Senhwa Biosciences, Inc.

A worldwide partnering opportunity for Silmitasertib as a potential COVID-19 therapy

Bringing Hope to Life

December 2020

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Senhwa Biosciences
Company overview and BD objective

Founded: 2012
Headquarter: Taipei, TW
Subsidiary: San Diego, US
Public Listing: TPEx: 6492
Shares: 89.6 Million*
Mkt Cap: $800 Million*

** As of 10/30/2020*

- A development-stage oncology company with two targeted small molecules in clinical trials, one of which has recently been implicated as a COVID-19 treatment
- Rapid prosecution of the mechanism by which silmitasertib exerts anti-viral and inflammatory response effects in patients with COVID-19
- Collaborations established, with more being finalized, to further test the preclinical & clinical benefits of silmitasertib against COVID-19
- Seeking a global partner for the development and commercialization of silmitasertib (CX-4945) a small molecule CK2 inhibitor for the treatment of COVID-19

Senhwa Biosciences Current Pipeline Status

Program	Indication	Preclinical	Phase 1/ Expansion	Phase 2	Pivotal	Sponsor/ Funded
Pidnarulex (CX-5461) 	Breast Cancer		CA			SU2C/CBCF*
	Breast, Ovarian, Prostate, Other solid tumors		CA, US			
	Prostate cancer (PARPi combo)		AU			PCF/Pfizer+
Silmitasertib (CX-4945) 	Cholangio-carcinoma		US, KR, TW			
	Advanced Basal Cell Carcinoma		US			
	Medullo-blastoma		US			NIH/CTEP**
	COVID-19	US, TW		US		

* Stand Up To Cancer Grant Winner of 2016. SU2C funded phase I study conducted by Canadian Clinical Trial Groups (CCTG). Also funded by Canadian Breast Cancer Foundation (CBCF).

** Fully funded by NIH/CTEP and conducted by Pediatric Brain Tumor Consortium (PBTC).

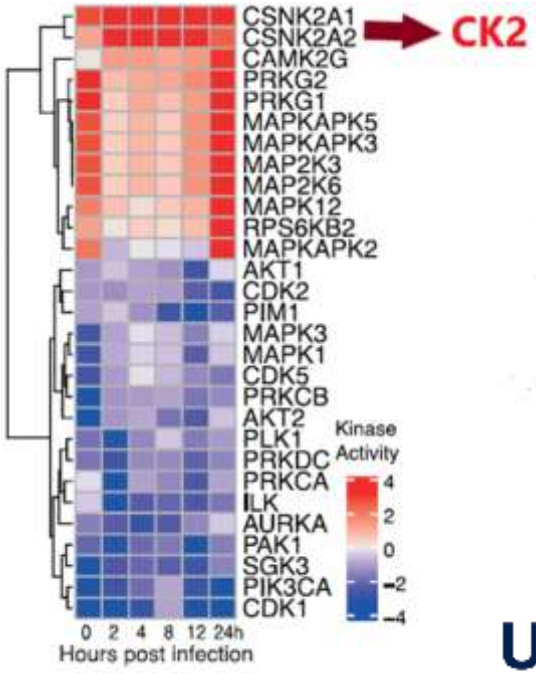
+PCF-Pfizer Global Challenge Awards Winner of 2020.

Silmitasertib Summary

- Potential to be the first dual-action treatment for COVID-19, inhibiting cell-to-cell viral spread and dampening the virus-provoked dysregulated host inflammatory response
- The drug exploits coronavirus dependence on a host enzyme, which should present a high barrier to emerging viral resistance
- In vitro evidence demonstrates reduction of SARS-CoV-2 replication, and there are several in vivo preclinical studies currently underway
- Has been consistently shown to inhibit multiple cytokines in vitro, in vivo, and in human clinical trials (IL6, IL8, TNFα, and IL17)
- Has a proven safety and tolerability profile in over 200 human subjects from multiple Phase 1, Phase 1 expansion and Phase 2 cancer trials
- Early indication of potential for human efficacy under an eIND in a hospitalized US patient who had exhausted all other treatment options
- Several clinical trials in COVID-19 patients are planned or underway
- An oral therapy that could easily be taken at home or in the hospital

How was silmitasertib first linked with COVID-19?

Signaling Changes in Host Cells in Response to SARS-CoV-2 Infection. Kinases depicting a strong change in activity upon infection.

