Fulcrum Therapeutics

COVID-19 Program

June 2020

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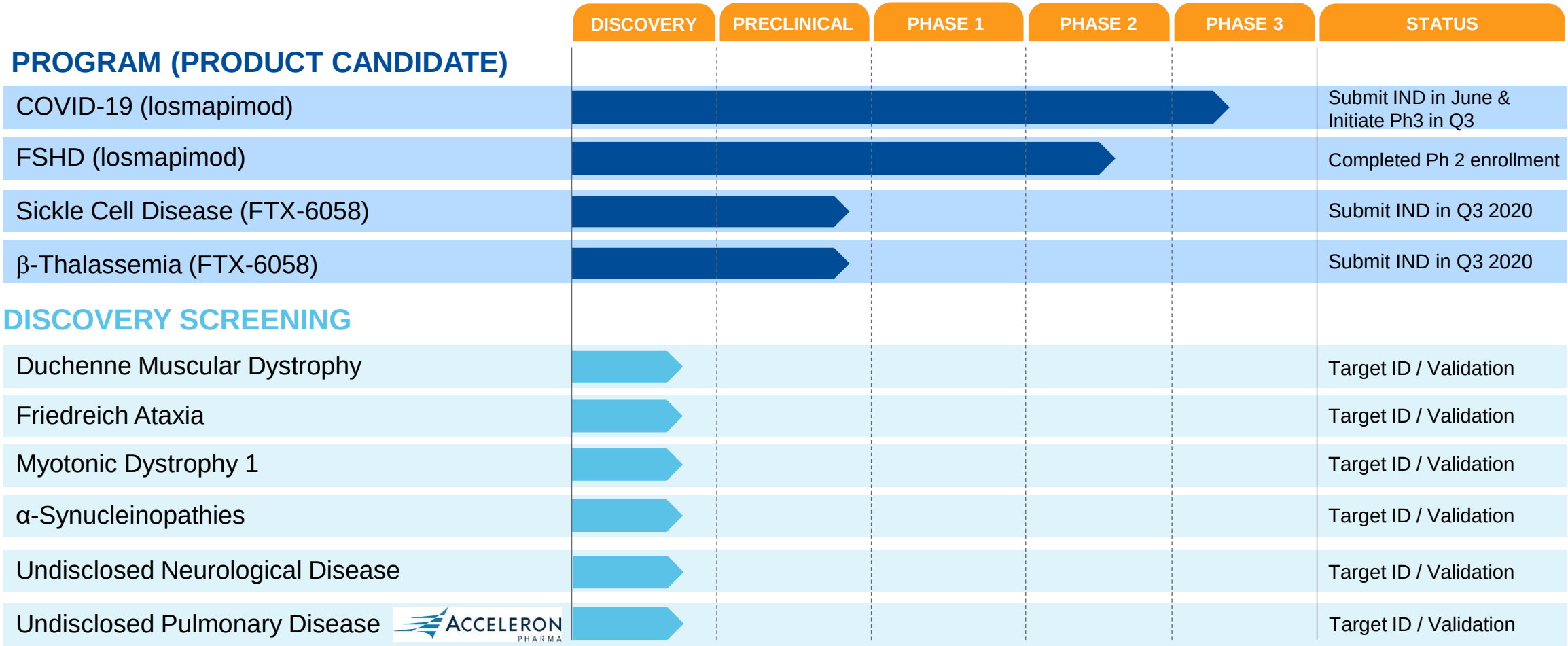
Fulcrum Pipeline

Multiple clinical programs advancing in 2H 2020



Additional screens & FulcrumSeek planned for 2020

Increasingly robust development portfolio with multiple near-term catalysts

Losmapimod
COVID-19

- Rapid progress and strong KOL support
- IND Filed June 2020
- **Initiate Phase 3 trial in Q3 2020**

Losmapimod
FSHD

- ReDUX4 Phase 2b Interim Analysis 3Q 2020
- **ReDUX4 Phase Topline Data 1Q2021**
- Ongoing Phase 2 Open Label Study
- Ongoing Open Label Extension

FTX-6058
Sickle Cell Disease & β-Thalassemia

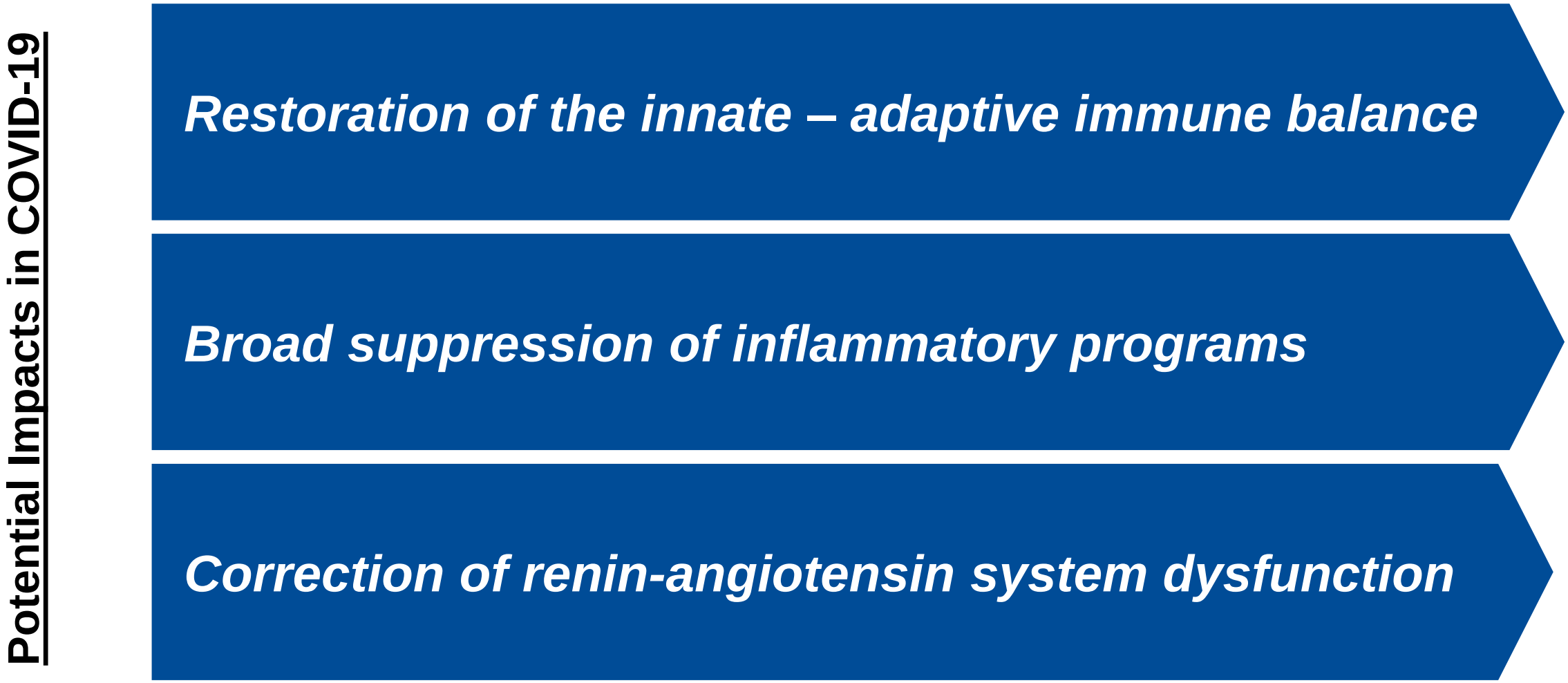
- IND Filing Q3 2020
- **Phase 1 Initiation in SCD Q4 2020**
- Ongoing preclinical investigation for β-Thalassemia

