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Evaluating the Efficacy of a SARS-CoV-2 Preventative Drug in a Hamster Model

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INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a novel coronavirus similar to SARS-CoV and to betacoronaviruses that have been detected in other species, has spread across the world with dire effects on healthcare systems and economies. Suitable small animal models have been identified to emulate disease progression for development of vaccines and other therapies. The golden hamster (*Mesocricetus auratus*) is a widely used experimental animal model and has been reported to support replication of SARS-CoV-2.[1,2] Compound X, an FDA approved, proprietary drug has demonstrated the ability to kill SARS-CoV-2 in cell culture systems using median tissue culture infective dose assays ($TCID_{50}$).

AIMS

- Establish baseline infectivity of the SARS-CoV-2 USA-WA1/2020 isolate in inoculated hamsters, and its ability to transmit to sentinel hamsters comingled with inoculated hamsters at 1 day post infection (dpi).
- Establish whether compound X is protective during SARS-CoV-2 exposure.

Figure 1. Body Weight Changes

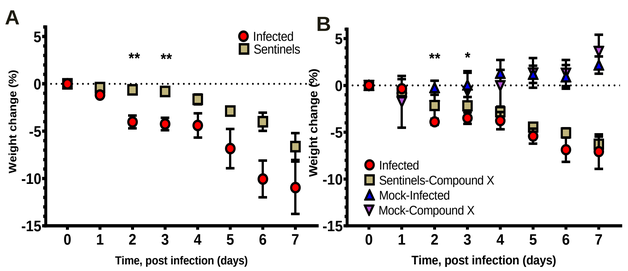

*Figure 1. Average weight change of hamsters during study. Graphs depict the average weight change per day as a percentage. Weights were recorded on Day 0 (inoculation) and daily for the duration of each study (7 days). Error bars are standard error. (A) Experiment 1 Hamsters, n=4, 1-3 dpi, n=2, 4-7 dpi. Statistically different using student's unpaired t test, **P ≤ 0.005 (B) Experiment 2 Hamsters, n=8, 1-3 dpi., n=4 4-7 dpi. Infected and Sentinels-compound X treated, statistically different using ANOVA , * P≤ 0.05,**P ≤ 0.005.*

Figure 2. Experiment 1 Lung Images

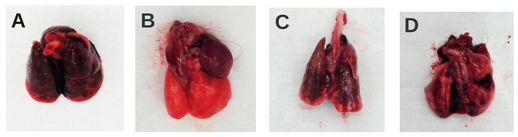

Figure 2. Macroscopic images of pulmonary damage (A) Infected hamster, 3 dpi. (B) Sentinel hamster, 3 dpi (2 days post contact). (C) Infected hamster, 7 dpi. (D) Sentinel hamster, 7 dpi (6 days post contact).

METHODS

Experiment 1 Infection of Hamsters.

- Three-month-old male Syrian hamsters were obtained from Envigo.
- Under isoflurane anesthesia, four hamsters were inoculated with 5 x10^5 $TCID_{50}$ [in 100µL Modified Eagles Media (MEM)] intranasally. Four sentinel hamsters were placed as cage mates with each infected hamster at 1 dpi.
- Body weight and temperature of all hamsters were monitored daily. Two cages (4 animals) were euthanized at 3 dpi and at 7 dpi.
- Nasal wash (NW) and lung lavage (LL) were performed at necropsy. Samples were collected for RNA and viral titer. (nasal turbinates, trachea, lungs, brain, spleen, kidneys, intestine, and blood).
- NW, LL, trachea, lung and nasal turbinates (NT) were tested for infectivity using cell culture method ($TCID_{50}$).
- NW, LL, NT, spleen, kidney, brain and intestine were assessed for viral RNA titer using real time RT-PCR.

Experiment 2 Infection of Hamsters.

- Four cages of hamsters (8), assigned as sentinels, began compound X treatment (25 µL per nostril) 48 hours prior to comingling and every 12 hours for the duration of the experiment.
- Other than the treatment with compound X, experiment 2 was conducted in the same manner as experiment 1.
- 2 hamsters were mock-infected concurrently. 2 hamsters were treated with compound X and comingled with the mock hamsters. These 4 hamsters were necropsied 7 dpi.