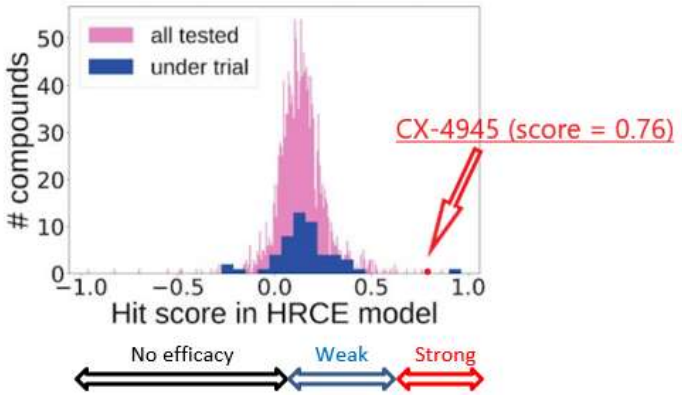


UCSF

Source: Bouhaddou M, Memon D, Meyer B, et al. The Global Phosphorylation Landscape of SARS-CoV-2 Infection. Cell. Published online 2020. doi:10.1016/j.cell.2020.06.034 https://www.cell.com/cell/fulltext/S0092-8674(20)30811-4

Evaluation of 1,670 molecules for their ability to suppress the impacts of the SARS-CoV-2 virus on phenomic profiles of human cells

Chemical Suppressor screens in HRCE cells pretreated with each compound, then infected with SARS-CoV-2. Silmitasertib and Remdesivir were 2 of all drugs tested that had high 'on-disease scores' and low 'off-disease scores'.



Institute for ANTIVIRAL RESEARCH

Source: Heiser et al. Identification of potential treatments for COVID-19 through artificial intelligence-enabled phenomic analysis of human cells infected with SARS-CoV-2, bioRxiv 2020.04.21.054387; https://doi.org/10.1101/2020.04.21.054387

Silmitasertib is a Potent and Selective Inhibitor of Casein Kinase 2 (CK2) Enzymatic Activity

- Silmitasertib is 1600-fold more potent than TBB at inhibiting CK2

Comparison of CK2 inhibitors		
Compound Name	CX-4945	TBB (4,5,6,7- tetrabromobenzotriazole)
IC50 (nM) against CK2	1	1600

- Silmitasertib displays high specificity for CK2 relative to other kinases

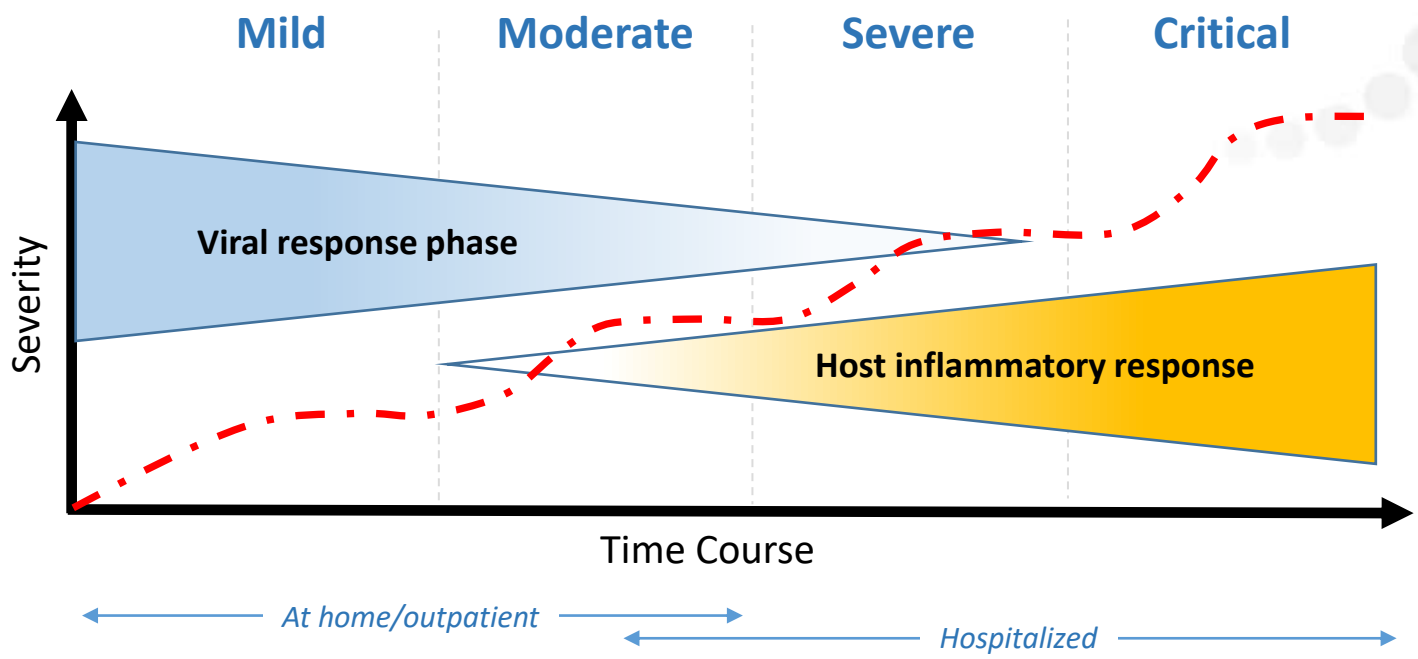
Silmitasertib evaluation in a biochemical kinase screen.
Using a single concentration of 500 nmol/L (500-fold greater than the IC50 of CK2), only 7 of the 238 kinases tested were inhibited by more than 90% and those 7 were further subjected to IC50 determination (Column 1, Table 1). In relevant cell-based functional assays for FLT3, PIM1, and CDK1, silmitasertib was functionally inactive against these kinases.