Losmapimod opportunity in COVID-19

Potential to transform COVID-19 into a milder and treatable disease

- p38 MAPK pathway is activated and plays a key role in the pathophysiology of severe viral infections, including COVID-19
- Losmapimod is an extensively studied (>3,600 subjects), potent, specific and orally bioavailable p38α/β inhibitor
- Losmapimod could impact multiple components of the disease and alleviate COVID-19 morbidity and mortality
- Losmapimod clinical data across multiple diseases demonstrate potential activity against the pathogenic processes in COVID-19
- Supportive FDA engagement, recommendation to proceed directly to pivotal Phase 3 trial

Evidence supports multiple impacts of p38 inhibition on COVID-19 pathology

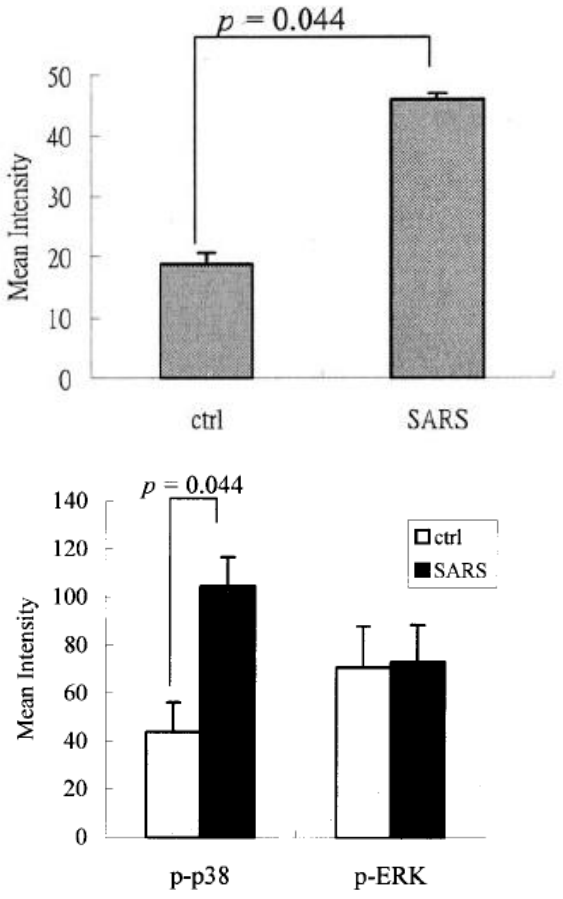


p38 is activated upon infection with SARS-CoV

Human Subjects

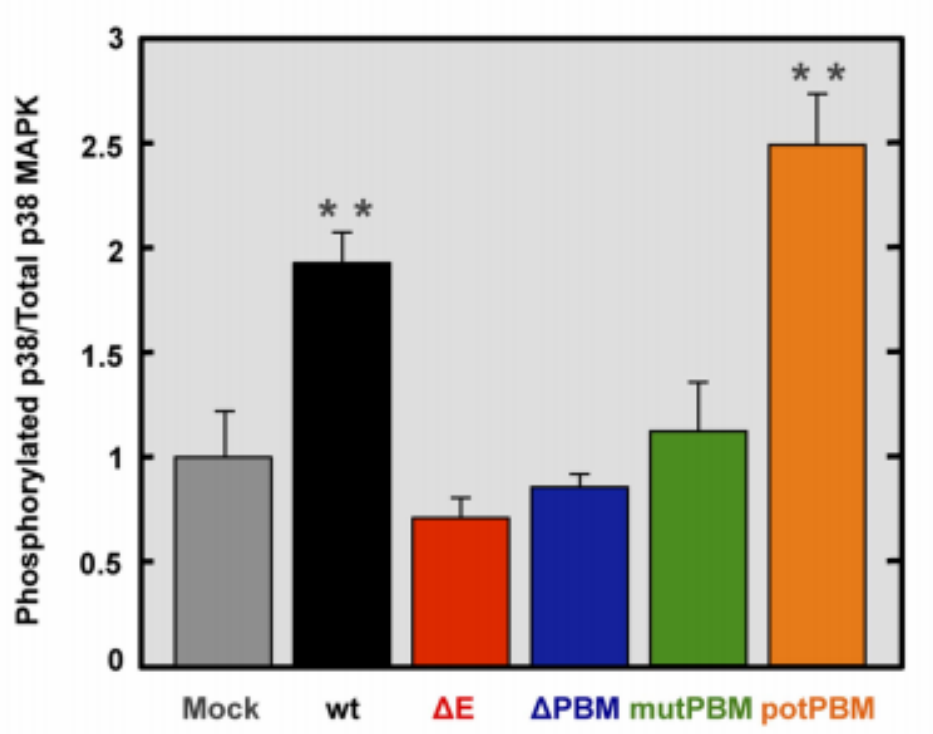
SARS patients had an increase in leukocyte cells phospho-p38

p38 pathway, but not ERK pathway, elevated in CD14 cells (monocytes)



Mouse Model of SARS-CoV

SARS-CoV activates the host inflammatory response and signals via p38 MAPK



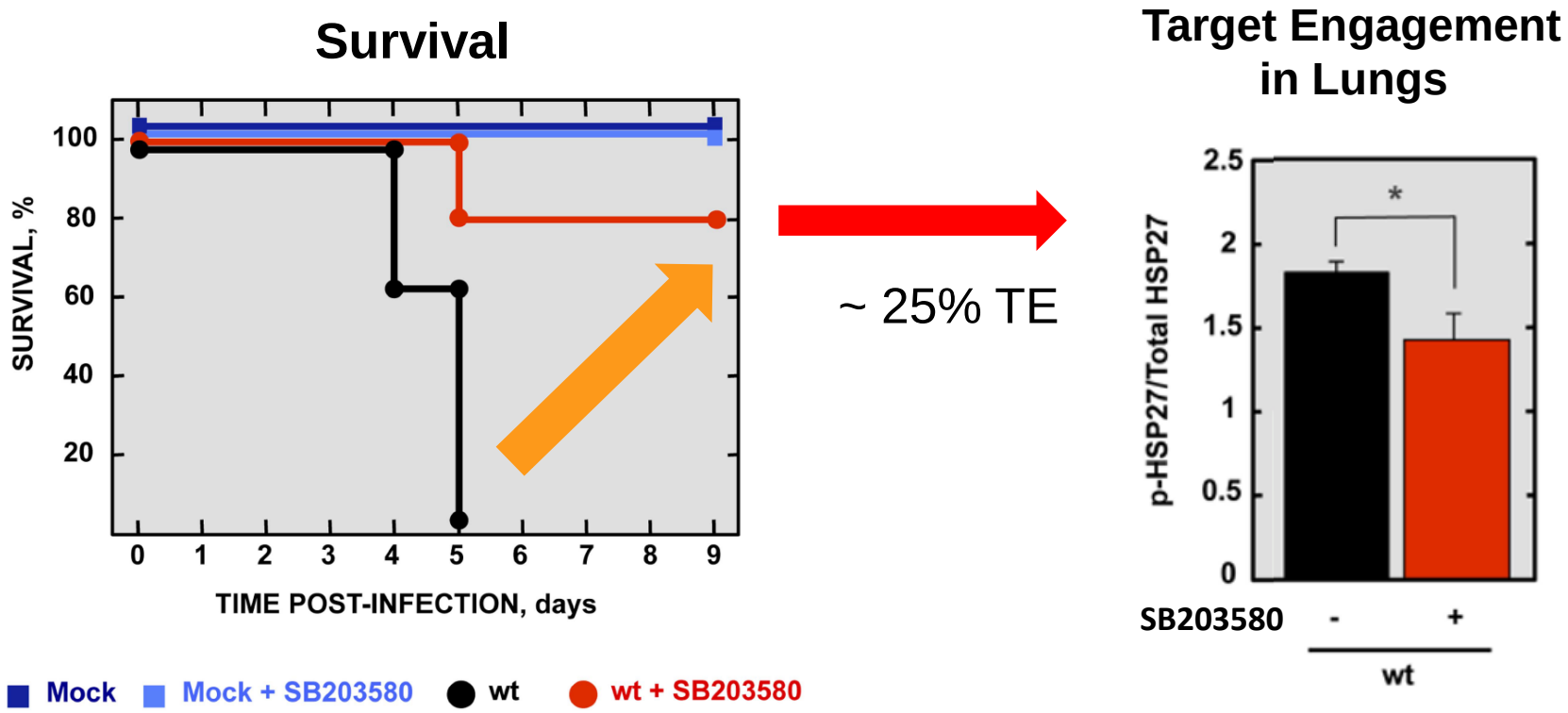
Additionally, emerging data has shown p38 activation in human SARS-CoV-2 infections

