**Supplementary Information**

*Supplementary Figures*



**Supplementary Figure 1 | Primary data of infection experiments showing inhibition of SARS-CoV-2, RSV, and IAV by atpenin A5, phenformin, and metformin.** Images show **A** Calu-3 cells infected with icSARS-CoV-2-mNG **B** A549 cells infected with the respiratory syncytial virus and **C** A549 cells infected with influenza A virus treated with the indicated compounds and concentrations.

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**Supplementary Figure 2 | tSNE plots of cell types for the individual single-cell expression datasets of viral infection.** Panels show **A** CHETAH-derived cell type annotation of the dengue dataset, based on a PBMC reference, and **B** CHETAH-derived cell type annotation of the BALF1 dataset, based on a single cell lung atlas. Panel **C** shows the same tSNE-plot as **B** of the BALF1 dataset but color coded for donors’ health or COVID status. **D** Manual cell type annotation of the influenza H1N1 dataset.

*Supplementary Tables*

Supplementary Table S1 - Differentially active pathways in SARS-CoV-2 infected individuals

Supplementary Table S2 - Virus-host-interactions

Supplementary Table S3 - High-confidence tier-1 and tier-2 targets (Fig. 3)

Supplementary Table S4 - Frequency of tier-1 targets

Supplementary Table S5 - Broad-spectrum antiviral targets

Supplementary Table S6 - Viral protein copy numbers

Supplementary Table S7 - Viral replication reactions

Supplementary Table S8 - Blood Serum constraints

Supplementary Table S9 - Dengue dataset cell type annotation

*Supplementary Data*

Supplementary Data S1 - Metabolic map of predicted shared tier-1 targets (blue) and broad-spectrum antiviral targets (red) across human metabolism. The map was created following the SBGN standard [(Touré et al., 2021)](https://paperpile.com/c/oCpVFD/I3vR) using Recon2Map [(Noronha et al., 2017)](https://paperpile.com/c/oCpVFD/RLYq) based on the MINERVA platform [(Gawron et al., 2016)](https://paperpile.com/c/oCpVFD/Flsl).

Supplementary Data S2 - Viral replication rates, predicted tier-1/tier-2 targets and metadata for all reconstructed context-specific models.