Table 1. IC_{50} determinations for CX-4945 against selected kinases from the 238-kinase selectivity panel

Kinase	IC_{50} (nmol/L)	Kinase	IC_{50} (nmol/L)
CK2α	1	PI3Kβ	>500
CK2α′	1	PI3Kδ	>500
DAPK3	17	PI3Kγ	>500
FLT3	35	PDK1	>500
TBK1	35	AKT1	>500
CLK3	41	AKT2	>500
HIPK3	45	AKT3	>500
PIM1	46	mTOR	>500
CDK1/cyclin B	56	p70S6K	>500

Source: Siddiqui-Jain et al. Cancer Res; 70(24) December 15, 2010.

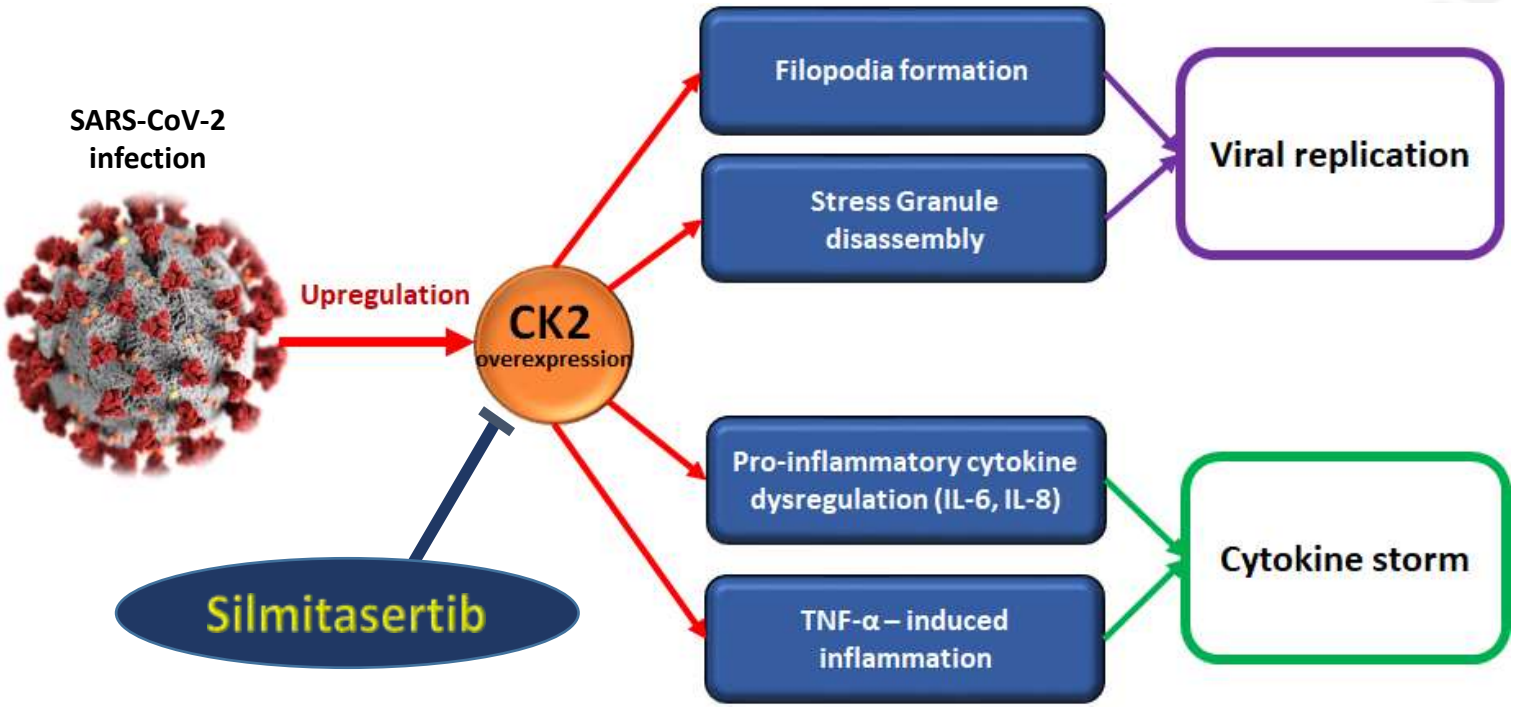
Symptomatic COVID-19: Stages of Infection



