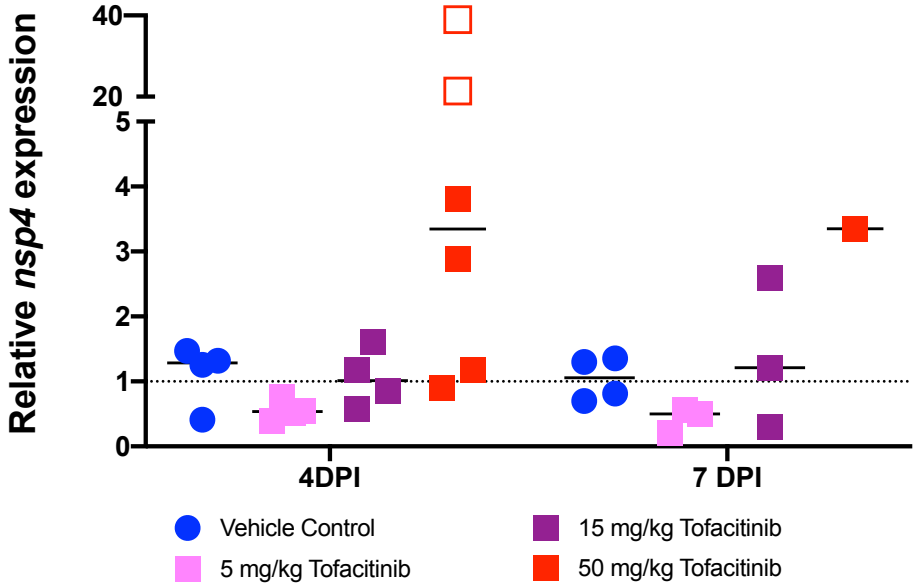
Baricitinib

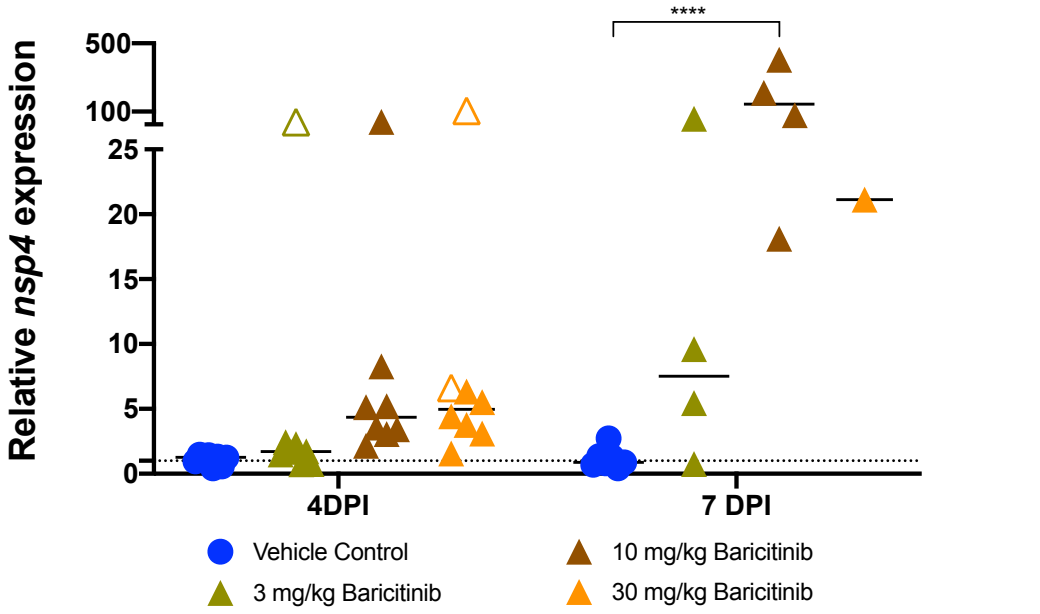
Viral Titers





Viral RNA

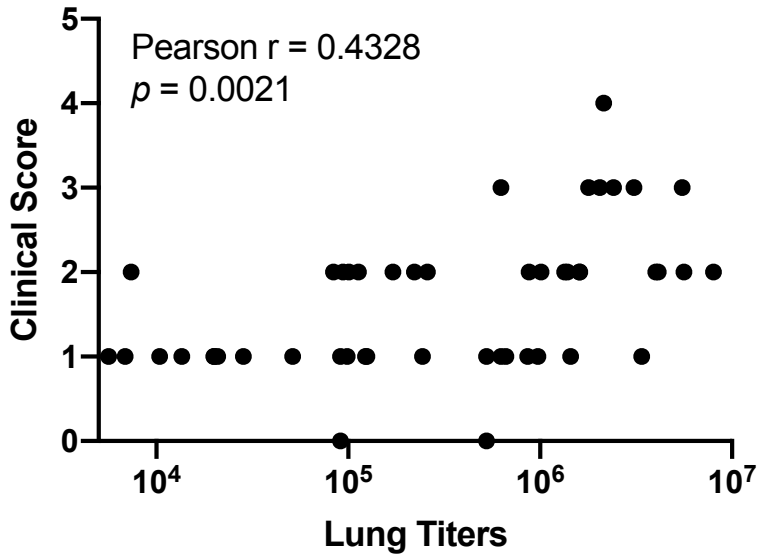


