Long-Acting IM Injection of Niclosamide (DWRX2003) as a Broad Host-Directed Therapeutic Against SARS-CoV-2 and Other Viral Infections

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DAEWOONG THERAPEUTICS

Efficacy

Niclosamide

- **DWRX2003 is a long-acting intramuscular injection of niclosamide, an old anthelmintic with long safety history with no evidence of systemic toxicity, carcinogenicity, mutagenicity, teratogenicity, and embryotoxicity.**

Mode of Action

Mechanism		Effect
SKP2 Inhibition	Antiviral	Prevent degradation of host cell autophagy regulator BECN1
Endosomal pH Neutralization	Antiviral	Block virus entry Inhibit viral replication or maturation
STAT3 Inhibition	Anti-Inflammatory	Suppress inflammatory cell infiltration Prevent cytokine storm
TMEM16A Inhibition	Anti-Inflammatory	Improve vasoconstriction Improve ARDS and breathlessness by >90% Reduce CV risks (myocardial hypertrophy)

- **Niclosamide has recently been identified as a SARS-CoV-2 inhibitor with a potency >40x higher than Remdesivir by Institut Pasteur Korea**

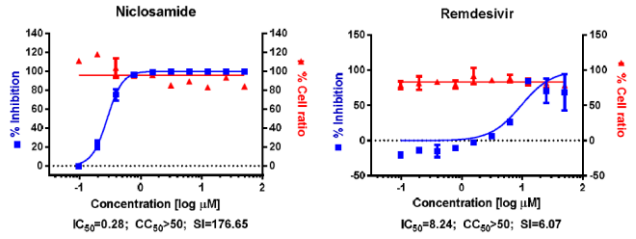
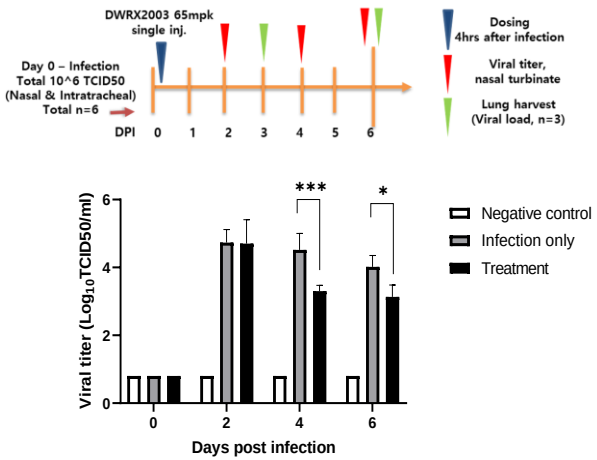


Figure 1. Dose-response curve analysis by cytopathic effect of SARS-CoV-2 in Vero cells. The blue squares represent inhibition of virus infection (%) and the red triangles represent cell viability (%). Means ± SD were calculated from duplicate experiments (Jeon et al., 2020).

SARS-CoV-2 (COVID-19)



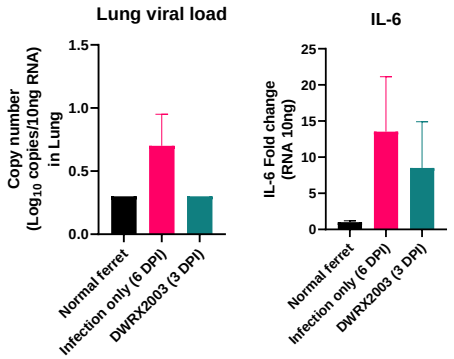


Figure 2-1. Schematic illustration of therapeutic efficacy study on SARS-CoV-2 infected ferret model.
Figure 2-2. Virus titer of nasal turbinate on 2, 4, 6 DPI
Figure 2-3. Lung viral load
Figure 2-4. Lung IL-6 level

Other Virus Infections

- **Niclosamide's broad host-directed antiviral MoA also applied to MERS-Cov, SARS-CoV, and IVA.**

MERS-CoV

Virus: Mouse-adapted MERS-CoV Huh7 p2, 5 x 10^7 PFU/mL
Inoculum: 20 uL vol (1 x 10^5 PFU) inoculated IN after isoflurane sedation
Mouse: ad5-hDpp4 TG mouse
Test Compound: 900 mg/ 3.75 mL DWRX2003
1) 28 uL (225 mg/kg) IM
2) 40 uL (320 mg/kg) IM
Dosing Time: administered 24 hr after virus infection
Read-out: Survival, titer by $TCID_{50}$