Lee, et al., Journal of Immunology. 2004; Huang et al. MedRx 2020; Jimenez-Guardeño J et.al, PLOS Pathology. 2014

p38 inhibition reduces mortality in older mice infected with SARS-CoV-1

- p38 inhibition at ~25% target engagement prevented mortality from SARS-COV-1 in mice
- In clinical trials at proposed 15 mg BID dose, Losmapimod has demonstrated sustained 40-70% target engagement in blood and tissue

- 6 mg/kg IP SB203580
- N=5 per group with 3 replicates

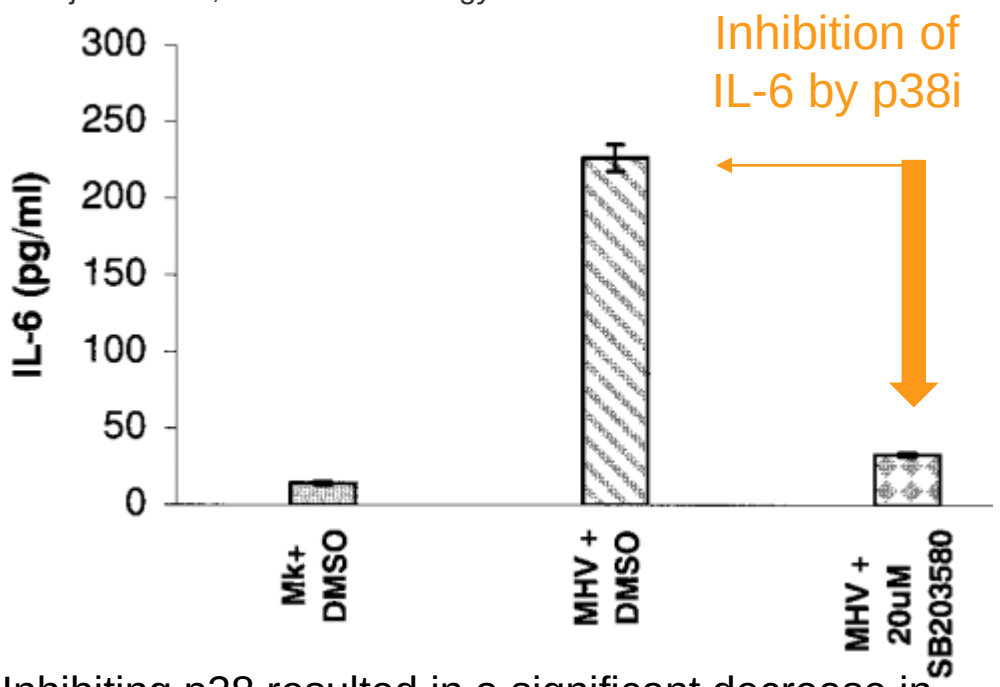


Jimenez-Guardeño J et.al, PLOS Pathology. 2014; Fulcrum Clinical Data

Efficacy of p38 inhibitors in preclinical viral models

Mouse Hepatitis (Coronavirus) Virus

Banerjee S et.al, Journal of Virology. 2002



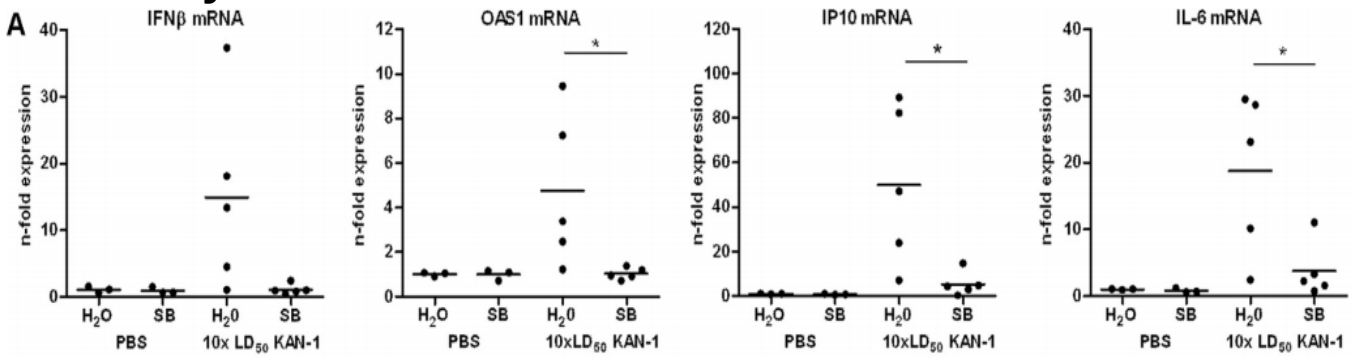
Inhibiting p38 resulted in a significant decrease in IL-6 secretion in MHV-infected cells

Numerous additional references of p38 in viral models available
Chen Y, et al., Journal of Exp Med. 2017
He F, et al., Journal Trans Med. 2019
Shapiro et al., PNAS. 1998
Lordanov et al., Mol Cell Bio. 2000
Griego et al., Journal Immunology. 2000