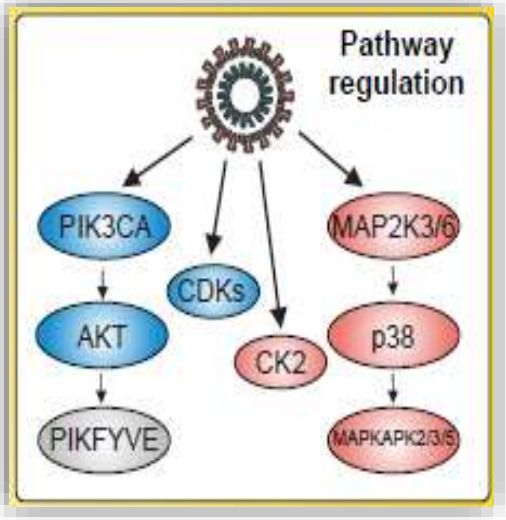
Clinical signs & symptoms	Mild constitutional symptoms, fever, dry cough, lymphopenia	Shortness of breath with and without hypoxia, abnormal chest imaging, transaminitis	ARDS, SIRS, cardiac failure, high troponin, cytokine storm

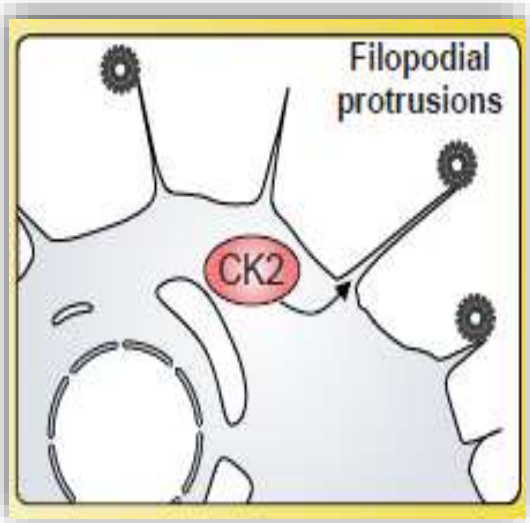
Source: Adapted from Siddiqi (2020) J Heart Lung Transplant 39:405-7

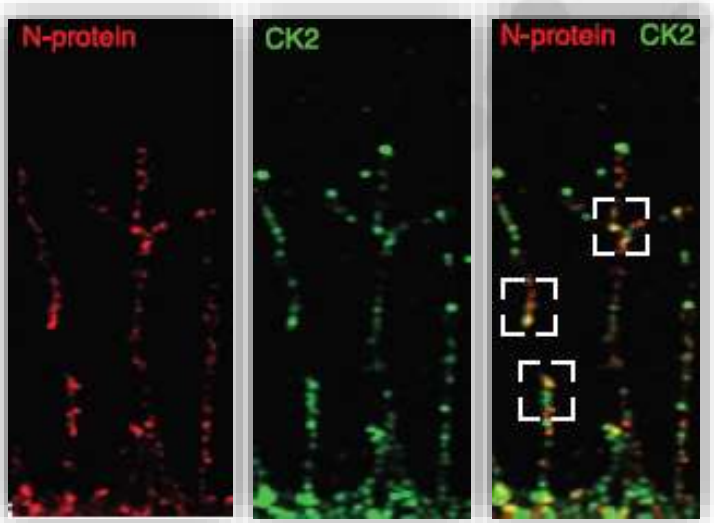
Silmitasertib has potential to reduce viral spread and to limit cytokine storm through complimentary actions



CK2 Upregulation Promoted by SARS-CoV-2 Infection and Co-localizes with Viral Proteins at Actin Protrusions