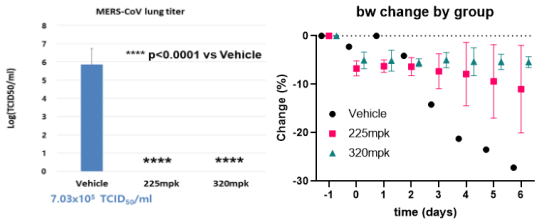


Figure 3. Schematic illustration and results from prophylactic efficacy study on MERS-CoV infected ad5-HDPP4 mouse model

Influenza A (H1N1)

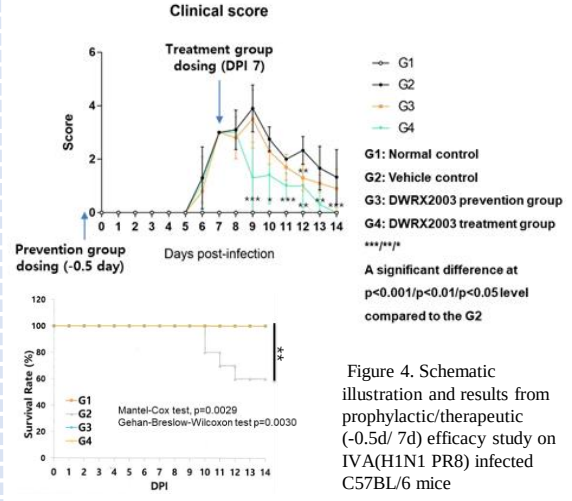


Figure 4. Schematic illustration and results from prophylactic/therapeutic (-0.5d/ 7d) efficacy study on IVA(H1N1 PR8) infected C57BL/6 mice

Anti-inflammatory

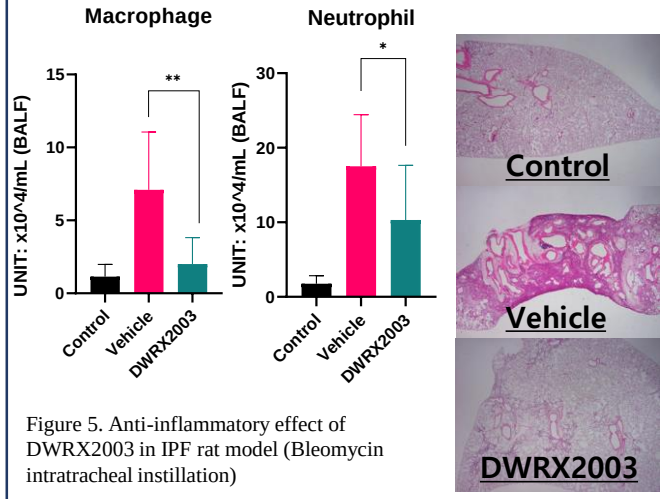


Figure 5. Anti-inflammatory effect of DWRX2003 in IPF rat model (Bleomycin intratracheal instillation)

Pharmacokinetics

- **A Single IM injection of niclosamide maintained plasma concentration above the IC50(0.28uM) for 14 days. Conversely, niclosamide PO cleared around 24hr by first-pass effect, and when repeated, resulted in concentration spikes with intermediary lapses failing to provide a constant therapeutic window.**
- **Drastic increase in bioavailability was observed for IM vs PO (2.97% → 35.5%)**

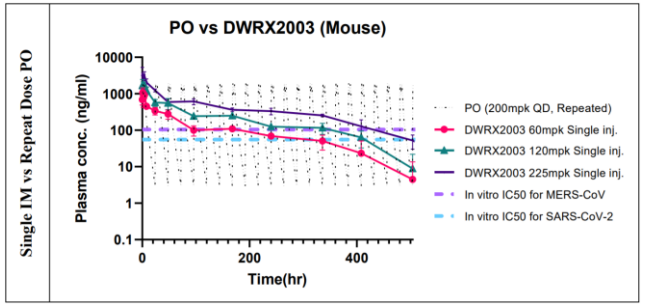


Figure 6. PK profile comparison of niclosamide PO and DWRX2003 (Niclosamide sustained-release injectable) for SARS-CoV2 and MERS-CoV.