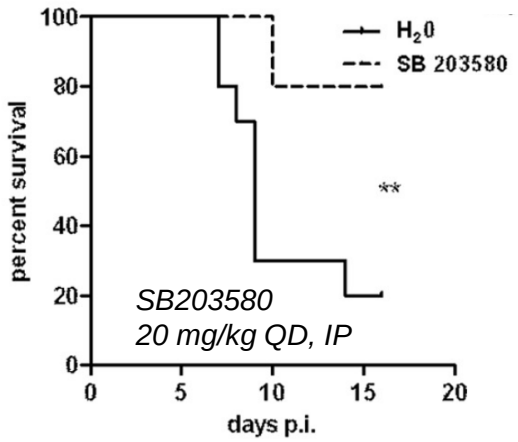
H5N1 Influenza model

Reduced Inflammatory Cytokines

Inhibiting p38 induced early suppression of cytokine amplification



Increased Survival

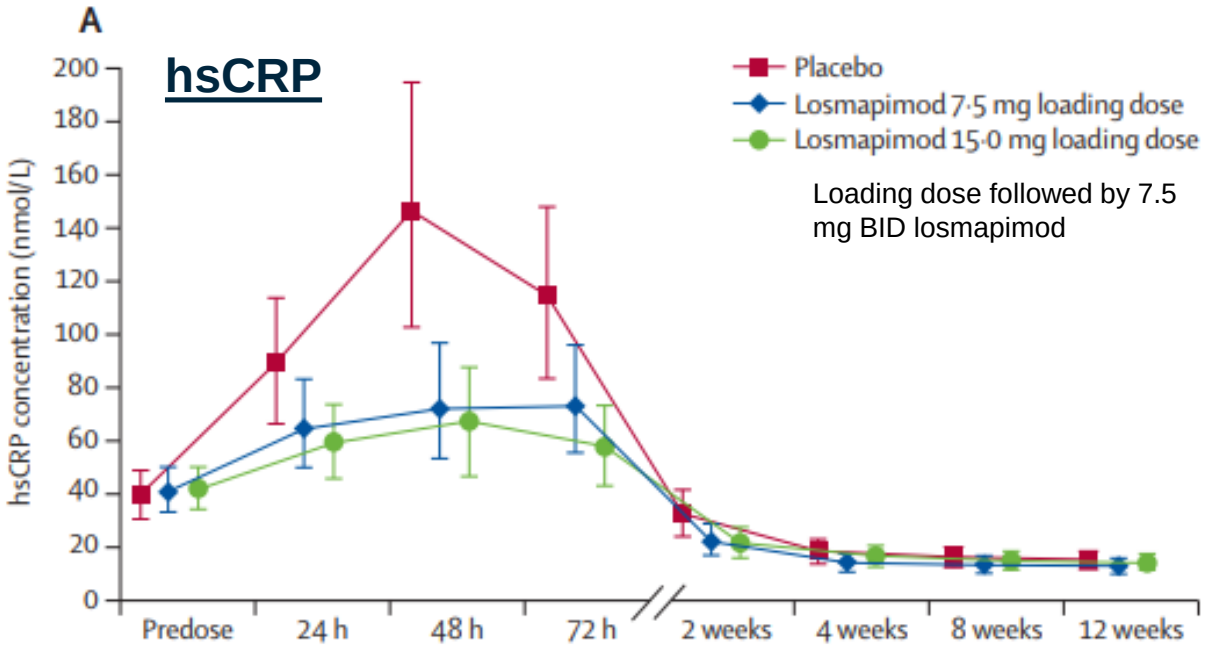


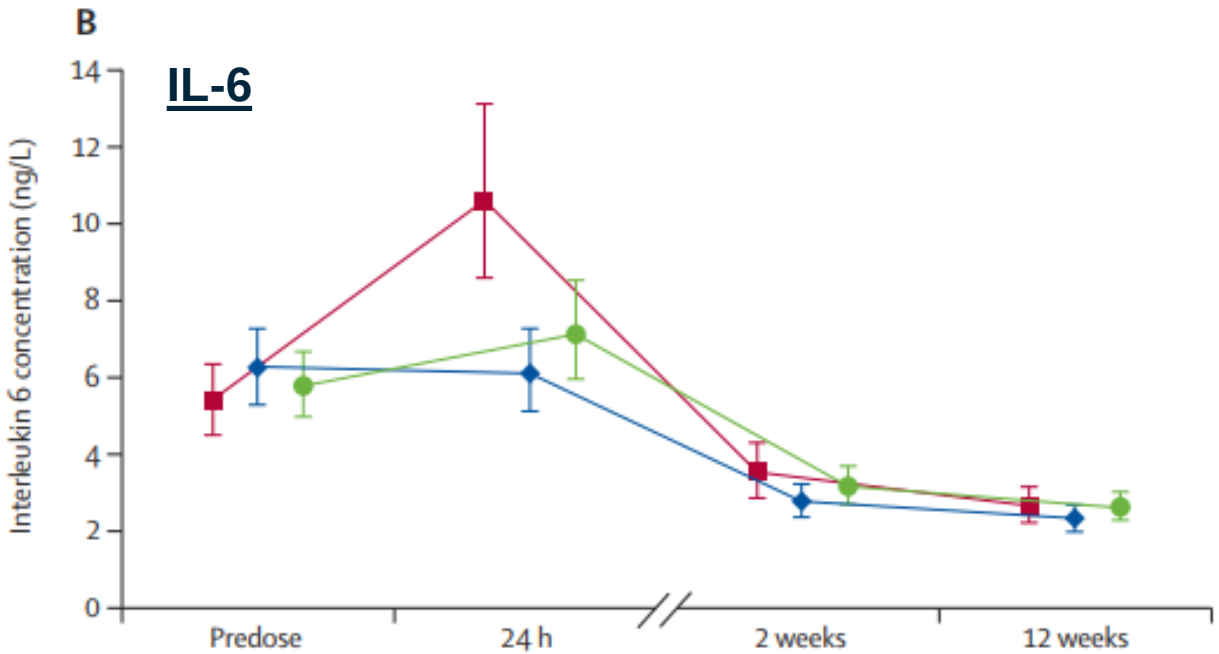
Additional data suggests targeting individual cytokines (e.g., IL-6, TNFα, etc.) insufficient to protect mice from H5N1 induced lethality

Borgeling Y et.al, Journal of Biological Chemistry. 2014; Salomon R et al., PNAS. 2007

Losmapimod acutely reduces inflammatory markers such as hsCRP and IL-6 in human diseases

Phase 2 trial – Patients with Non-ST-segment Elevation Myocardial Infarction





Additional clinical evidence of losmapimod reduction of acute inflammatory markers:

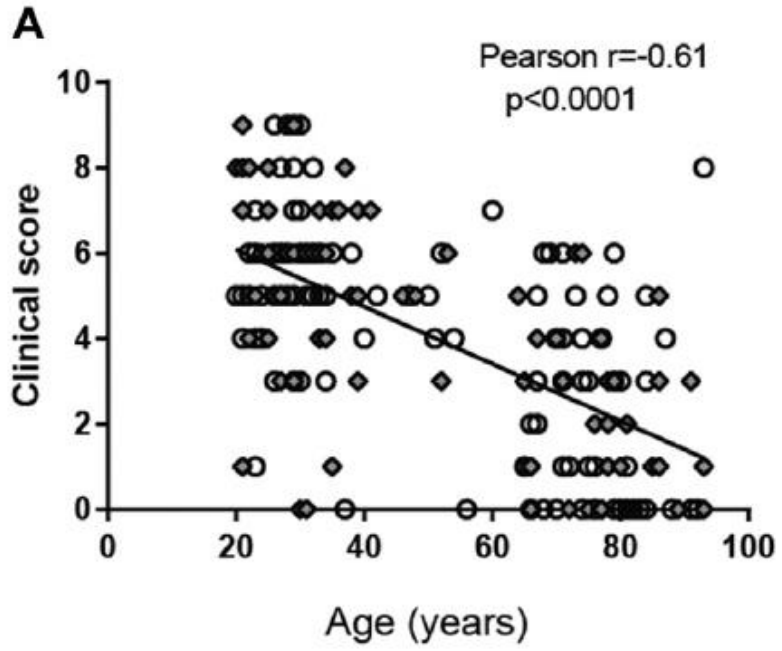
- **Sustained CRP treatment effects seen over 12 weeks in subjects with COPD following treatment with losmapimod**
- **hsCRP reduction in subjects with Acute Coronary Syndrome following treatment with losmapimod**
- **IL-6 reduction of ~60% 3 hours post treatment in subjects with active rheumatoid arthritis**

