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Supplemental Information

Synergistic and Antagonistic Drug Combinations against SARS-CoV-2

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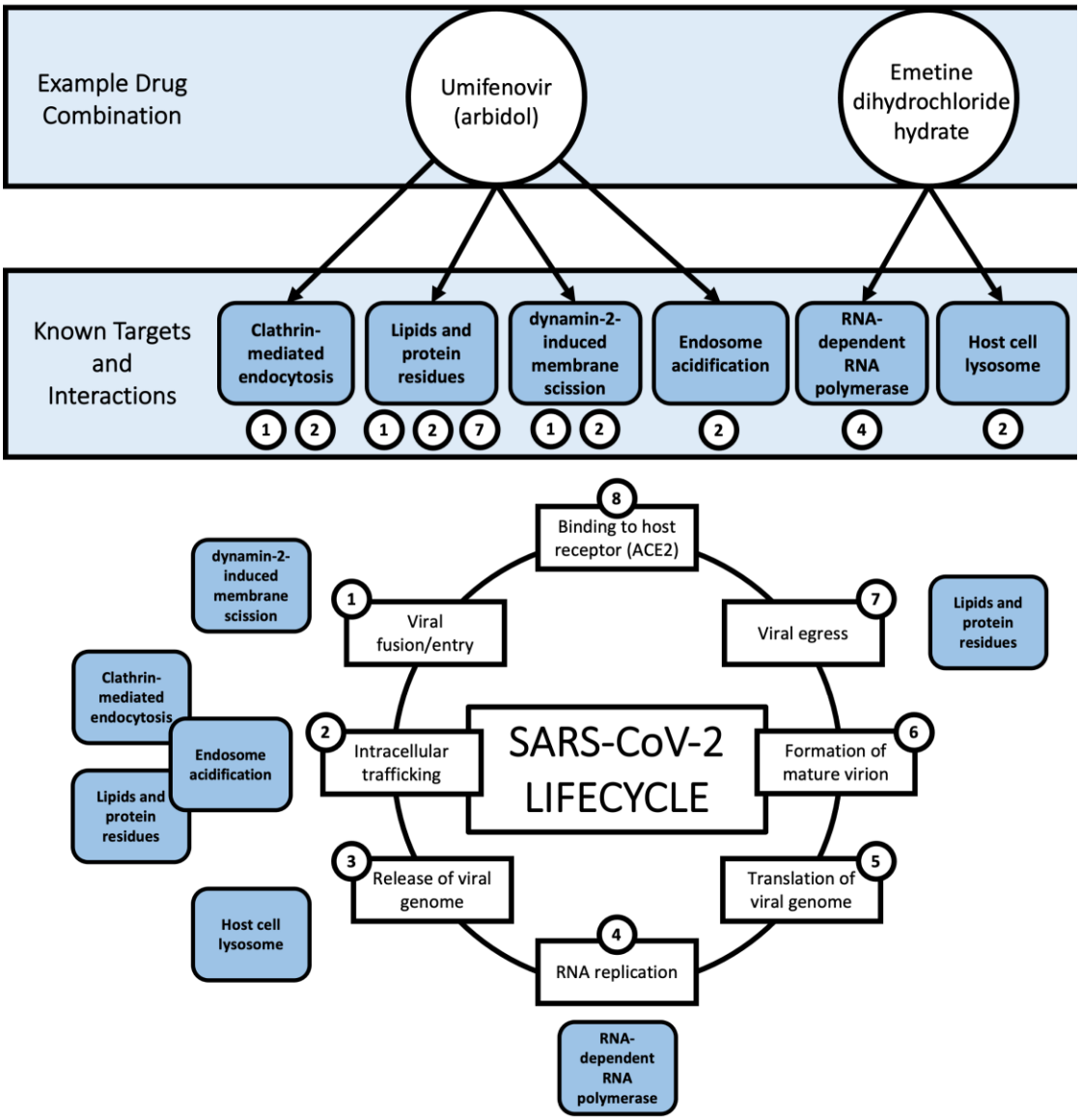

Fig. S1. Example (umifenovir + emetine dihydrochloride hydrate) of the rationale behind mixture selection, i.e., interference with different steps of the COVID-19 lifecycle. All known targets and interactions were taken from the literature and are not necessarily specific to SARS-CoV-2. Umifenovir's proposed mechanisms of action involve clathrin-mediated endocytosis [1,2], lipids and protein residues [3], dynamin-2-induced membrane scission [1], and endosome acidification [1]. Emetine's proposed mechanisms of action involve RNA replication/RNA-dependent RNA polymerase [4] and the host cell lysosome [4]. The viral lifecycle of SARS-CoV-2 was inspired by Fig. 1. of da Costa et. al 2020.[5]

Supplemental Tables (provided as separate Excel file):

Table S1. Compound sources and annotations (ID, name, structure, mechanism of action)

Table S2. Raw data for batch validation

Table S3. Raw data for matrix combination screening

Table S4. Summary of synergy in CPE assay

Supplemental references:

1. Boriskin, Y, Leneva, I, Pecheur, E-I and Polyak, S (2008). Arbidol: A Broad-Spectrum Antiviral Compound that Blocks Viral Fusion. *Curr. Med. Chem.* **15**: 997–1005.

2. Blaising, J, Lévy, PL, Polyak, SJ, Stanifer, M, Boulant, S and Pécheur, EI (2013). Arbidol inhibits viral entry by interfering with clathrin-dependent trafficking. *Antiviral Res.* **100**: 215–219.

3. Blaising, J, Polyak, SJ and Pécheur, EI (2014). Arbidol as a broad-spectrum antiviral: An update. *Antiviral Res.* **107**: 84–94.

4. Yang, S, Xu, M, Lee, EM, Gorshkov, K, Shiryaev, SA, He, S, *et al.* (2018). Emetine inhibits Zika and Ebola virus infections through two molecular mechanisms: inhibiting viral replication and decreasing viral entry. *Cell Discov.* **4**: 31.

5. da Costa, VG, Moreli, ML and Saivish, MV (2020). The emergence of SARS, MERS and novel SARS-2 coronaviruses in the 21st century. *Arch. Virol.* **165**: 1517–1526.