Poster # 1244031

Efficacy of Potential Antiviral Therapeutics Against SARS-CoV-2 in Mice

Adam Bess[1], Frej Berglind[2], Supratik Mukpodahyay[1], Michal Brylinski[3], Nicholas Griggs[4], Tiffany Cho[4], Chris Galliano[5], and Kishor M. Wasan[5,6]

1. Department of Computer Sciences, Louisiana State University, Baton Rouge, LA, USA; 2. Department of Mathematics, Louisiana State University, Baton Rouge, LA, USA; 3. Department of Biological Sciences, Louisiana State University, Baton Rouge, LA, USA; 4. SafeBridge Regulatory & Life Sciences Group (Trinity Consultants), Mountain View, CA, USA; 5. Skymount Medical US Inc., New Orleans, LA, USA; 6. Department of Urologic Sciences, Faculty of Medicine, University of British Columbia, Vancouver, BC, Canada

PURPOSE

The objective of this study was to test the *in vivo* efficacy of two potential antiviral therapeutics, SM-4 (G5) and SM-19 (G6), identified by our artificial intelligence DeepDrug™ software against SARS-CoV-2, the causative agent of COVID-19, in the ACE2 mouse model.

OBJECTIVE

The objective of this project was to determine the anti-viral activity of two novel therapeutics, SM-4 (G5) and SM-19 (G6) against SARS-CoV-2 in an infected ACE2 mouse model.

METHODS

Six hours following challenge with 5 x 103 $TCID_{50}$ SARS-CoV-2, human transgenic female K18-hACE2 (B6.Cg-Tg(K18-ACE2)2PrlmnJ) mice were orally administered placebo, SM-4 at 50 mg/kg, or SM-19 50/100 mg/kg combination once a day for 6 consecutive days. The concentration of virus in the lungs was determined by RT-qPCR. Briefly, RNA was extracted from samples stored in RNA/DNA Shield using the Quick-RNA Viral Kit (Zymo Research) according to the manufacturer's protocol. RT-qPCR was performed using the following RT-PCR cycling conditions: 50°C for 15 min (RT), then 95 °C for 2 min (denature), then 40 cycles of 10s at 95°C, 45s at 62°C. Primers used for SARS-CoV-2 detection: 2019-nCoV_N1-F 5'-GACCCCAAAATCAGCGAAAT-3' 2019-nCoV_N1-R 5'-TCTGGTTACTGCCAGTTGAATCTG -3' Probe: 2019-nCoV_N1-P: 5'-FAM-ACCCCGCATTACGTTTGGTGGACC-BHQ1-3'.

Additional experimental endpoints were also determined including body weight and body weight change and clinical chemistry determinations such as BUN, AST, and ALT levels.

Table 1. DeepDrug™ AI Platform.

AI SYSTEM	DESCRIPTION	BENEFIT TO PLATFORM PARTNER
eSynth	New Molecule Synthesis Engine	Synthesize New Molecules and New Chemical Entities based on Protein Targets
eToxPred	Fragment based toxicity analysis (SVM, ET, Deep Belief Network)	Creates a 2/3/4 Drug Interaction Graph to let researchers analyze Pharmacological Index and if 2/3/4 drug combinations are toxic or not
eDrugRes	Graph Convolutional Neural Network based bacterial antibiotic susceptibility	AI Network with an entire volume known components of antibiotics to break down existing antibiotics to recompile to make new novel antibiotics
eVir	Peptide-based, protein-protein interaction led drug discovery (Graph Node Embeddings, MultiLayer Perceptron, Siamese Network) Dose-response based results	A Model of all known protein interactions from SARS COV 2003, SARS COV2, MERS and other Coronavirus which enables the syntheses of efficacy models from existing drugs or synthesizes new chemical entities from known protein targets
eComb	Drug combination synergy analysis and drug-drug interaction prediction (BLISS, MuSyC, PDDIs, Neural Network based)	A Next generation analysis engine that scores efficacy, synergy and toxicity of 2,3,4,5 or greater drug combinations to look at combination analysis for new indications