Newby L, et al., Lancet 2014; GSK Clinical Data;

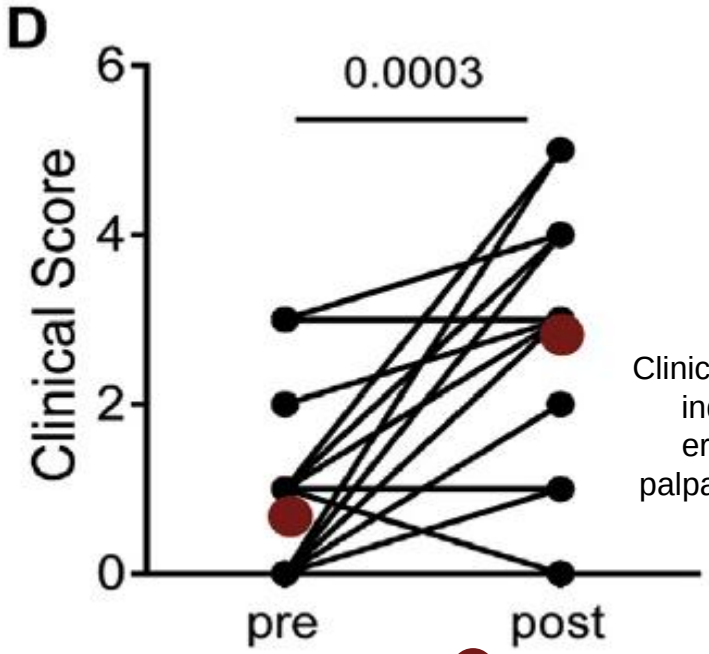
Losmapimod restored the adaptive immune response to viral challenge in older adults

- Exaggerated acute inflammatory response in older subjects involve p38 activation
- Losmapimod pretreatment at 15 mg BID dose significantly enhanced the clinical response to VZV antigen challenge in the skin of 13/18 older subjects

Adaptive Immune Response Decreased by Age



Adaptive immune response restored with losmapimod



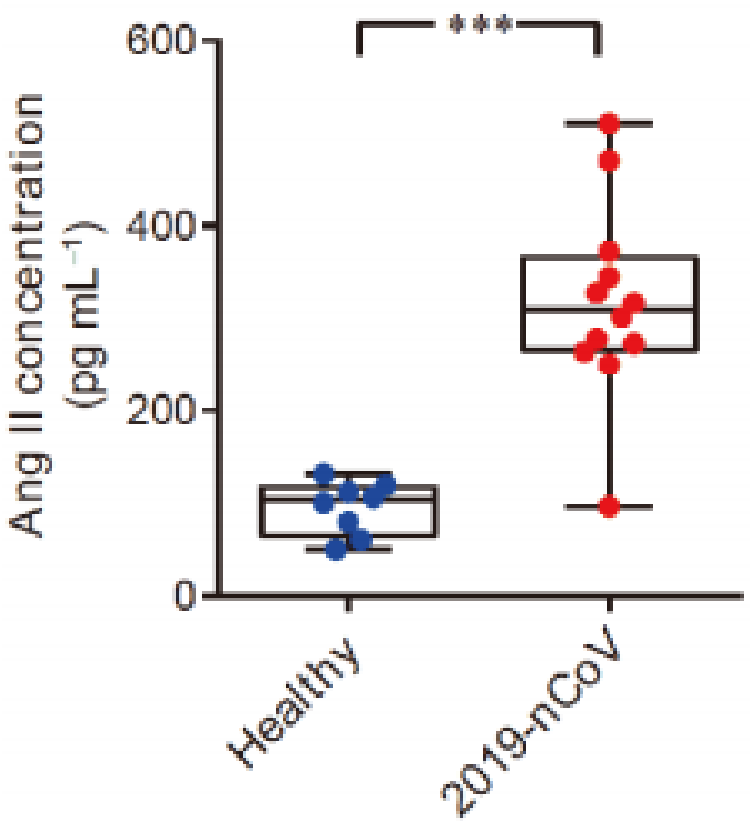
Clinical score based on induration diameter, erythema index and palpability of the lesion on day 3

Mean Clinical Score

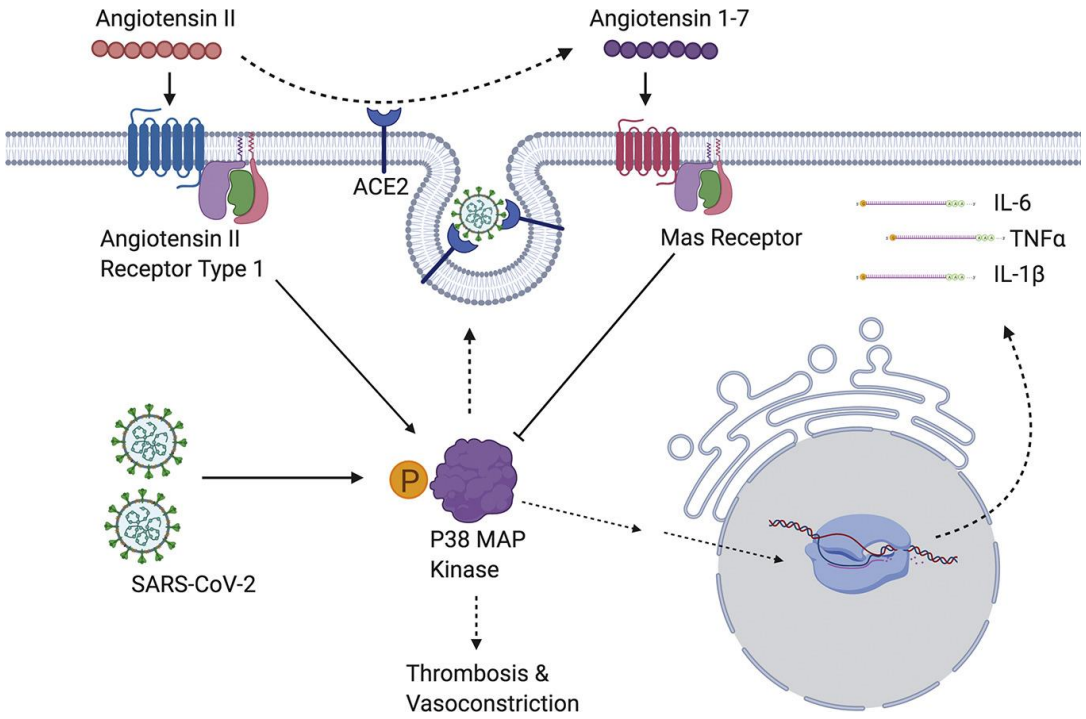
Vukmanovic-Stejic M, et al., Journal of Allergy Clin Immunol 2018