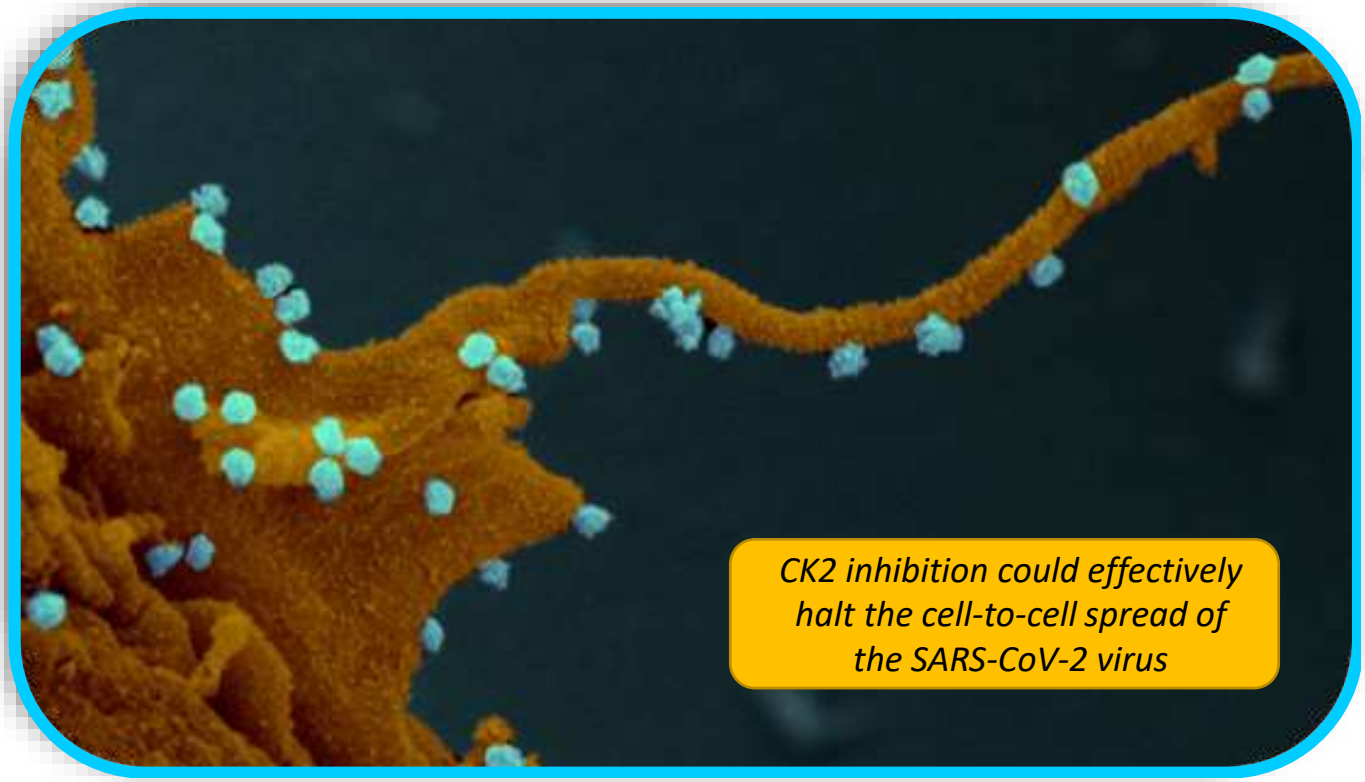




- At 24 hours post-infection, cells express **CK2 along thin filopodia** (actin protrusions), **partially co-localized with** the SARS-CoV-2 **N (nucleocapsid) protein**
  - **Phosphorylated N protein** binds to and **assists with packaging of viral RNA**
  - **Shuttling of** SARS-CoV-1 **N protein** from nucleus to cytoplasm is **dependent upon CK2**
- ***These data suggest CK2 activity regulates the SARS-CoV-2 life cycle***

Sources: Bouhaddou et al, The Global Phosphorylation Landscape of SARS-CoV-2 Infection, Cell, Aug 2020: 685-712.e19; Surjit (2005) J. Virol. 79:11476–86.

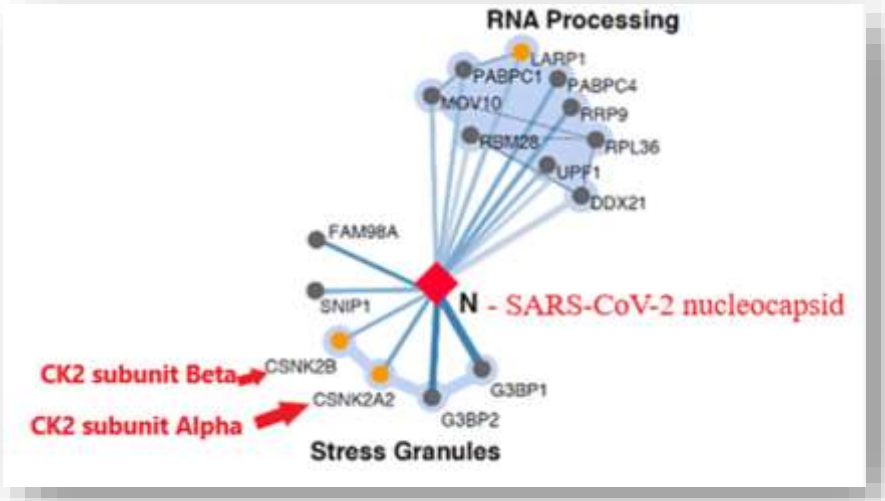
CK2 Promotes Formation of Filopodial Protrusions from SARS-CoV-2 Infected Cells