Figure 3. Experiment 2 Lung Images

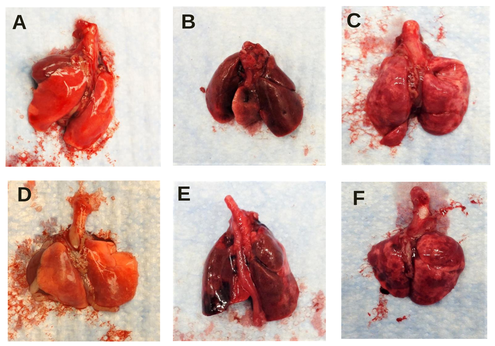

Figure 3. Macroscopic images of pulmonary damage (A) Mock-infected hamster, 7 dpi. (B) Infected hamster, 3 dpi. (C) Infected hamster, 7 dpi. (D) Mock sentinel hamster, 7 dpi. (E) Sentinel hamster, 3 dpi. (F) Sentinel hamster, 7 dpi. D, E, and F were treated with compound X. Bottom photos are cage mates of top photos

RESULTS

- SARS-CoV-2 replicated efficiently in both inoculated and naturally infected hamsters as indicated by weight loss (Fig. 1) and viral titers in the nasal mucosa and respiratory tract (Fig. 4).
- Transmission from infected to sentinel hamsters occurs in a very short time, as previously reported[3].
- SARS-CoV-2 replicated efficiently in respiratory epithelial cells with peak viral load detected soon after inoculation, followed by rapid clearance of infectious virus by 7 dpi (Figure 4). Despite rapid clearance, clinical evidence of lung lesions are visible (Fig 2 C, D, Figure 3 C, E).
- Peak viral loads were detected at 3 dpi; lesser or no infectious virus was detected at 7 dpi despite the continued detection of high copies of viral RNA (Fig. 5).

Figure 4. Infectious Viral Titers

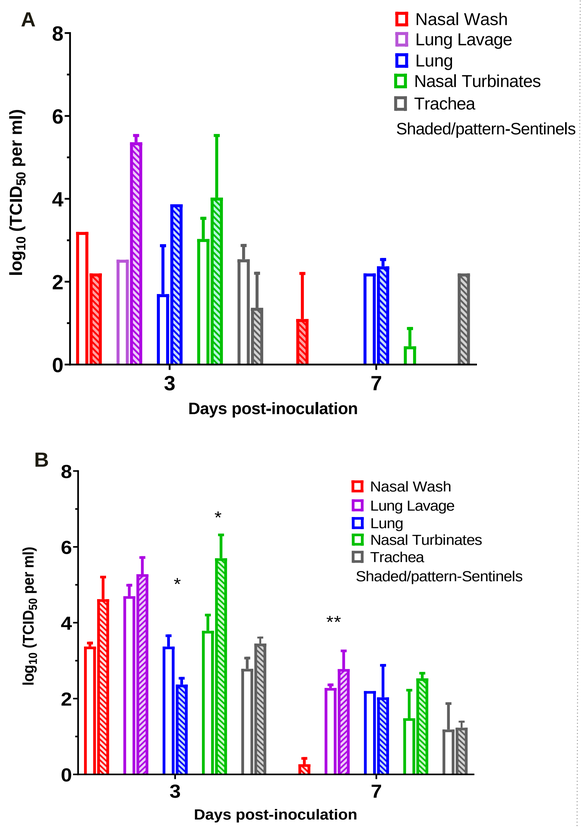

*Figure 4. Viral load detected in various tissues of hamsters. (A) Experiment 1 at 3 and 7 dpi. (B) Experiment 2 at 3 and 7 dpi. (Sentinel hamsters treated with compound X). Mean ±S.E.M. Statistically different using student's unpaired t test, ** p ≤0.005; *p ≤ 0.05.*

Figure 5. RNA Titers

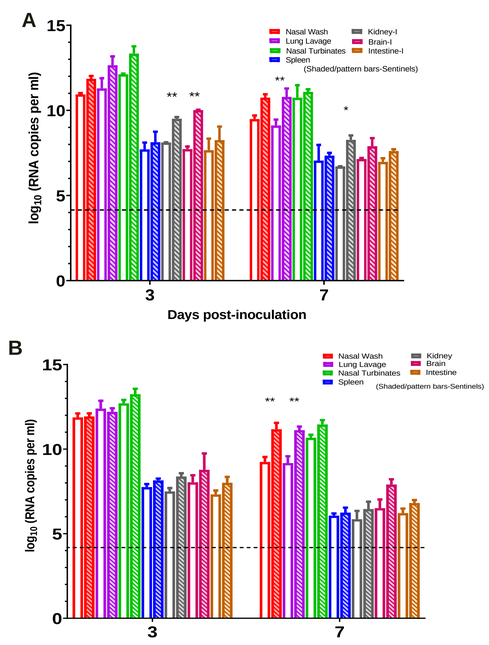

*Figure 5. Viral RNA load detected in various tissues of hamsters. (A) Experiment 1 at 3 and 7 dpi. (B) Experiment 2 at 3 and 7 dpi. (Sentinel hamsters treated with compound X). Mean ±S.E.M. Statistically different using student's unpaired t test, ** p ≤0.005; *p ≤ 0.05. Broken line is detection limit of 4.21.*

CONCLUSIONS

- SARS-CoV-2 USA-WA1/2020 readily infects hamsters, producing detectable pathology and making a good system for testing therapeutics and vaccine efficacy.
- Despite previously being shown to be virucidal, compound X failed to prevent SARS-CoV-2 transmission in hamsters under continuous exposure conditions.

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