Renin-Angiotensin system imbalance may be corrected by p38 inhibition

Angiotensin II is elevated in COVID-19 patients and correlates with viral load and severity of lung injury



Liu Y et al, Sci China Life Sci 2020

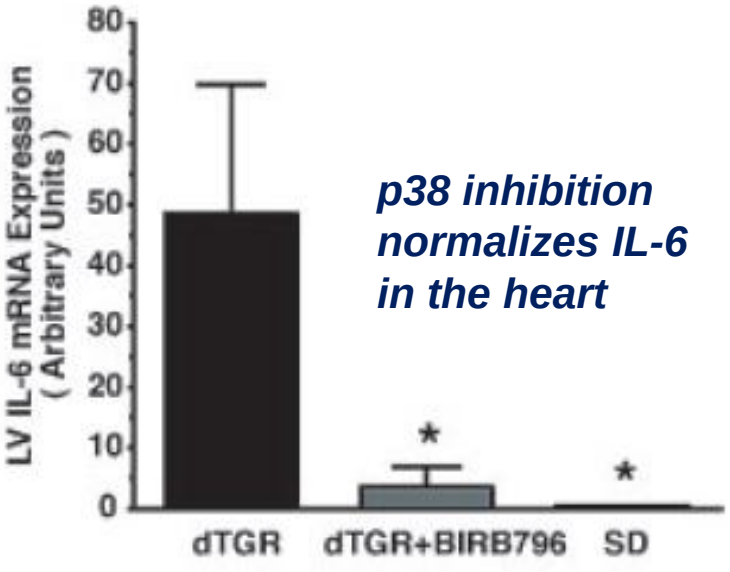


Grimes et al., JMCC 2020.

p38 inhibition shown to improve Angiotensin II driven pathology

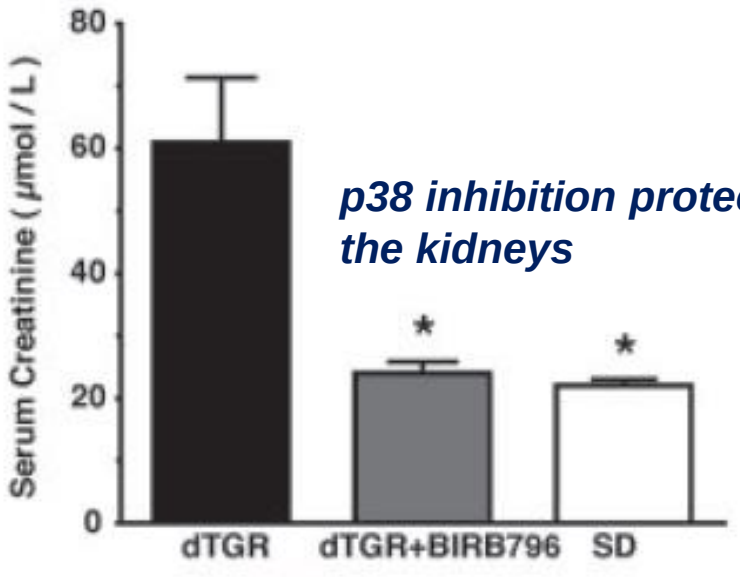
p38 inhibition reduced cardiac fibrosis, connective tissue growth factor, tumor necrosis factor, interleukin-6, and macrophage infiltration in transgenic rats with human renin and angiotensinogen and elevated ANG II

Cardiac IL-6 mRNA Expression



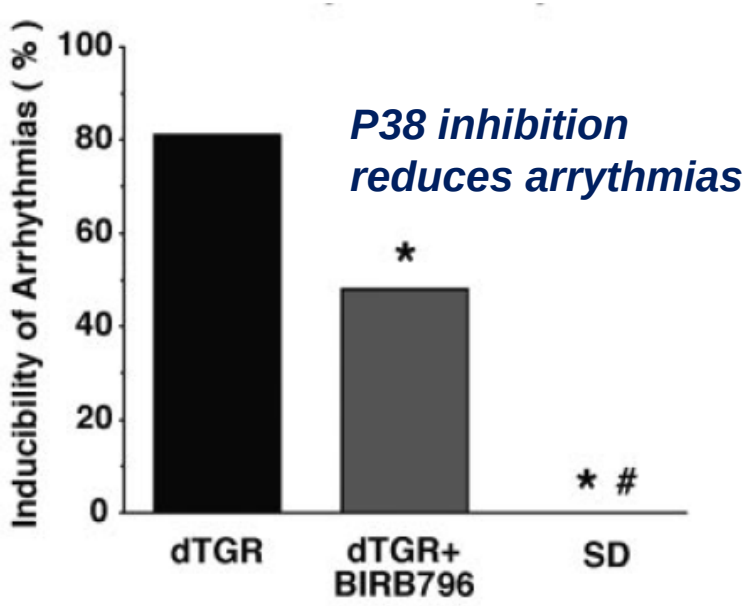
p38 inhibition normalizes IL-6 in the heart