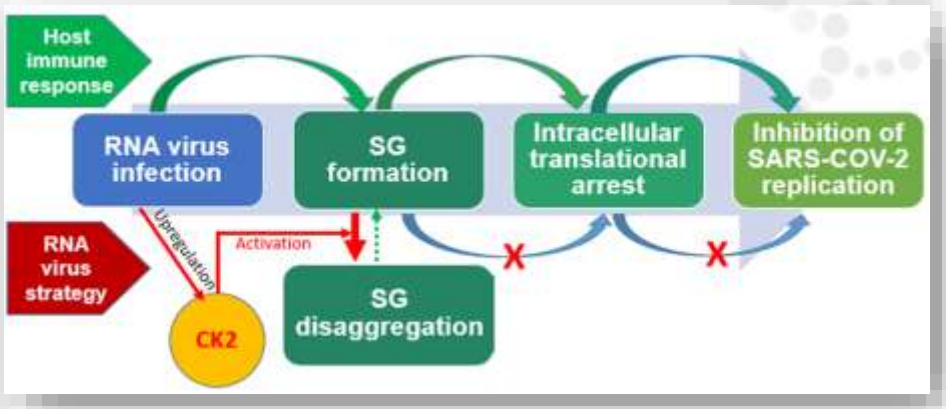


SARS-CoV-2 hijacks infected host cells to **upregulate CK2** and **drive formation of filopodia** from which virus is released to infect neighboring cells.

Source: QBI at UCSF; https://www.youtube.com/watch?v=RjFFGCsu2lk&feature=youtu.be

Coronavirus Infection of Host Cells Triggers Stress Granule Formation, but viral activation of CK2 is a countermeasure



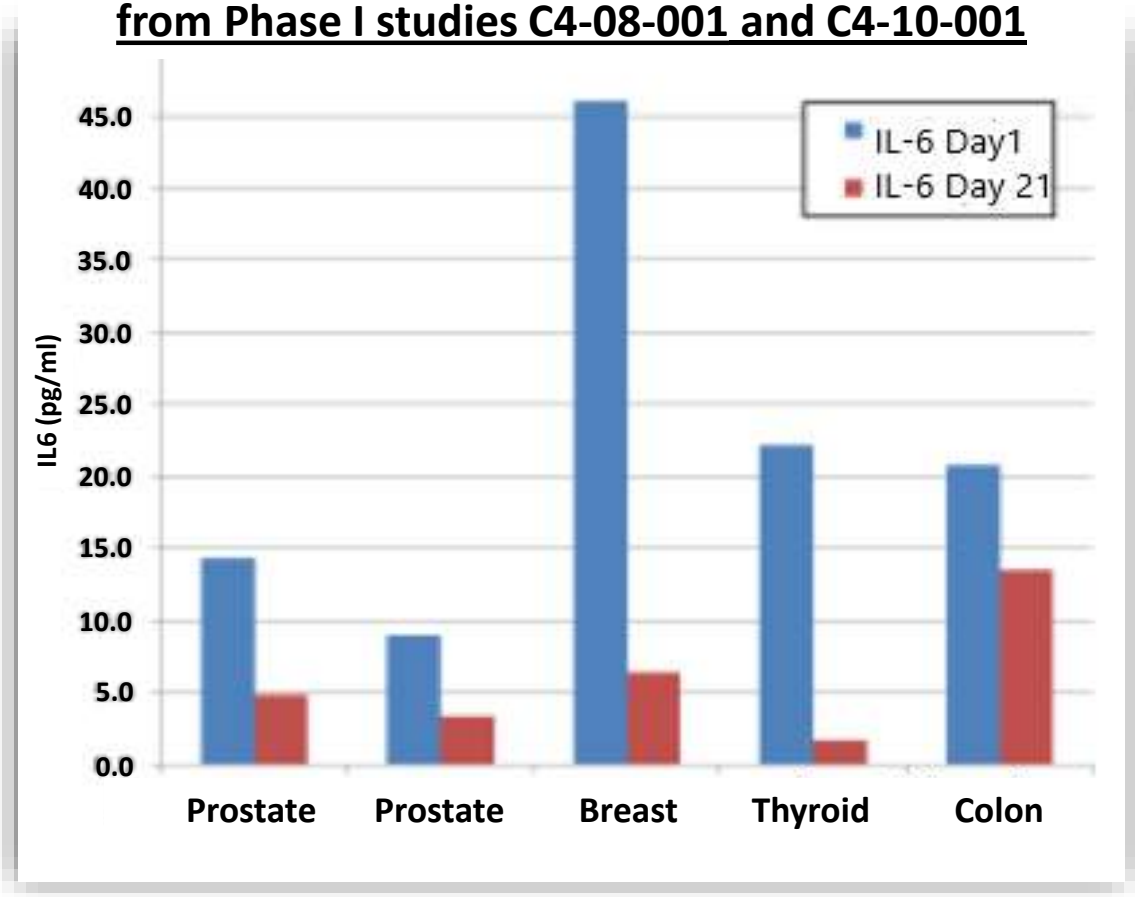


- SGs inhibit replication of coronaviruses (MERS-CoV) and other viruses
- The SARS-CoV-2 nucleocapsid (N-protein) interacts with CK2 and G3BP1/2 (SG proteins)
- **CK2 phosphorylates G3BP1** at Ser149, which promotes SG disaggregation, **and benefits viral replication**
- **Silmitasertib** inhibition of CK2 is expected to **inhibit this activity**

