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

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**

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<tr>
<th>Mechanism</th>
<th>Effect</th>
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<td>SKP2 Inhibition</td>
<td>Prevent degradation of host cell autophagy regulator BECN1</td>
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<td>Endosomal pH Neutralization</td>
<td>Block virus entry to inhibit viral replication or maturation</td>
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<td>STAT3 Inhibition</td>
<td>Suppress inflammatory cell infiltration to prevent cytokine storm</td>
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<tr>
<td>TMEM16A Inhibition</td>
<td>Improve vasoconstriction to improve ARDS and breathlessness by &gt;90% and reduce CV risks (myocardial hypertrophy)</td>
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Niclosamide has recently been identified as a SARS-CoV-2 inhibitor with a potency >40x higher than Remdesivir by Institut Pasteur Korea.

**Efficacy**

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

**Pharmacokinetics**

- A single IM injection of niclosamide maintained plasma concentration above the IC50 for 14 days. Conversely, niclosamide PO cleared around 24 hr 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%).

**Other Virus Infections**

- MERS-CoV
  - Virus: Mouse-adapted MERS-CoV Huh7/p2, 5 x 10^5 PFU/mL
  - Inoculum: 20 uL (vol x 1 x 10^4 PFU) intratracheal instillation
  - Mouse: Ad5-hDPP4 TG mouse
  - Test Compound: 900 mg/3.75 mL DWRX2003
  - Control: Vehicle
  - DWRX2003

- Influenza A (H1N1)
  - Clinical score
  - Treatment group vs Vehicle control

- Anti-inflammatory

- SARS-CoV-2 (COVID-19)
  - Lung viral load
  - IL-6

- 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 stability (%). Means ± SD were calculated from duplicate experiments (Jeon et al., 2020).

- Figure 2. Schematic illustration of therapeutic efficacy study on SARS-CoV-2 infected ferret model.

- Figure 3. Schematic illustration and results from prophylactic efficacy study on MERS-CoV infected ad5-hDPP4 mouse model

- Figure 4. Schematic illustration and results from prophylactic/therapeutic (4x5d/7d) efficacy study on IVA(H1N1 PR8) infected C57BL/6 mice

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

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

Disclosure Statement

-Reviewed and approved in accordance with researches described in this poster. In addition, the author serves as a consultant to Daewoong Therapeutics which is developing products related to Pasteur Korea.

**References**

- SKP2 Inhibition - Prevent degradation of host cell autophagy regulator BECN1
- Endosomal pH Neutralization - Block virus entry to inhibit viral replication or maturation
- STAT3 Inhibition - Suppress inflammatory cell infiltration to prevent cytokine storm
- TMEM16A Inhibition - Improve vasoconstriction to improve ARDS and breathlessness by >90% and reduce CV risks (myocardial hypertrophy)

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**Figure Legends**

- Figure 2: Schematic illustration of therapeutic efficacy study on SARS-CoV-2 infected ferret model.
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