Serum Creatinine



p38 inhibition protected the kidneys

Inducibility of Arrythmias



P38 inhibition reduces arrythmias

Park J et.al, Hypertension. 2007

Evidence supports multiple impacts of p38 inhibition on COVID-19 pathology

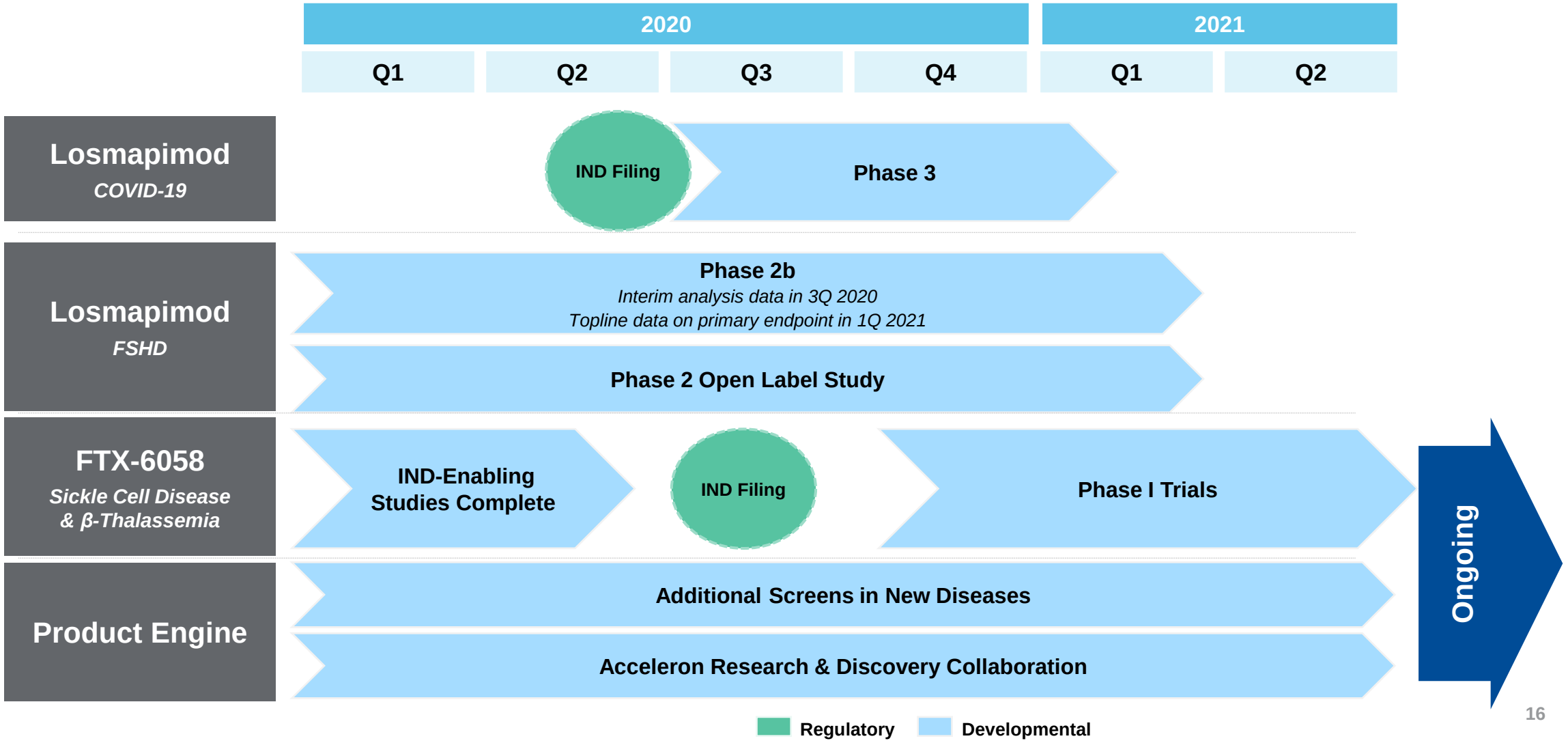
Potential Impact in COVID-19	Supporting Evidence
Restoration of the adaptive – innate immune balance	▪ Exaggerated acute inflammatory responses in older individuals hinder adaptive immunity; Many of the implicated inflammatory mediators, including macrophage polarization and the NLRP3 inflammasome, are associated with activation of p38 MAPK signaling ▪ Losmapimod treatment resulted in the timely resolution of acute inflammation and restored effective T-cell response to a viral antigen challenge in older human subjects
Broad suppression of inflammatory programs	▪ p38 activation is present early in patients with viral infections, including SARS-CoV-2 ▪ p38 inhibition has been shown preclinically to interrupt acute, viral driven inflammatory programs reducing morbidity & mortality of coronavirus and other severe viral infections ▪ Losmapimod significantly and rapidly reduced acute inflammatory biomarkers in clinical trials
Correction of renin-angiotensin system dysfunction	▪ SARS-CoV-2 infection leads to an angiotensin imbalance thought to underlie severe complications including hypertension, cardiac dysfunction, clotting, and end organ damage ▪ p38 MAPK inhibition has been shown to reduce Ang II-induced endothelial and organ damage in several experimental models

Losmapimod safety summary

- **>3,600 subjects treated in clinical trials**
  - Study duration varied from single dose to 52 weeks
  - Tested in at least 11 different adult indications
  - Tested in >30 Countries
  - Tested at single doses as high as 60 mg and in repeated doses as high as 15 mg BID and 20 mg QD
  - Exposure is approximately dose proportional
- **Losmapimod has been generally safe and very well tolerated**
  - Similar frequency and severity of AEs/SAEs as placebo
  - Similar frequency of discontinuation as placebo
  - No safety signals from the liver, the bone marrow, the heart, or the CNS
  - No increase in infections compared to placebo
  - Changes in vital signs, EKG, blood chemistry similar to placebo
  - Did not show any of the safety signals observed with earlier generation p38 inhibitors

Opportunity for continued rapid progress through H1 2021

Cash runway into 1Q2022



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COVID-19 Additional Materials

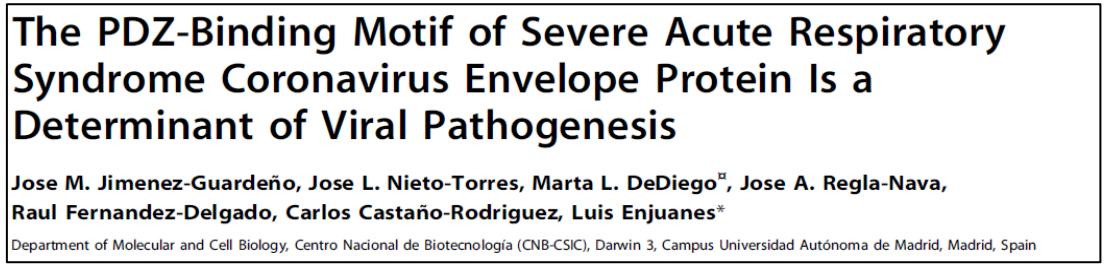
Extensive support for use of losmapimod in treatment of acute infections including COVID-19

Key Literature Support

p38 MAPK inhibition: A promising therapeutic approach for COVID-19

Joseph M. Grimes[a], Kevin V. Grimes[b,*]

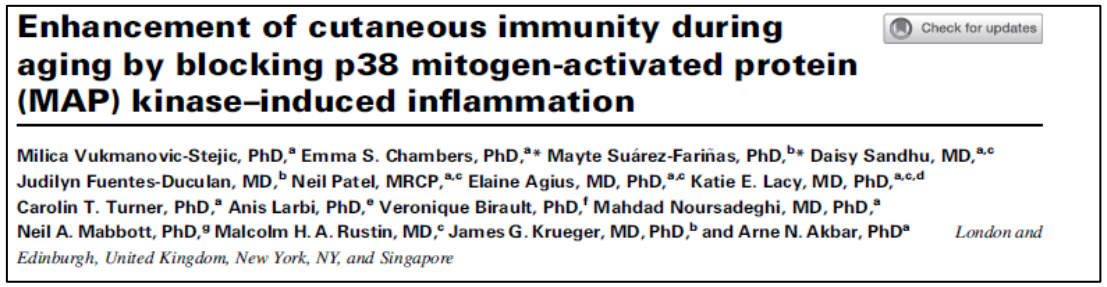
[a] Vagelos College of Physicians And Surgeons, Columbia University; 630 W. 168th St, New York, NY 10032, United States of America
[b] Chemical and Systems Biology, Stanford University, Stanford, CA; 269 Campus Drive CCSR 3145, Stanford, CA 94305, United States of America



The PDZ-Binding Motif of Severe Acute Respiratory Syndrome Coronavirus Envelope Protein Is a Determinant of Viral Pathogenesis

Jose M. Jimenez-Guardeño, Jose L. Nieto-Torres, Marta L. DeDiego¤, Jose A. Regla-Nava, Raul Fernandez-Delgado, Carlos Castaño-Rodriguez, Luis Enjuanes*