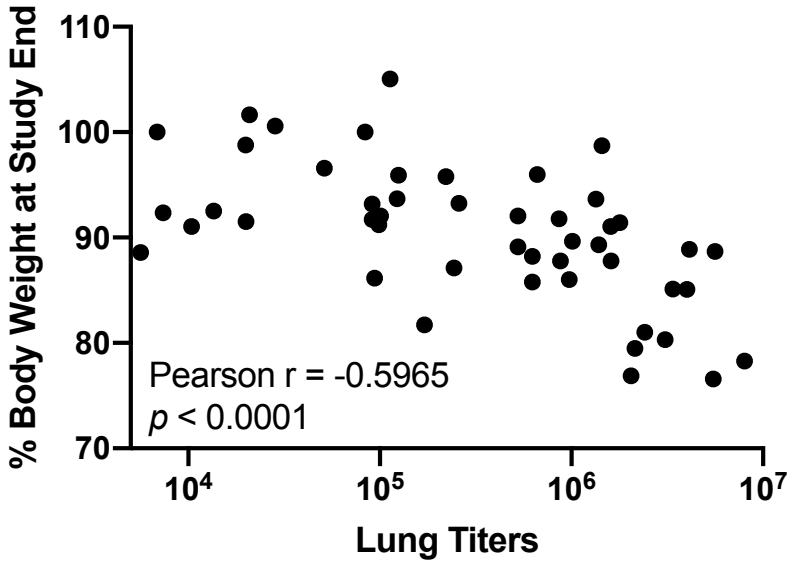


Open Symbols = Found Dead

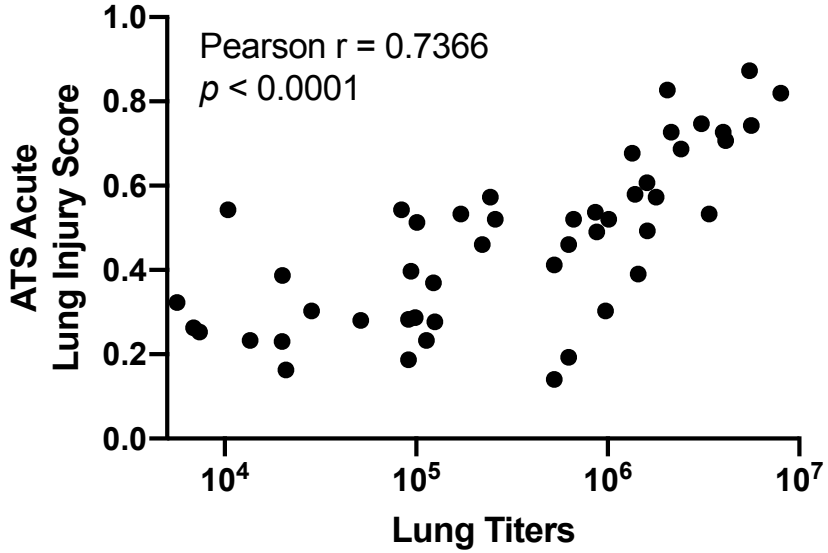
Correlation Between Viral Lung Titers and Clinical Disease & Lung Pathology