Sources: Nakagawa (2018) J. Virol. 92; Reineke (2017) Mol Cell Biol; Gordon (2020) bioRxiv 2020.03.22.002386

Silmitasertib has been shown to reduce levels of inflammatory cytokines in clinical oncology studies

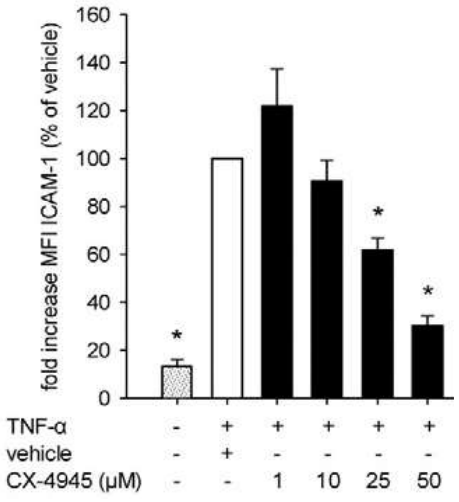
Plasma levels of IL-6 in CX-4945-treated patients from Phase I studies C4-08-001 and C4-10-001



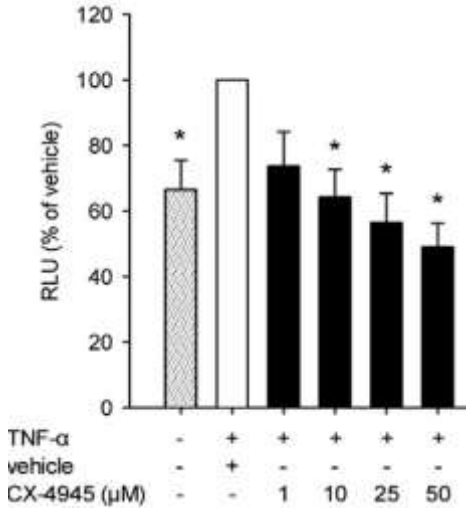
Source: Senhwa, data on file

Silmitasertib has been shown in preclinical studies to reduce the pro-inflammatory effects of TNF-α in cells

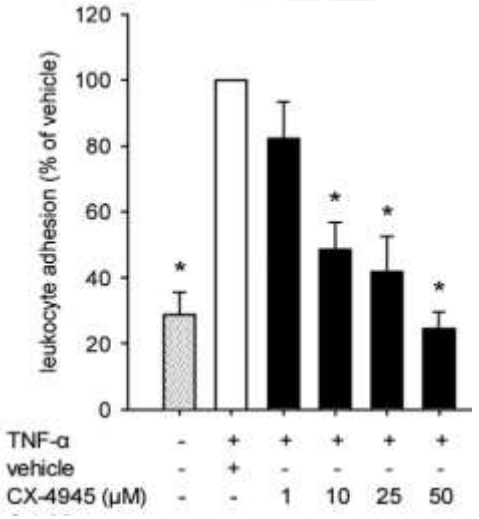
TNF-α driven surface protein expression



Subcellular localization of p65



Leukocyte–endothelial cell interaction



TNF- α is a major proinflammatory cytokine that plays a key prominent role in pathogenesis of cytokine storm. A team at Saarland University (Hamburg/Saar, Germany) found that CX-4945 effectively suppressed the activity of CK2, a key regulator of leukocyte–endothelial cell interaction in inflammation, by affecting the transcriptional activity of the NF-κB complex.

Source: Ampofo, Emmanuel, et al. "Inhibition of protein kinase CK2 suppresses tumor necrosis factor (TNF)-α-induced leukocyte–endothelial cell interaction." Biochemical et Biophysical Acta (BBA)-Molecular Basis of Disease 1852.10 (2015): 2123-2136.

Preclinical data indicate Silmitasertib inhibition of SARS-CoV-2, with additional studies underway

Calu-3 cell line
(Human lung cancer cells)

Cells pretreated with test compounds prior to infection with SARS CoV2. Sample well data normalized to DMSO control wells and plotted vs drug concentration for the IC50 and CC50.*

IC50	Hill	CC50	SI
1.056	-2.27	34.65	> 32

Ongoing Studies:

- Other in vitro studies (e.g. in Caco-2 cells)
- Pan-coronavirus (e.g. sars, mers) in vitro study to show dependence upon functional human CK2 enzyme (implications for broader application)
- Several in vivo studies, including in Tg mice models and hamster model to test impact on viral load, lung pathology and immune markers

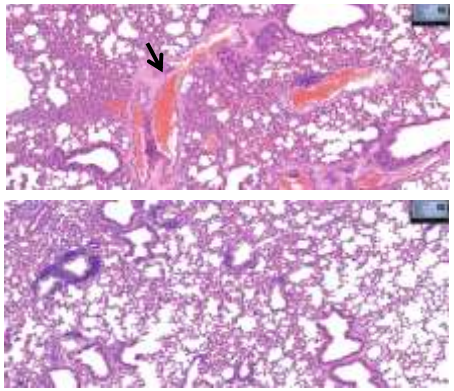
* *Source: Available under CDA*

Silmitasertib reduces pathological inflammation caused by COVID-19 in infected transgenic mice