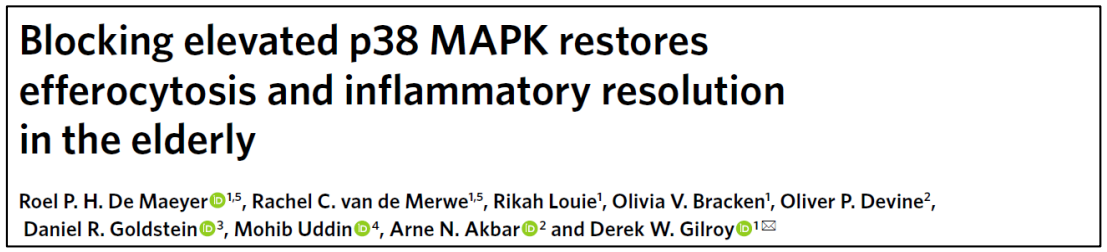
Department of Molecular and Cell Biology, Centro Nacional de Biotecnología (CNB-CSIC), Darwin 3, Campus Universidad Autónoma de Madrid, Madrid, Spain



Enhancement of cutaneous immunity during aging by blocking p38 mitogen-activated protein (MAP) kinase–induced inflammation

Check for updates

Milica Vukmanovic-Stejic, PhD,[a] Emma S. Chambers, PhD,[a]* Mayte Suárez-Fariñas, PhD,[b]* Daisy Sandhu, MD,[a,c] Judilyn Fuentes-Duculan, MD,[b] Neil Patel, MRCP,[a,c] Elaine Agius, MD, PhD,[a,c] Katie E. Lacy, MD, PhD,[a,c,d] Carolin T. Turner, PhD,[a] Anis Larbi, PhD,[e] Veronique Birault, PhD,[f] Mahdad Noursadeghi, MD, PhD,[a] Neil A. Mabbott, PhD,[g] Malcolm H. A. Rustin, MD,[c] James G. Krueger, MD, PhD,[b] and Arne N. Akbar, PhD[a] London and Edinburgh, United Kingdom, New York, NY, and Singapore



Blocking elevated p38 MAPK restores efferocytosis and inflammatory resolution in the elderly

Roel P. H. De Maeyer[1,5], Rachel C. van de Merwe[1,5], Rikah Louie[1], Olivia V. Bracken[1], Oliver P. Devine[2], Daniel R. Goldstein[3], Mohib Uddin[4], Arne N. Akbar[2] and Derek W. Gilroy[1]✉

Annotated Review of Literature available in Appendix

1. Siddiqi HK et al. J Heart Lung Transplant. 2020
2. Ruan Q et al. Intensive Care Med. 2020 Mar 3
3. Zhou F et al. Lancet. 2020
4. **Nagata N et al. Am J Pathol. 2008**
5. Lee CH et al. J Immunol. 2004.
6. Huang et al. MedRx 2020
7. **Jimenez-Guardeño JM et al. PLOS Pathog. 2014**
8. Kono M et al. Antiviral Res. 2008
9. Dong Y et al. Antiviral Res. 2020
10. Kindrachuk D et al. Anti Microb Agents & Chem. 2015
11. Liu et al. Int Immunopharmacol. 2009
12. Shapiro L et al. PNAS. 1998
13. Iordanov MS et al. Mol Cell Bio. 2000
14. Salomon R et al. PNAS. 2007
15. Griego SD et al. J Immunol. 2000
16. Banerjee S et al. J Virology. 2002
17. Börgeling Y et al. J Biol Chem. 2014
18. Chen Y et al. J Exp Med. 2017
19. He F et al. J Transl Med. 2019
20. Genovese M et al. J Rheumatol. 2011
21. Christie J et al. Crit Care Med. 2015
22. Newby L et al. Lancet. 2014
23. Blanco-Melo D et al. Cell. 2020
24. **Vukmanovic-Stejic M et al. J Allergy Clin Immunol. 2018**
25. **De Maeyer RPH et al,, Nature Immunology 2020**
26. **Grimes et al. JMCC 2020**
27. Liu Y et al, Sci China Life Sci 2020
28. Park J et.al, Hypertension. 2007
29. Cadavid D et al. FSHD IRC Poster. 2019

Key Papers bolded

Extensive literature supporting rationale for losmapimod in viral infections, including COVID-19 (1 of 2)

Evidence	References
• Acute lung injury, acute respiratory distress syndrome, pulmonary edema, and cardiomyopathy drive COVID-19 mortality • Older patients are at greatest risk of COVID-19 mortality	• Siddiqi HK et al. J Heart Lung Transplant. 2020 • Ruan Q et al. Intensive Care Med. 2020 Mar 3
• Human SARS-CoV-2 pathology is recapitulated in SARS-CoV-1 mice • Exaggerated acute inflammatory response and lymphopenia correlate with mortality in human with COVID-19 and older mice infected with SARS-CoV-1	• Zhou F et al. Lancet. 2020 • Nagata N et al. Am J Pathol. 2008
• SARS-CoV-1 and SARS-CoV-2 activates the p38 MAPK pathway in peripheral blood early in the infection	• Lee CH et al. J Immunol. 2004. • Huang et al. MedRx 2020
• SARS-CoV envelope protein (E) activates the host's inflammatory response via p38 signaling	• Jimenez-Guardeño JM et al. PLOS Pathog. 2014
• Several nonclinical studies have shown evidence of p38 inhibition reducing viral replication including with coronavirus	• Kono M et al. Antiviral Res. 2008 • Dong Y et al. Antiviral Res. 2020 • Kindrachuk D et al. Anti Microb Agents & Chem. 2015
• p38 inhibition reduces mortality in older mice infected with SARS-CoV-1	• Jimenez-Guardeño J et al. PLOS Pathog. 2014
• p38 inhibition reduces lung mucous production in mice models of toxic airway injury	• Liu et al. Int Immunopharmacol. 2009

Extensive literature supporting rationale for losmapimod in viral infections, including COVID-19 (2 of 2)

Evidence	References
• Nonclinical efficacy of p38 inhibition also observed in other models of severe viral pneumonitis and other severe viral infections	• Shapiro L et al. PNAS. 1998 • Iordanov MS et al. Mol Cell Bio. 2000 • Salomon R et al. PNAS. 2007 • Griego SD et al. J Immunol. 2000 • Banerjee S et al. J Virology. 2002 • Börgeling Y et al. J Biol Chem. 2014 • Chen Y et al. J Exp Med. 2017 • He F et al. J Transl Med. 2019
• Clinical data with Losmapimod (at current doses) and other p38 inhibitors acutely reduce inflammatory markers associated with COVID-19 severity	• Genovese M et al. J Rheumatol. 2011 • Christie J et al. Crit Care Med. 2015 • Newby L et al. Lancet. 2014
• In vivo data indicates SARS-Cov-2 can induce profoundly lower immune response to infection vs other virus	• Blanco-Melo D et al. Cell. 2020
• Inhibition of p38 with 15 mg losmapimod BID dose in older subjects restored the adaptive immune response to viral challenge • Exaggerated acute inflammatory response in older subjects is driven to a large extent by p38 activation • Losmapimod restores inflammation resolution in older subjects	• Vukmanovic-Stejic M et al. J Allergy Clin Immunol. 2018 • De Maeyer RPH et al,, Nature Immunology 2020
• p38 inhibition shown to improve Angiotensin II (increased in COVID-19) driven pathology, including survival, organ damage, and arrhythmogenic potential	• Grimes et al. JMCC 2020 • Liu Y et al, Sci China Life Sci 2020 • Park J et.al, Hypertension. 2007
• Losmapimod is a highly selective p38 inhibitor at advanced stage of clinical development with excellent safety data profile	• Cadavid D et al. FSHD IRC Poster. 2019

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