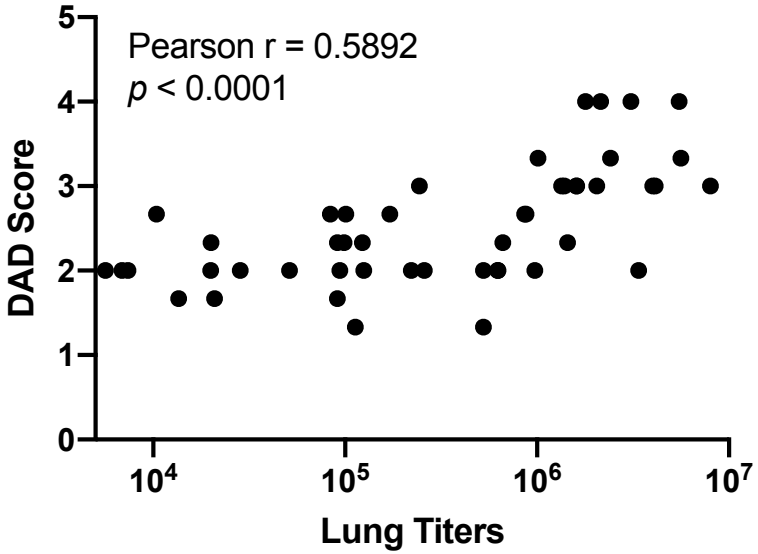
Clinical Disease





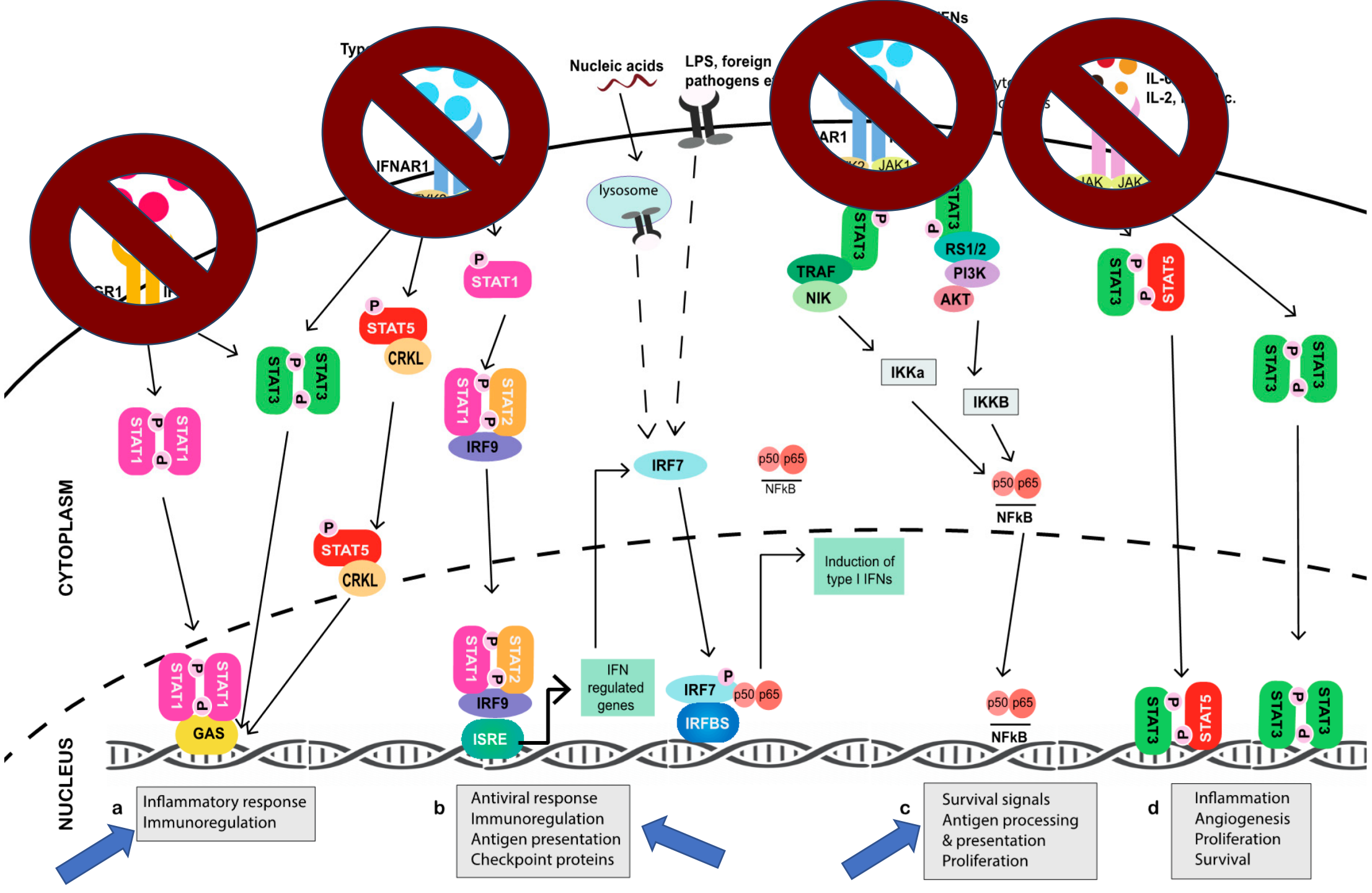
Lung Pathology





Summary of Findings

- Baricitinib treatment exacerbates clinical disease at any dose in a mouse model of pathogenic SARS-CoV-2 infection, while tofacitinib treatment is detrimental primarily at high doses.
- JAK inhibitors at high doses increase SARS-CoV-2-induced lung pathology.
- Baricitinib treatment results in augmented viral replication and impaired viral clearance.
- Worsened clinical disease and increased lung pathology scores correlate with higher lung viral titers.
- Monotherapy with Jak inhibitors in COVID-19 patients may result in enhanced replication of virus, leading to exacerbation or relapse of respiratory disease.



Owen *et al*, *Cancers*, 2019

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