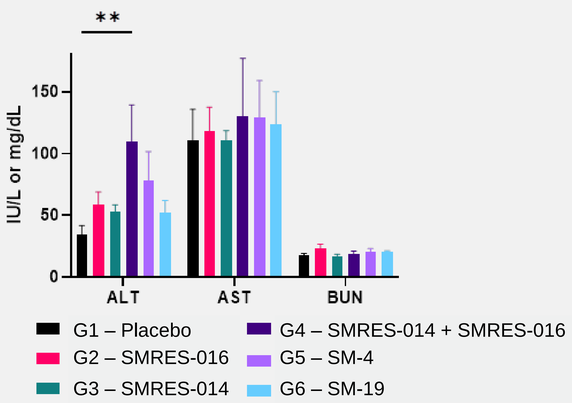
RESULTS

SM-4 (G5 - mebendazole) and SM-19 (G6 – mebendazole + SMRES-016 [imatinib]) treatment resulted in a 44.2% and 42.3% reduction in lung viral load compared to non-treated placebo control, respectively (**Table 2**). There were no significant differences in body weight and all clinical chemistry determinations evaluated (*i.e.*, kidney and liver enzymes) between the different treatment groups.

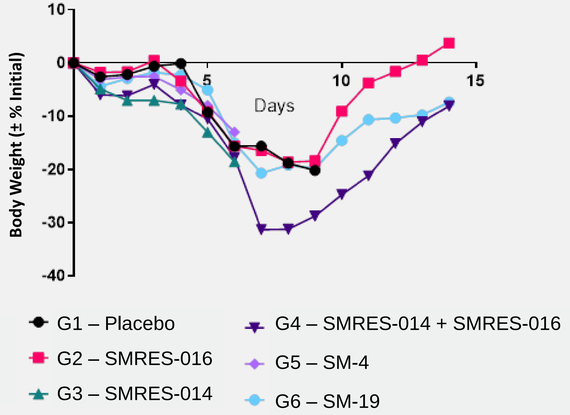
Table 2. Lung RT-qPCR data for SARS-CoV-2 virus following 6 days of treatment in K18-hACE2 mice orally administered with either SM-4 (50 mg/kg) or SM-19 drug combination (50/100 mg) once daily for 6 consecutive days.

Treatment Group	N	Lung RT-qPCR Mean ± SD (x 10^7)	% Reduction Compared to Control
Untreated Control	7	7.81 ± 6.0	-
SM-4	7	4.36 ± 2.2	44.2%
SM-19	7	4.5 ± 4.9	42.3%

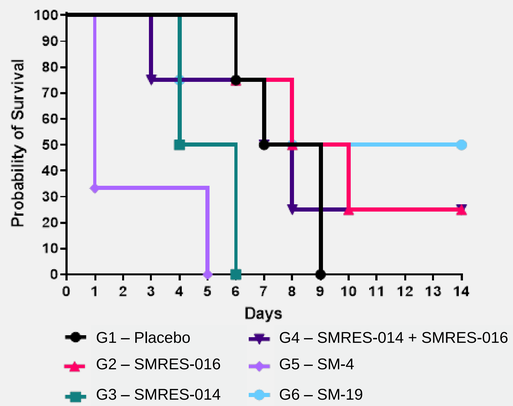
Mean Serum ALT, AST, and BUN Levels at Day 6



Group Mean Percent Body Weight Change



Percent Survival by Group



CONCLUSIONS

Taken together these preliminary findings suggest that these novel compounds may have significant *in vivo* activity against SARS-CoV-2 at non-toxic doses. By using the predictive algorithm of DeepDrug™ as a tool to identify and repurpose existing compounds, we were able to test the highest ranked drugs for their efficacy against SARS-CoV-2 in an *in vitro* and *in vivo* setting. Future directions include identifying other efficacious treatments.

ACKNOWLEDGEMENTS

The authors would like to thank Skymount Medical for funding this work. Studies were performed at IITRI (Chicago, IL).

REFERENCES

1. Bess A, Berglind F, Mukhopadhyay S, Brylinski M, Griggs N, Cho T, Galliano C, Wasan KM. Artificial intelligence for the discovery of novel antimicrobial agents for emerging infectious diseases. Drug Discov Today. 2022 Apr;27(4):1099-1107.