Histopathology

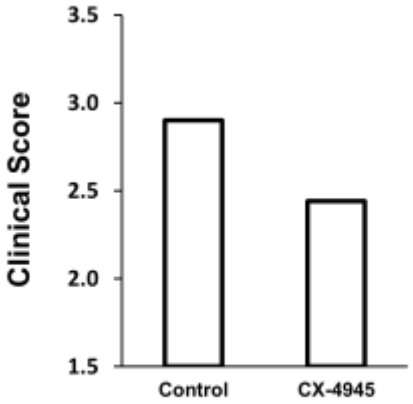
Control

CX-4945

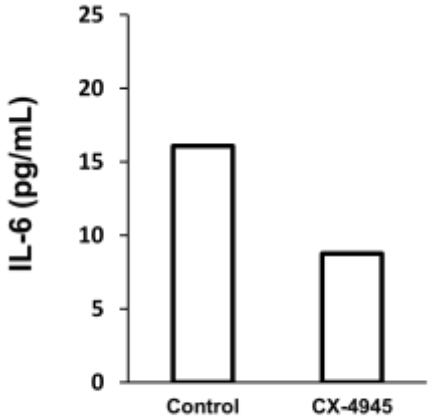


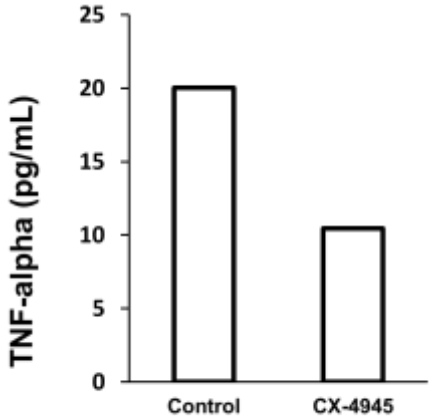
Histopathology of the lungs in transgenic mice infected with SARS-CoV-2

- Animal Model: AAV/hACE2 B6 mice
- Virus Strain: SARS-CoV-2 TCDC#4



Plasma multiplex





* *Source: Available under CDA*

Silmitasertib is safe and well tolerated with data from over 200 patients from clinical oncology trials

- Three completed phase I clinical oncology trials have demonstrated that silmitasertib is safe and well tolerated
- Silmitasertib is currently in ongoing phase I and I/II studies for basal cell carcinoma, cholangiocarcinoma, and medulloblastoma
- Most common adverse events are gastrointestinal, which have been effectively managed in clinical trials with physician-directed protocols

Silmitasertib showed an early sign of clinical benefit in a severe COVID-19 patient under an emergency IND

- In August 2020, a single patient with severe COVID-19 pneumonia who had exhausted all reasonable therapies, was treated with silmitasertib;

Patient Age:	64 years
Location:	Arizona, US
Prior Therapy:	Remdesivir, Dexamethasone, Ceftriaxone, Azithromycin and Enoxaparin
Pre-Tx Status:	Remained hypoxic and required up to 2 liters of supplemental oxygen daily
Response:	Oxygen requirement was weaned to room air in 24 hours after the first dose administration
Outcome:	Patient discharged from the hospital 5 days after being treated with Silmitasertib.

Ongoing Silmitasertib Clinical SARS-CoV-2 Studies

Organization/ Institution	Location	Experiment Outline
University of Arizona College of Medicine/ Banner* – Uni. Medical Center Phoenix.	AZ, US	Phase II multi-center, randomized, two-armed controlled interventional prospective IIT study to assess the safety, clinical benefit, and anti-viral activity of Silmitasertib in up to 40 patients with **severe** COVID-19.
Center for Advanced Research and Education (CARE)	GA, US	Phase II, investigator-initiated, placebo-controlled clinical investigation of the safety and clinical benefit of silmitasertib in 20 patients with **moderate** COVID-19.

* Banner Health System, 3 medical centers and 28 hospitals across 6 States, HQ in Arizona

Active discussions are also underway with federal bodies in several countries for the inclusion of silmitasertib in government sponsored clinical trials

A safe oral COVID-19 drug could be used in multiple care settings to slow patient and disease progression

- Oral dose form is convenient and cost-effective for outpatient use
- Broad use could reduce viral shedding and hospitalizations
- Silmitasertib is not broadly immunosuppressive or cytotoxic to T-cells like dexamethasone

- Use in hospital may rescue some patients from cytokine storm
- Additional potential to avoid progression to the critical phase
- The average cost of 1 ICU day in the US is $4K, and $6K with a ventilator

Silmitasertib Summary

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